EUROPEAN CHEMICALS AGENCY

Helsinki, 30 June 2020

Addressees
Registrants of JS_120-93-4_ETU listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
20/09/2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 2-imidazolidone
EC number: 204-436-4
CAS number: 120-93-4

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***5 October 2023.***

A. Requirements applicable to all the Registrants subject to Annex IX of REACH

1. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: OECD TG 443) in rats, oral route specified as follows:

    - At least two weeks premating exposure duration for the parental (P0) generation;
    - Dose level setting shall aim to induce systemic toxicity at the highest dose level;
    - Cohort 1A (Reproductive toxicity);
    - Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation which shall be followed to weaning;and
    - Cohorts 2A and 2B (Developmental neurotoxicity);

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.

To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annexes VII, VIII and IX of REACH, if you have registered a substance at 100-1000 tpa;

Registrants are only required to share the costs of information that they must submit to fulfil the information requirements for their registration.

The Appendices state the reasons for the requests for information to fulfil the requirements

set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix A: Reasons for the requests to comply with Annex IX of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII to IX to REACH.

1. **Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.)**

The basic test design of an extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex IX to REACH, if the available repeated dose toxicity studies indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. Furthermore column 2 defines the conditions under which the study design needs to be expanded.

You have provided the following studies:

1) An **OECD TG 422** Combined repeated dose toxicity sudy with the reproduction/developmental toxicity screening test (2013),

2) An **OECD TG 408** Repeated dose 90-day oral toxicity study (2018),

3) An **OECD TG 407** Repeated dose 28-day oral toxicity study (2002), and

4) A non-guideline **14-day mechanistic study** (2018).

We have assessed this information and identified the following issue(s):

- Issue 1: Triggers for the information requirement at Annex IX

You consider that no adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies, and/or that these studies did not reveal other concerns in relation with reproductive toxicity: You have provided the following waiver: *"According to REACH Annex IX, the two-generation reproductive toxicity study (or EOGRTS) is required if the 28- or 90-day study indicates adverse effects on reproductive organs or tissues. Based on the results of a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test with the registered substance according to OECD Guideline 422 ([redacted] 2012) there are no triggers for the two-generation reproductive toxicity study (or EOGRTS)."*

However, adverse effects on reproductive organs or tissues or other concerns in relation with reproductive toxicity are observed in available studies. More specifically,

1. In the OECD TG 422 screening test (2013) thyroid gland absolute weight increased in males at the highest dose in the absence of excessive other toxicity. Thyroid gland follicular hypertrophy/hyperplasia was observed at the highest dose in 10/10 of males and in 5/10 females.

2. The OECD TG 408 90-day study (2018) showed increased thyroid gland absolute weights in males at the highest dose in the absence of excessive other toxicity. Thyroid gland follicular hypertrophy/hyperplasia was seen at the highest dose.

3. In the OECD TG 407 28-day study (2002) thyroid gland follicular hypertrophy/hyperplasia was observed in male and female animals at all test doses.

In addition, testicular tubular giant cells and tubular hypoplasia (1/5 males, mid-dose, 2/5 males, highest dose) and cellular debris in the epididymides (all males, highest dose) in the absence of excessive general toxicity.

4. In the 14-day mechanistic oral study (2018), effects in thyroid gland and thyroid related hormones were observed. In males, absolute thyroid gland weight increased, T4 and T3 levels decreased, and TSH level increased, all both at the mid and high dose level. In females, T4 levels decreased at high dose level, and TSH levels increased at mid and high dose levels.

Therefore, an EOGRT study according to OECD TG 443 as specified in this decision is an information requirement for your registration, because Column 1 criteria at Annex IX, section 8.7.3 are met.

Based on the above, the information you provided does not fulfil the information requirement.

- Issue 2: The study provided is not in line with the requirements in OECD TG 443 as specified under REACH

To be considered compliant and enable concluding if the Substance is a reproductive toxicant, the study has to meet the requirements of OECD TG 443 as specified in REACH.

The OECD TG 422 study you provided does not cover all relevant life stages required in OECD TG 443, as the extensive postnatal investigations of the fully exposed F1 generation up to the adulthood are not included. Furthermore, the statistical power of the information provided is not sufficient because it does not fulfil the criterion of 20 pregnant females for each test group as required OECD TG 443. In addition, the criteria for extension of the Cohort 1B are met for the Substance and there is a particular concern for developmental neurotoxicity according to column 2 of Annex IX, Section 8.7.3. and information for those properties are missing.

The OECD TG 408 and the OECD TG 407 studies you provided do not meet the requirement of OECD TG 443 as effects on mating, fertility, pregnancy, lactation and postnatal development of the fully exposed F1 generation up to the adulthood are not investigated. In addition, the criteria for extension of the Cohort 1B are met for the Substance and there is a particular concern for developmental neurotoxicity according to column 2 of Annex IX, Section 8.7.3. and information for those properties are missing. Therefore, these studies do not fulfil the criteria set in OECD TG 443.

Based on the above, the information you provided does not fulfil the information requirement.

The specifications for the study design

Premating exposure duration and dose-level setting

A 2-week premating exposure duration for P0 animals is sufficient for your Substance, because the F1 animals of Cohort 1B are mated to produce the F2 generation and, thus, the premating exposure duration will be 10 weeks for these Cohort 1B animals.

Therefore, the requested premating exposure duration is at least two weeks.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects. A descending sequence of dose levels should be

selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

You have to provide a justification with your study results that demonstrates that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

Cohorts 1A and 1B belong to the basic study design and shall be included.

Extension of Cohort 1B

If the Column 2 conditions of 8.7.3., Annex IX are met, Cohort 1B must be extended.

The extension is inter alia required, if the use of the registered substance is leading to significant exposure of consumers and professionals (column 2, first paragraph, lit. (a) of Section 8.7.3., Annex IX) and there are indications of one or more relevant modes of action related to endocrine disruption from available *in vivo* studies or non-animal approaches (column 2, first paragraph, lit. (b), third indent of Section 8.7.3., Annex IX).

- The use of the Substance is leading to significant exposure of workers and consumers, because the Substance is used in coating, textiles, inks and toners (PROCs e.g. 4, 5, 7, 8a, 9, 10, 11, 13, 14, 19, 21).

- Finally, there are indications of one or more modes of action related to endocrine disruption because changes in organs and parameters sensitive to endocrine activity are observed, i.e. thyroid effects, more notably hypertrophy/hyperplasia seen in histopathology and/or changes in thyroid hormone levels were observed in four studies as specified above. In addition, in 28-day study testicular and epididymal findings were observed (testicular tubular giant cells and tubular hypoplasia; and cellular debris in the epididymides).

Therefore, Cohort 1B must be extended.

The F2 generation shall be followed to weaning allowing assessment of nursing and lactation of the F1 parents and postnatal development of F2 offspring. Investigations for F2 pups must be similar to those requested for F1 pups in OECD TG 443 and described in OECD GD 151[2]. It is recommended to aim to 20 litter per dose group in order to have similar statistical power for investigations than in P0 generation.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity.

Existing information on the Substance itself derived from available *in vivo* studies specified above show evidence of thyroid toxicity, more notably thyroid hypertrophy and hyperplasia seen in histopathology and effect on the thyroid hormone levels. Thyroid toxicity rises a

[2] http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2013)10&doclanguage=en

particular concern on developmental neurotoxicity[3].

Therefore, the developmental neurotoxicity Cohorts 2A and 2B need to be conducted.

The study must be performed in rats with oral[4] administration.

In your comments you have agreed to provide the required information according to Annex IX, Section 8.7.3.

Further expansion of the study design

No triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including Cohort 3 if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex IX. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[5].

Deadline to submit the requested information

In the draft decision communicated to you, the time indicated to provide the requested information was 24 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline to 36 months. You sought to justify this request by explaining that the time span of 24 months for conducting an Extended one-generation reproductive toxicity study is rather challenging, e.g. due to the limited capacity of test laboratories. You included a document provided by the relevant testing laboratory, presenting the study schedule, and total time required to perform the test. ECHA has evaluated your request and the documentation from the laboratory, and considers your justifications acceptable. Therefore, ECHA has granted the request and set the deadline to 36 months for this specific test.

[3] ECHA Guidance R.7a, Section R.7.6.
[4] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[5] ECHA Guidance R.7a, Section R.7.6.

Appendix B: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

The compliance check was initiated on 13 March 2019.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and amended the deadline.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix C: Observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries'[6].

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/ impurity.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.
   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[7].

[6] https://echa.europa.eu/practical-guides
[7] https://echa.europa.eu/manuals

5. List of references of the ECHA Guidance and other guidance/ reference documents[8]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[9]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents[10]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document supporting the OECD TG 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD151.

[8] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[9] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[10] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix D: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.