

Helsinki, 05 February 2020

**Addressees**

Registrants of JS\_6104-30-9 listed in the last Appendix of this decision

**Date of submission for the jointly submitted dossier subject of this decision**

31 October 2017

**Registered substance subject to this decision, hereafter 'the Substance'**

Substance name: N,N''-(isobutylidene)diurea

EC number: 228-055-8

CAS number: 6104-30-9

**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 **13 May 2022**.

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

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route, specified as follows:
  - At least two weeks pre-mating 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) without extension to mate the Cohort 1B animals to produce the F2 generation.

**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 to X of REACH, if you have registered a substance at above 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 Appendix on general considerations addresses issues relevant for several requests while the other 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>.

Approved<sup>1</sup> under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

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<sup>1</sup> 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 X of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier at a tonnage above 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to REACH.

### 1. Extended one-generation reproductive toxicity study (Annex X, 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 X to REACH. Furthermore Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have adapted this information requirement by using weight of evidence according to Annex XI, Section 1.2. In your justification for the weight of evidence approach the following independent sources of information (lines of evidence) are presented:

1. [REDACTED] A Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test according to the OECD TG 422 with the Substance;
2. [REDACTED] "one-generation" study (reproduction and fertility effects) (no guideline followed) with the Substance;
3. [REDACTED] sub-chronic (90-day) toxicity study according to the OECD TG 408 with the Substance;
4. QSAR predictions from VEGA QSAR models and QSAR toolbox on estrogen receptor binding and developmental/reproductive toxicity.
5. A waiving argument compiling information from the above OECD TG 422, 408, "one-generation" study, QSAR predictions and a pre-natal developmental toxicity study (OECD TG 414) conducted with the Substance in rats. You conclude on that basis that *"the available data is considered adequate for the purpose of classification and labeling as well as risk assessment and conducting an additional one-generation study according to OECD 443 guideline with the basic study design is not justifiable scientifically as the outcome of this study can be predicted based on the available data and for animal welfare reasons"*.

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

In order to allow a conclusion to be reached on the absence of reproductive toxicity (sexual function and fertility and toxicity to offspring) for the Substance in a weight of evidence adaptation, the justification must cover the key elements (parameters) foreseen to be investigated in an EOGRT study with an equivalent test design to that requested in this decision.

ECHA has assessed to what extent the information submitted enables a conclusion on each of these aspects and identified the following deficiencies:

*'Sexual function and fertility' and 'toxicity to offspring'*

Information on toxicity to the offspring (Cohort 1A) after exposure from in utero, peri- and postnatal periods up to adulthood is a key parameter foreseen to be investigated in OECD TG 443.

The OECD TG 422 study (1) provides screening level information on toxicity to the offspring up to PND 4 but not to adulthood. Based on the information provided, the study (2) presented as a "one-generation" study was designed to investigate the mating behaviour of animals and does not provide any information on toxicity to the offspring. The OECD TG 408 study (3) provides information on exposure of adult animals but only informs on organ toxicity and does not provide information on functional fertility or on toxicity to offspring up to adulthood as foreseen to be investigated in OECD TG 443. Similarly, the predictions obtained from the VEGA QSAR models and QSAR toolbox (4) on estrogen receptor binding and developmental/reproductive toxicity do not provide information on toxicity to the offspring after exposure from in utero, peri- and postnatal periods up to adulthood. Your waiving argument (5) which refers to the information addressed above and argues that a conclusion can be reached on the basis of the available data does not provide any additional justification addressing the absence of this key parameter.

In conclusion, none of the sources of information alone or combined allows to conclude whether the Substance has or has not hazardous properties related to 'sexual function and fertility' or 'developmental toxicity' to offspring. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

#### The specifications for the study design

##### *Premating exposure duration and dose-level setting*

In the draft decision notified to you, the length of the pre-mating exposure period was ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

In your comment to the draft decision you indicated that, contrary to ECHA's initial conclusions requiring a 10-week pre-mating exposure period, available substance-specific information in the dossier supports a shorter pre-mating exposure duration than 10 weeks. ECHA has reviewed your comments and agrees with your conclusions.

A pre-mating period of at least 2 weeks for P0 animals is sufficient for your Substance since information obtained from the sub-chronic toxicity study (3) and from the one-generation reproductive toxicity study (2) adequately cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects of the Substance on fertility.

Therefore, the requested pre-mating 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 must be included.

Species and route selection

The study must be performed in rats with oral<sup>2</sup> administration.

*Further expansion of the study design*

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or 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 X. 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<sup>3</sup>.

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<sup>2</sup> ECHA Guidance R.7a, Section R.7.6.2.3.2.

<sup>3</sup> 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 03 April 2019.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

ECHA took into account your comments and amended the request.

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'<sup>4</sup>.

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. 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"<sup>5</sup>.

<sup>4</sup> <https://echa.europa.eu/practical-guides>

<sup>5</sup> <https://echa.europa.eu/manuals>

5. List of references of the ECHA Guidance and other guidance/ reference documents<sup>6</sup>

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)<sup>7</sup>

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<sup>8</sup>

Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.

Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

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<sup>6</sup> <https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>

<sup>7</sup> <https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across>

<sup>8</sup> <http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm>

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

<b>Registrant Name</b>	<b>Registration number</b>	<b>(Highest) Data requirements to be fulfilled</b>
[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.