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Helsinki, 08 December 2021

Addressees
Registrant(s) of 3710-84-7_JS as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
31/07/2019

Registered substance subject to this decision ("the Substance")
Substance name: N,N-diethylhydroxylamine
EC number: 223-055-4
CAS number: 3710-84-7

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***17 March 2025***.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex IX of REACH

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

You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

- Reasons for the request(s) are explained in the appendix entitled "Reasons to request information required under Annex IX of REACH".

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, 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 to request information required under Annex IX of REACH

1. Extended one-generation reproductive toxicity study

The basic test design of an extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is an information requirement under Annex IX Section 8.7.3. 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 a waiver in the dossier stating that *"the extended one-generation reproductive toxicity study does not need to be conducted because there are no results from available repeated dose toxicity studies that indicate adverse effects on reproductive organs or tissues, or reveal other concerns in relation with reproductive toxicity".*

We have assessed this information and identified the following issues:

As already mentioned above, an EOGRT study is required if the available repeated dose toxicity studies indicate adverse effects or concerns related to reproductive toxicity.

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.

However, adverse effects on reproductive organs or tissues or other concerns in relation with reproductive toxicity are observed in the repeated dose toxicity study (OECD TG 408) performed with the Substance, which is available in your dossier. More specifically, the epididymal sperm counts and daily sperm production rates were 18 and 22% lower in mid- and high-dose groups, respectively, than in the control group (with dose response). Moreover, the epididymal sperm counts were not reversible during the non-dosing period.

In your comments on the draft decision you state that "*the Registrants do not consider the variations in sperm parameters as treatment related which is in line with the conclusions of the study report*". You also quote the study report which states that *"Given the dose-relationship of these findings, a test item effect was considered to be likely, however, the magnitude of the changes being low and in absence of test item-related histopathological findings in the right testis and epididymis at the high-dose, the changes were considered non-adverse."*

You also mention that *"At the end of the 6-week treatment-free period, all sperm analysis data in males previously given 500 mg/kg/day were similar to controls, generally within Historical Control Data and considered as reversible, except for epididymal sperm count which was still slightly but not statistically lower than controls (375.9 vs. 456.8 10^6/g cauda: -18%) and within Historical Control Data."*

In your comments you seek to highlight that the variations in sperm analysis are not considered treatment related. This is conflicting with your comment on the above paragraph. To support that argument, you have indicated that:

1. The variations observed for the daily sperm production rate, mean number of testicular sperm head and mean number of epididymal sperm count at all dose levels including the high dose are within historical control data (HCD). For the latter, the variations remained slight and within historical control data in recovery animals.
2. The percentage of motile epididymal sperm and of normal sperm morphology are within historical control data at all dose-levels.

3. The testes and epididymides weights as well as the histopathology examination were normal in all groups.
4. The variations in the percentage of abnormal flagellum sperm are clearly not dose-related and within historical control data at all dose-levels. The percentage of sperm with no flagellum is outside of HCD at high dose, however this is due to one male animal.

The sperm parameters you have indicated above (1.) were within the HCD, however close to the lower end values for the high dose (HD) group. More detailed, daily sperm production rate in the HD group was statistically significantly decreased by 22% having a value of 16.6 (10^6/g testis/day), with HCD 16.5-25.9 (10^6/g testis/day). Mean number of testicular sperm head was statistically significantly decreased by 22% having a value of 101 (10^6/g testis), with HCD 100.7-157.8 (10^6/g testis).

ECHA considers that the dose-dependent reduction in sperm numbers and sperm production rates are likely to be treatment-related effects. Reduction on sperm parameters by 22% cannot be regarded as low magnitude or confirmed as non-adverse, since no data from reproductive toxicity studies were provided in your dossier and therefore you have not provided any information on functional fertility, i.e. mating and reproductive performance. According to ECHA Guidance R.7a *"Adverse effects on sexual function and fertility include any effect of a substance that has the potential to interfere with sexual function and fertility. This includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport…".* No changes in sperm motility or morphology, and no changes in testes and epididymides weights and histopathology examination do not diminish the concern on spermatogenesis and other sperm parameters (reduced mean sperm numbers, mean number of testicular sperm head and daily sperm production rate), which could lead to adverse effects on functional fertility.

The fact that the epididymal sperm counts were not completely reversible at the end of the 6-week dosing-free period, enhances the concern.

In addition, your claim that the percentage of abnormal flagellum sperm is clearly not dose-related and within HCD (point 4) is not accurate because it is reported that in the low and mid dose groups there was a significant increase of 11-fold (2.2%) and 22.5-fold (4.5%), respectively, compared to control (0.2%). Both values were outside of the HCD [0-2%]. However, as the high dose group value (0.1%) is lower than the control value, ECHA considered that overall there is no concern on sperm morphology.

ECHA agrees that the increase of percentage of sperm with no flagellum at high dose is caused by outliers.

As explained above, the findings on sperm parameters analysis, namely the dose-dependent and statistically significant decrease in number of epididymal sperm, the number of testicular sperm heads and the daily sperm production rate, indicate a concern related to reproductive toxicity that needs to be further investigated.

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.

The specifications for the study design

Premating exposure duration and dose-level setting

The length of premating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

However, 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.

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.

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 professionals because the Substance is used by professionals as colour stabilizer (film/photographic industry) and coating (PROCs 1, 2, 3, 4, 8a, 8b, 9, 10, 11, 13, 15).

In your comments on the proposed amendment, you consider that '*non-significant exposure may be possible*'. In particular, you consider that RCRs of up to [redacted] may be considered as establishing not significant exposure and you refer to R.5 Guidance.

In response to your comments, ECHA notes that the relevant guidance regarding 'Guidance for uses leading to significant exposure' in the context of requesting extension of Cohort 1B is not R.5, but R.7a, version 6.0, page 525. R.5 Guidance provides general guidance on exposure based adaptations whereas R.7a provides very specific guidance on the identification of uses leading to significant exposure with respect to triggering the extension of Cohort 1B. According to the first bullet point on page 525 explaining uses leading to justifying the extension of Cohort 1B;

- " If the substance is intended to be used in the EU by consumers (i.e. members of the public) or professionals, either neat or in a chemical mixture and there is one very

wide use or several limited uses potentially affecting many consumers and/or professionals, then this is considered as meeting the criterion;"

ECHA notes that you have listed in your registration dossier two uses of the substance in IUCLID in section 3.5.4 Widespread uses by professional workers: Colour stabilizer (film/photographic industry), and Use in coating by professional worker.

As you have listed the above uses in IUCLID as widespread uses by professionals, the significant exposure trigger is met for extension of Cohort 1B. Moreover, ECHA notes that both uses list sector use SU 22: Professional uses: Public domain (administration, education, entertainment, services, craftsmen). This further demonstrates that the uses are 'very wide use'.

Contrary to your comments on the proposal for amendment ECHA considers therefore that the uses reported in your registration dossier lead to significant exposure justifying the extension of Cohort 1B.

Furthermore, you have not demonstrated that exposure resulting in an RCR of [redacted] can be considered to be not significant, as it is not well below 1.

In addition, there are indications of one or more modes of action related to endocrine disruption because in the provided OECD TG 408 study performed with the Substance, dose-dependent and statistically significant decrease in number of epididymal sperm, the number of testicular sperm heads and the daily sperm production rate were observed.

In your comments on the proposed amendment, you acknowledge that based on the raw data of the OECD TG 408 study, the dose-dependent and statistically significant decrease in number of epididymal sperm is obvious, with effects also observed in the recovery animals. Furthermore, you acknowledge that the decrease in the number of testicular sperm heads and daily sperm production rate is evident, however still within the historical control data and reversible in the recovery animals. You refer to your initial comments on the draft decision and re-iterate that the effects are minor, reversible, and non-adverse as no changes were reported in the testis or epididymis weight or histopathology.

ECHA notes that, as further explained above, the dose-dependent and statistically significant decrease in number of epididymal sperm, the number of testicular sperm heads and the daily sperm production rate are a concern for spermatogenesis. Furthermore, changes in sperm parameters are an indication of one or more relevant modes of action related to endocrine disruption (estrogen/androgen-mediated or steroidogenesis-related; OECD GD 150, Table C.3.4).

In addition, you question the human relevance of the effects on sperm parameters. ECHA notes that in the absence of further knowledge and proof, it is assumed that biologically relevant findings in animals are also relevant to humans.

Finally, you consider that since no changes were noted in thyroid (organ weight, histopathology, hormone levels), and only minor effects were observed in adrenals, there is no evidence of an endocrine mode of action. ECHA notes that lack of effects in thyroid and/or adrenals do not exclude sex steroid hormone related mode of action.

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. It is recommended to aim at 20 litters per dose group.

Species and route selection

Based on ECHA Guidance R.7a, Section R.7.6.2.3.2., the study must be performed in rats with oral administration.

Further expansion of the study design

No triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and/or Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including 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 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 R.7a, Section R.7.6.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

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

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

3. 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 on How to report robust study summaries[2].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - 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.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[3].

[2] https://echa.europa.eu/practical-guides
[3] https://echa.europa.eu/manuals

Appendix C: Procedure

The Substance is listed in the Community rolling action plan (CoRAP) and the substance evaluation started in 2019.

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 06 March 2020.

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

ECHA took into account your comments and did not amend the request.

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

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s) and referred the modified draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

Deadline

In your comments on the proposed amendment, you requested an extension of the deadline to provide information from 24 to 36 months from the date of adoption of the decision. Upon request, you provided documentary evidence from a test laboratory.

On this basis, ECHA has granted the request and extended the deadline to 36 months.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-76 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix D: List of references - ECHA Guidance[4] and other supporting documents

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 where relevant.

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 where relevant.

Read-across assessment framework (RAAF, March 2017)[5]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[5]

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.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[6]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

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

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

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Appendix E: Addressees of this decision and their corresponding information requirements

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.