~~Confidential~~

Helsinki, 07 December 2021

Addressees
Registrant(s) of JS_39072-70-3 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
25/04/2013

Registered substance subject to this decision ("the Substance")
Substance name: N,N''-hexane-1,6-diylbis[N'-benzylurea]
EC number: 254-274-3
CAS number: 39072-70-3

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 ***12 September 2023***.

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

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

1. Long-term toxicity testing on aquatic invertebrates also requested below (triggered by Annex VII, Section 9.1.1., column 2)

B. Information required from all the Registrants subject to Annex VIII of REACH

1. Long-term toxicity testing on fish also requested below (triggered by Annex VIII, Section 9.1.3., column 2)

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

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit)

3. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211)

4. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)

Reasons for the request(s) are explained in the following appendices:

- Appendices entitled "Reasons to request information required under Annexes VII to IX of REACH", respectively.

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 and VIII to REACH, for registration at 10-100 tpa
- 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". 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 VII of REACH

1. Long-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.). Long-term toxicity testing on aquatic invertebrates must be considered (Section 9.1.1., Column 2) if the substance is poorly water soluble.

You have provided an OECD TG 202 study but no information on long-term toxicity on aquatic invertebrates for the Substance.

We have assessed this information and identified the following issue:

Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests do not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (ECHA Guidance R.7.8.5).

In the provided OECD TG 105 study, the saturation concentration of the Substance in water was determined to be 0.057 mg/L at 19.9 °C, pH 7.8.

Therefore, the Substance is poorly water soluble and information on long-term toxicity on aquatic invertebrates must be provided.

The examination of the information provided, as well as the selection of the requested test and the test design are addressed under Appendix C.3.

Appendix B: Reasons to request information required under Annex VIII of REACH

1. Long-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.). Long-term toxicity testing on fish must be considered (Section 9.1.3., Column 2) if the substance is poorly water soluble.

You have provided an OECD TG 203 study but no information on long-term toxicity on aquatic invertebrates for the Substance.

We have assessed this information and identified the following issue:

Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests do not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (ECHA Guidance R.7.8.5).

As already explained under Section A.1, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

The examination of the information provided, as well as the selection of the requested test and the test design are addressed under section C.4.

Appendix C: Reasons to request information required under Annex IX of REACH

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

A Sub-chronic toxicity study (90 day) is a standard information requirement under Annex IX to REACH.

You have provided a key study

- a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, OECD TG 422, made in 2013, reliability 1, according to GLP.

You have also provided the following adaptation: *"As shown in a Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test (OECD 422) in which female rats were even treated for 42-53 days, no substance-induced effects have been observed up to the limit dose. These data suggest that prolongation of treatment up to 90 days is unlikely to induce any adverse effects. Considering animal welfare, it is hence not justifiable to perform another study, which is unlikely to add any further information to the evaluation of the risk of the test substance to human health."*

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

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 408. The following key parameter(s) of this test guideline include, among others:

1. dosing of the Substance daily for a period of 90 days until the scheduled termination of the study;
2. organ weight and histopathological investigations conducted using 10 per sex per group.

The Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) that you provided has:

- the exposure duration of 42-53 days (for females) and 28 days (for males).
- organ weight and histopathological investigations only conducted.

Therefore, this information is rejected.

Concerning the adaptation you proposed, you have provided no legal basis for that adaptation and it is not clear whether it corresponds to any of the adaptations set out in Annex IX, Section 8.6.2 or in Annex XI, Sections 1-3.

Animal welfare does not constitute as such a valid justification to omit the standard information requirements of Annexes VII – X or a valid adaptation to these information requirements.

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

Information on the design of the study to be performed

Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because the Substance is reported to occur in granular form without a significant proportion of particles of inhalable size.

Therefore the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance.

In your comments on the initial draft decision, you agreed to perform the study.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in one species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.

You have provided:

- a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, OECD TG 422, made in 2013, reliability 1, according to GLP.

You have also provided the following adaptation:
"*As shown in a Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test (OECD 422), no substance-induced effects have been observed for the reproduction organs in male and female rats treated up to the limit dose of 1000 mg/kg/d. Fertility and reproductive performance were also unaffected by treatment. Furthermore, pups of animals treated with the test item did neither exhibit any malformations nor showed alterations in body weight, sex ratio or organ development (macroscopically). Considering these data, it is unlikely that adverse effects will be detected in a further study. Due to animal welfare, it is therefore not justified to perform any further studies, which do most likely not add any further information to the evaluation of the toxicity of the test item*."

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

In order to be considered compliant and enable assessing if the Substance is a developmental toxicant, information provided has to meet the requirements of OECD TG 414 in one species, e.g., external, skeletal and visceral malformations and variations has to be investigated as described in OECD TG 414.

You have not provided information following OECD TG 414. Instead, you have provided a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422). This study does not inform on skeletal and visceral malformations and variations as required by OECD TG 414.

Therefore, this study does not fulfil the information requirement.

Concerning the adaptation you proposed, you have provided no legal basis for that adaptation and it is not clear whether it corresponds to any of the adaptations set out in Annex IX, Section 8.6.2 or in Annex XI, Sections 1-3. Animal welfare does not constitute as such a valid justification to omit the standard information requirements of Annexes VII – X or a valid adaptation to these information requirements.

In your comments on the initial draft decision you propose an adaptation based on Column 2 of Annex IX, Section 8.7.2. You explain/argue that

- low toxicity was observed in the Reproduction Developmental Toxicity Screening study,
- your intention is to take blood samples in the sub-chronic study and provide further information on low bioavailability,
- in the professional uses, the workers are well protected.

According to Annex IX, Section 8.7.2. "*The studies do not need to be conducted if: the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests*

available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure." Please note that these criteria are considered cumulative, i.e., all of them need to be met.

We note that at present experimental support to your adaptation is inadequate. More notably, the information provided does not demonstrate that no systemic absorption occurs. Furthermore, considering the PROCs that you have specified in your Chemical Safety Report, e.g. PROC 5 (multistage and/or significant contact), 10 (roller application or brushing), 11 (non-industrial spraying) and 13 (treatment of articles by dipping and pouring), worker exposure is considered likely and the third criterion set for this adaptation is not met.

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

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[2] administration of the Substance.

3. Long-term toxicity testing on aquatic invertebrates

Long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

You have provided a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification:

"*In Annex IX of Regulation (EC) No 1907/2006, it is laid down that long-term toxicity to aquatic invertebrates shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on aquatic invertebrates. According to Annex I of this regulation, the chemical safety assessment triggers further action when the substance or the preparation meets the criteria for classification as dangerous according to Directive 67/548/EEC or Directive 1999/45/EC or is assessed to be a PBT or vPvB. The hazard assessment of the submission item reveals neither a need to classify the substance as dangerous to the environment, nor is it a PBT or vPvB substance, nor are there any further indications that the substance may be hazardous to the environment. Therefore, a long-term toxicity study in aquatic invertebrates is not provided*".

We have assessed this information and identified the following issue:

Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to aquatic invertebrates under Column 1. It must be understood as a trigger for providing further information on aquatic invertebrates if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

Therefore, your adaptation is rejected and the information requirement is not fulfilled.

Study design

The Substance is difficult to test due to the low water solubility (0.057 mg/L at 19.9 °C, pH 7.8). OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the

[2] ECHA Guidance R.7a, Section R.7.6.2.3.2.

properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 211. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

In your comments to the initial draft decision you agree to perform the study with the Substance, according to OECD TG 211 and to the recommendations of OECD GD 23.

4. Long-term toxicity testing on fish

Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

You have provided a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification:

"*In Annex IX of Regulation (EC) No 1907/2006, it is laid down that long-term toxicity to fish shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on fish. According to Annex I of this regulation, the chemical safety assessment triggers further action when the substance or the preparation meets the criteria for classification as dangerous according to Directive 67/548/EEC or Directive 1999/45/EC or is assessed to be a PBT or vPvB. The hazard assessment of the submission item reveals neither a need to classify the substance as dangerous to the environment, nor is it a PBT or vPvB substance, nor are there any further indications that the substance may be hazardous to the environment. Therefore, and for reasons of animal welfare, a long-term toxicity study in fish is not provided*".

We have assessed this information and identified the following issues:

a) Your interpretation of the legal basis used in your justification is incorrect

Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to fish under Column 1. It must be understood as a trigger for providing further information on fish if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

Therefore, your adaptation is rejected and the information requirement is not fulfilled.

b) Animal welfare is not a legal basis to omit the required information

Animal welfare does not constitute as such a valid justification to omit the standard information requirements of Annexes VII – X or a valid adaptation to these information requirements.

Although you acknowledge in your comments to the draft decision that animal welfare as such does not constitute a valid justification to omit the information requirement, you refer to Article 25(1) of REACH to insist that animal testing should be used as a last resort.

Article 25(1) of REACH states that animal testing must be used as a last resort. In particular, valid tests already available must not be duplicated and the possibilities for valid adaptations of experimental testing must be considered. However, as explained above, that article does not preclude your obligation to fulfil the standard information requirement, either by performing experimental testing or by providing a valid adaptation.

c) Substance-tailored exposure-driven testing

In your comments to the initial draft decision you propose to perform the study conditional on the results of the long-term toxicity study on aquatic invertebrates (requested by this decision, see A.1 and C.3). You claim that environmental exposure to the Substance is not significant and you expect that the long-term toxicity test on aquatic invertebrates will suffice to demonstrate the safe use of the Substance throughout its entire life cycle. You suggest that long-term testing on fish could probably be adapted in accordance with REACH, Annex XI, Section 3: ('Substance-tailored exposure-driven testing') once the results of the long-term toxicity testing on aquatic invertebrates are available.

Under Annex XI, Section 3, long-term toxicity testing on fish may be omitted based on a rigorous exposure assessment in accordance with Annex I, Section 5. In order for Annex XI, Section 3 to be applicable, exposure from the Substance must be absent or negligible: the Substance must be handled under strictly controlled conditions (Annex XI, Section 3.2(b)), or be permanently embedded in a matrix or otherwise rigorously contained by technical means (Annex XI, Section 3.2(c)). Alternatively, all the following conditions must be met (Annex XI, Section 3.2(a):

i. the absence or no significant exposure in all scenarios of the manufacture and all identified uses referred to in Annex VI, Section 3.5., and
ii. a PNEC can be derived from available data, which:
    - must be relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes and therefore must be based on reliable information on the hazardous properties of the substance on at least three trophic levels;
    - must take into account the increased uncertainty resulting from the omission of the information requirement, in this case by selecting an appropriate assessment factor (AF) as described in ECHA Guidance R.10.3.
iii. the ratio between the results of the exposure assessment (PECs) and the PNEC are always well below 1

However, the chemical safety report in your registration dossier does not provide an exposure assessment and a risk characterisation for the Substance. In the absence of this information, no rigorous exposure assessment in accordance with Annex I, Section 5 is possible and an adaptation based on Annex XI, Section 3 cannot apply. Then, you have not demonstrated the absence or no significant exposure in all scenarios of the manufacture and all identified uses referred to in Annex VI. Therefore, condition i of Annex XI, Section 3.2(a); criteria for Annex XI, Section 3.2(b); or Annex XI, Section 3.2(c) cannot be met.

Furthermore, as explained above under A.1, B.1, C.3, and C.4, your dossier does not include reliable information on the hazardous properties of the Substance on at least three trophic levels. ECHA particularly points out that if information on long-term or chronic toxicity on three trophic levels is not available for the Substance then an appropriate PNEC cannot be derived and condition ii of Annex XI, Section 3.2(a) cannot be met.

We finally remind that for any adaptation adequate justification and documentation need to be provided.

Study design

To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (ECHA Guidance R.7.8.2.).

OECD TG 210 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix C.3.

Appendix D: 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[3].

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[4].

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

Appendix E: Procedure

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 1 December 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(s).

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 F: List of references - ECHA Guidance[5] 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)[6]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[7]

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[8]

[5] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[6] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[7] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[8] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

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

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.

Appendix G: 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]
[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.