EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114290543-47-01/F Helsinki, 5 February 2015

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For N,N''-(isobutylidene)diurea, EC No 228-055-8 (CAS No 6104-30-9), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration for N,N''-(isobutylidene)diurea, EC No 228-055-8 (CAS No 6104-30-9), submitted by [redacted] (Registrant).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates submitted after 24 July 2014, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

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

The compliance check was initiated on 5 June 2013.

On 6 November 2013, ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 6 December 2013, ECHA received comments from the Registrant. The ECHA Secretariat considered the Registrant's comments and did not amend the draft decision. This consideration is reflected in the statement of reasons (section III), whereas no amendments to the information required (section II) were made.

On 24 July 2014, ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification. Subsequently, proposals for amendment to the draft decision were submitted.

On 29 August 2014, ECHA notified the Registrant of the proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposals for amendment received and modified Section III of the draft decision.

The present decision relates solely to a compliance check requesting information for

- spectral data (nuclear magnetic resonance or mass spectrum) (Annex VI, 2.3.5.),
- high-pressure liquid chromatogram, gas chromatogram (Annex VI, 2.3.6.),
- *in vitro* gene mutation study in bacteria, (Annex VII, 8.4.1.),
- sub-chronic toxicity study (90-day), oral route (Annex IX, 8.6.2.) and
- pre-natal developmental toxicity study (Annex X, 8.7.2.).

The information requirement relating to the standard information requirement of a two-generation reproductive toxicity study (Annex X, 8.7.3.) is addressed in a separate decision although all endpoints were initially addressed together in the same draft decision.

On 8 September 2014 ECHA referred the draft decision to the Member State Committee.

By 29 September 2014, in accordance to Article 51(5), the Registrant provided comments on the proposals for amendment. In addition, the Registrant provided comments on the draft decision. The Member State Committee took the comments on the proposals for amendment of the Registrant into account. The Member State Committee did not take into account the Registrant's comments on the draft decision as they were not related to the proposals for amendment made and are therefore considered outside the scope of Article 51(5).

A unanimous agreement of the Member State Committee on the draft decision relating to to the spectral data, high pressure liquid chromatogram, gas chromatogram, in vitro gene mutation study in bacteria, sub-chronic toxicity study and pre-natal developmental toxicity study was reached on 13 October 2014 in a written procedure launched on 2 October 2014.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

A. Information in the technical dossier related to the identity of the substance

Pursuant to Articles 41(1)(a), 41(3), 10(a)(ii) and Annex VI, Section 2 of the REACH Regulation the Registrant shall submit the following information for the registered substance subject to the present decision:

1. Spectral data (nuclear magnetic resonance or mass spectrum) (Annex VI, 2.3.5.);
2. High-pressure liquid chromatogram, gas chromatogram (Annex VI, 2.3.6.).

B. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 41(1), 41(3), 10(a)(vii), 12(1)(a) and 13 and Annexes VII, IX and X of the REACH Regulation, the Registrant shall submit the following information using the indicated test methods and the registered substance subject to the present decision:

1. *In vitro* gene mutation study in bacteria, (Annex VII, 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14./OECD 471) using one of the following strains: *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102, as specified in section III.B.3 below;

2. Sub-chronic toxicity study (90-day), oral route (Annex IX, 8.6.2; test method: EU B.26/OECD 408) in rats;
3. Pre-natal developmental toxicity study (Annex X, 8.7.2.; test method: EU B.31/OECD 414) in rabbits, oral route.

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated registration to ECHA by **13 February 2017.** The timeline has been set to allow for sequential testing as appropriate.

Note for consideration by the Registrant:

The Registrant may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

III. Statement of reasons

Pursuant to Article 41(3) of the REACH Regulation, ECHA may require the Registrant to submit any information needed to bring the registration into compliance with the relevant information requirements.

A. Information in the technical dossier related to the identity of the substance

Pursuant to Article 10(a)(ii) of the REACH Regulation, the technical dossier shall contain information on the identity of the substance as specified in Annex VI, Section 2 of the REACH Regulation. In accordance with Annex VI, Section 2 the information provided shall be sufficient to enable the identification of the registered substance.

1. Spectral data (nuclear magnetic resonance (NMR) or mass spectrum (MS)) (Annex VI, 2.3.5.)

"Spectral data" is an information requirement as laid down in Annex VI, Section 2.3.5. of the REACH Regulation. Adequate information needs to be present in the technical dossier for the registered substance to meet this information requirement. It requires the submission of an ultra-violet (UV) spectrum and an infra-red (IR) spectrum, as well as of a nuclear magnetic resononce spectrum or a mass spectrum.

ECHA observes that the registration contains only IR spectral data. It does not contain any UV as well as NMR or MS spectral data which is required according to Annex VI, Section 2.3.5. of the REACH Regulation to support the identity of the registered substance. The Registrant presents the following justification for not providing further spectral information: *"N,N''-isobutylidene)diurea is of very limited solubility and volatility, therefore chromatographic methods, NMR and mass spectrometry could not be applied. It is not expected to gain any knowledge from UV-spectral information as no chromophore is present".*

ECHA accepts the justification for not providing the UV spectral information. However, the identity of the substance cannot be confirmed based exclusively on the infra-red data. Infra-red spectroscopy can identify the existence of certain functional groups, but the precise location and connectivity of these groups can only be ascertained by additional NMR or MS data. Further, the justification for not providing the NMR or MS spectral data cannot be followed by ECHA because based on the information on the water solubility provided in section 4.8 of the IUCLID dossier the substance is soluble in water. Hence it should be possible to provide a NMR or MS of the registered substance.

Therefore, pursuant to Article 41(1)(a) and (3) of the REACH Regulation, the Registrant is requested to submit the information derived from the registered substance subject to the present decision: NMR or mass spectrum including the description of the method used as specifically explained in the present decision. The Registrant shall ensure that the information is consistent throughout the dossier.

As for the reporting of the data in the registration dossier, the information shall be attached in IUCLID section 1.4.

2. High-pressure liquid chromatogram, gas chromatogram (Annex VI, 2.3.6.)

"High-pressure liquid chromatogram, gas chromatogram" is an information requirement as laid down in Annex VI, Section 2.3.6. of the REACH Regulation. Adequate information needs to be present in the technical dossier for the registered substance to meet this information requirement.

ECHA observes that the registration does not contain any chromatographic data which is required according to Annex VI Section 2.3.5. of the REACH Regulation to support the identity of the registered substance.

The Registrant presents the following justifications as the reason for not providing such information *"N,N''-isobutylidene)diurea is of very limited solubility and volatility , therefore chromatographic methods, NMR and mass spectrometry could not be applied".*

This information cannot be followed by ECHA as based on the information on the water solubility provided in section 4.8 of the IUCLID dossier the substance is soluble in water. Therefore it should be possible to provide chromatograhic analyses of the registered substance.

In the Registrant's comments on the draft decision, he *"agrees to perform the High-pressure liquid chromatogram as requested"* but *"doesn't agree to perform the gas chromatogram. N,N''-(isobutylidene)diurea (IBDU) is a solid substance which decomposes by temperatures over 170 °C."* ECHA confirms that, for this substance, providing only one of the two chromatograms mentioned in Section II.A.2 suffices.

Therefore, pursuant to Article 41(1)(a) and (3) of the REACH Regulation, the Registrant is requested to submit the information derived from the registered substance subject to the present decision: correct chromatographic data including a chromatogram and the description of the method(s) used, as specifically explained in the present decision. The Registrant shall ensure that the information is consistent throughout the dossier.

As for the reporting of the data in the registration dossier, the information shall be attached in IUCLID section 1.4.

B. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 10(a)(vii) and 12(1)(e) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities of 1000 tonnes or more per year shall contain as a minimum the information specified in Annexes VII, IX and X of the REACH Regulation.

1. *In vitro* gene mutation study in bacteria (Annex VII, 8.4.1.)

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The Registrant has provided the results of such a study from the year 1988, conducted according to OECD 471 with an assigned reliability score of 2. The study used four different strains of *S. typhimurium,* namely TA 1535, TA 1537, TA 98 and TA 100. The Registrant also reported on two further studies conducted according to OECD 474 (mammalian erythrocyte micronucleus test) and OECD 476 (*in vitro* mammalian cell gene mutation test).

According to paragraph 13 of the current OECD 471 test guideline (updated 1997), at least five strains of bacteria should be used. These should include four strains of *S. typhimurium* (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four *S. typhimurium* strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by *E. coli* WP2 strains or *S. typhimurium* TA102 which have an AT base pair at the primary reversion site. The studies conducted under OECD 474 and OECD 476 are not able to detect such mutagenic activity either.

Therefore, ECHA concludes that a test using *E. coli* WP2 uvrA, *E. coli* WP2 uvrA (pKM101) or *S. typhimurium* TA102 has not been submitted by the Registrant and that the test using one of these is required to conclude on *in vitro* gene mutation in bacteria.

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

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2 of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier, the Registrant has provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD 422) and another study record for a one-generation study on reproduction and fertility effects. However, the former study does not provide the information required by Annex IX, Section 8.6.2 because the exposure duration is less than 90 days. In turn, the following reasons prevent the latter study from fulfilling the said information requirement:

a. In the required information, the females should be non-pregnant during the study. This is not the case in the reported study.
b. In the required information, blood samples are to be taken and the several hematological and clinical biochemistry examinations are to be made at the end of the test period. The reported study does not mention any hematological examinations.
c. In the reported study, not all relevant organs/tissues have been investigated in gross necropsy. These investigations are expected in the required information.
d. A full histopathology is to be carried out on the preserved organs and tissues in the required information. However, according to the Registrant's report, histopathology was not examined in the one-generation study.

Furthermore, the Registrant has not provided any study record of a sub-chronic toxicity study (90-day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2. Instead, the Registrant has sought to adapt this information requirement. The justification of the adaptation given by the Registrant is that the study is scientifically unjustified: *"A one generation study with more than 12 weeks of exposure is available indicating that reduced food intake and reduced weight gain in pregnant females at high dose level were the only signs of toxicity. Furthermore no specific target organ and no other form of specific toxicity has been observed at dose levels up to 1000 mg/kg bw (Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test) or 1200 mg/kg bw (one generation study). Therefore the conduct of a 90 days study is scientifically unjustified as no further information gain is expected."* However, ECHA notes that this adaptation neither meets the general rules for adaptation in Annex XI, section 1 nor any of the specific adaptation possibilities in Annex IX, section 8.6.2. Therefore, the adaptation of the information requirement suggested by the Registrant cannot be accepted.

As explained above, the information available on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

In light of the physicochemical properties of the substance being a dust of non-inhalable size and the lack of information provided on the uses and human exposure, ECHA considers that testing by the oral route is most appropriate.

According to the test method EU B.26/OECD 408, the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD 408) in rats.

3. Pre-natal developmental toxicity study (Annex X, 8.7.2.)

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2, column 1; Annex X, Section 8.7.2, column 1; and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

ECHA observes that the technical dossier contains data (key study) on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material. This study fulfils the standard information requirement for a pre-natal developmental toxicity study in a first species (Annex IX, 8.7.2). The Registrant has not self-classified the substance for developmental toxicity. The substance does not have a harmonised classification for reproductive toxicity.

ECHA further observes that the Registrant has not provided any study record of a pre-natal developmental toxicity study in a second species in the dossier that would meet the information requirement of Annex X, Section 8.7.2. Instead, the Registrant has sought to adapt this information requirement. The justification of the adaptation given by the Registrant is that it is scientifically unjustified: *"The available teratogenicity study with female rats does not give any indication of maternal toxicity, fetotoxicity or teratogenicity at the limit dose of 1000 mg/kg bw. In addition a one generation study with more than 12 weeks of exposure is available indicating that reduced food intake and reduced weight gain in pregnant females at high dose level were the only signs of toxicity. Furthermore no specific target organ and no other form of specific toxicity has been observed at dose levels up to 1000 mg/kg bw (Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test) or 1200 mg/kg bw (one generation study). Therefore the conduct of a teratogenicity study in a 2nd species is scientifically unjustified as no further information gain is expected."*

This adaptation does not meet the specific rules for adaptation according Annex X, 8.7., column 2 or the general rules for adaptations according to Annex XI. ECHA notes that in the ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a: Endpoint Specific Guidance, R7.6.6.3 it is stated: *"At ≥1000 t/y, a study in a second species will normally be required when the first study is negative, unless weight of evidence assessment or specific data e.g. toxicokinetic data provide scientific justification not to conduct the study in a second species. This could be the case if available data demonstrate that for example the rat is the most relevant species for extrapolating to humans or if the rabbit is not a suitable model for testing for developmental toxicity."*

Therefore, the adaptation of the information requirement suggested by the Registrant cannot be accepted.

Accordingly, the information available on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The test in the first species was carried out by testing a rodent species and ECHA therefore considers that the test in a second species should be carried out in a non-rodent species. According to the test method EU B.31/OECD 414, the rabbit is the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rabbit as a second species to be used.

ECHA notes that it is the responsibility of the Registrant to decide whether to perform a limit test as per the relevant guideline.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31/OECD 414) in rabbits by the oral route.

C. Deadline for submitting the required information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 36 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a two-generation reproductive toxicity study (Annex X, 8.7.3.). As this endpoint is not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 24 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

IV. Adequate identification of the composition of the tested material

In carrying out the studies required by the present decision it is important to ensure that the particular sample of substance tested is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured. If the registration of the substance covers different grades, the sample used for the new studies must be suitable to assess these.

Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the studies to be assessed.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on ECHA's internet page at **http://echa.europa.eu/appeals/app_procedure_en.asp.** The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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Leena Ylä-Mononen
Director of Evaluation