EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114310220-76-01/F Helsinki, 9 October 2015

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

For dodecane-12-lactam, CAS No 947-04-6 (EC No 213-424-8), 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 dodecane-12-lactam, CAS No 947-04-6 (EC No 213-424-8), 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 3 September 2015, 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 21 November 2013.

On 8 January 2014 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 5 February 2014 ECHA received comments from the Registrant on the draft decision. Concerning the information requirement of Annex X, Section 8.7.3. the compliance check requirement to submit information of a two-generation reproductive toxicity study (EU B.35, OECD TG 416) or an extended one-generation reproductive toxicity study (EU B.56, OECD TG 443) has been removed from this draft decision due to the legislative amendments to the REACH Regulation regarding Annex X, Section 8.7.3. In light of this, ECHA Secretariat did not consider further the Registrant's comments concerning the information requirement of Annex X, Section 8.7.3. On the basis of this change of scope, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 3 September 2015 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.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

The present draft decision relates solely to a compliance check requesting information in the form of a *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.) and a pre-natal developmental toxicity study (Annex X, Section 8.7.2.). The other information requirement for toxicity to reproduction (Annex X, Section 8.7.3.) is addressed in a separate decision although all endpoints were initially addressed together in the same draft decision.

II. Information required

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

Pursuant to Articles 41(1), 41(3), 10(a)(vi) and/or (vii), 12(1)(e), 13 and Annexes VII 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, Section 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.1 below; and

2. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD 414) in rabbits, oral route;

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 requests in this decision, or to fulfil otherwise the information requirements with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

B. Deadline for submitting the required information

Pursuant to Articles 41(4) and 22(2) of the REACH Regulation the Registrant shall submit to ECHA by **17 October 2016** an update of the registration dossier containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report.

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 derived from the application of Annexes VII to XI

Pursuant to Articles 10(a)(vi) and/or (vii), 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 to X of the REACH Regulation.

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

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 Registrant has provided a test from the year 1991 according OECD 471 and GLP with an assigned reliability score of 1. The test used four different strains of *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 shown to be reliable and reproducible according to the OECD 471 guideline and an additional *S. typhimurium* strain TA 1538. The strain TA 1538 is not identified in the OECD 471 guideline as a strain of bacteria to be used and thus cannot be accepted to fulfil the requirement of a fifth strain.

However, since the test was conducted, significant changes have been made to OECD guideline 471 and this means that the study does not meet the requirements of the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

ECHA concludes that a test using *E. coli* WP2 uvrA, or *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.

In his comments to the draft decision, the Registrant seeks to adopt the standard information requirement by reading-across to the analogue substance ε-caprolactam (CAS No. 105-60-2). The Registrant has not updated his dossier with the studies intended to be read across. This hampers ECHA's ability to assess the read-across approach; however, ECHA has made the following observations:

i. The Registrant has not provided a credible scientific explanation as to why the results of an *In vitro* gene mutation study in *S. typhimurium* strain TA102 can be accurately predicted from analogue substance ε-caprolactam (CAS No. 105-60-2);

ii. The Registrant refers to similarities in a series of properties but failed to associate these properties with the properties to be read-across. There is no endpoint specific scientific explanation as to explain the basis of the prediction;

iii. The Registrant claims that the differences in the chain length (*i.e.* 6 additional

methylene groups), and the associated increase in lipophilicity, does not lead to a significant potential for bioaccumulation, and therefore, no changes in chemical and biological activities is to be expected. However, the Registrant has not substantiated his claim by providing supporting evidence that absence of bioaccumulation results in absence of any chemical or biological reactivity;

iv. The Registrant has based the read-across on a common functional group. The common functional group is assumed to determine toxicity. The Registrant has not attempted to make this assumption endpoint-specific (for instance provide evidence why the mutagenicity in *S. typhimurium* strain TA102 will only be dependent on this functional group). However, reliable prediction requires that identified structural differences on the toxicity profiles of the substances must be justified. Furthermore, the impact of identified structural differences on the chemical reactivity has not been addressed;

v. The Registrant claim of low bioavailability for both substances is contradicted by the data in the technical dossier. For the proposed source substance the toxicokinetics study concludes '*After oral administration radioactivity was rapidly absorbed and distributed throughout the animals including the foetuses*'; and '*Metabolism in liver prior to secretion into bile seems likely*'. For the registered substance, the available sub-chronic toxicity study has a LOAEL of 125 mg/kg/day (based on '*histological lesions*' in the liver of males). ECHA considers that these findings do not support the Registrant's claim of low bioavailability. In addition, the Registrant also failed to provide considerations on the biotransformation products of the source and target substances and of the potential of these substances to cause different toxic effects.

vi. ECHA observes that the NOAELs from the available sub-chronic toxicity studies on source and target substances are similar (29 mg/kg/day *v.* 25 mg/kg/day for source and target substance, respectively). However, ECHA notes that the toxicological effects caused by the source and target substances differ. For the registered substance (*i.e.* the target) the NOAEL is based on based on '*histological lesions*' in the liver of males at 125 mg/kg/day (LOAEL). For the proposed source substance the NOAEL is based on '*hyaline-droplet degeneration of the proximal convoluted tubules in the kidneys of male rats*' at 60 mg/kg/day (LOAEL); no other effects are reported for the proposed source substance. ECHA notes that hyaline droplets in the kidneys of male rats are normally not considered relevant for human health risk assessment. ECHA concludes that the Registrant has not demonstrated that for systemic toxicity effect that the effects of the registered substance can be accurately predicted from the results obtained with the proposed target substance.

Based on the deficiencies listed above ECHA considers that the proposed read-across is not acceptable.

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: Bacterial reverse mutation test (test method: 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.

2. Pre-natal developmental toxicity study (Annex X, Section 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).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material.

However, there is no information available for a pre-natal developmental toxicity study in a second species.

The technical dossier does not contain an adaptation in accordance with column 2 of Annex X, Section 8.7. or with the general rules of Annex XI for this standard information requirement.

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.

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.

In his comments to the draft decision, the Registrant seeks to adopt the standard information requirement by reading-across to the analogue substance ε-caprolactam (CAS No. 105-60-2). The Registrant has not updated his dossier with the studies intended to be read across. This hampers ECHA's ability to assess the read-across approach. However, the general deficiencies in the read-across approach already highlighted under points ii, iii, v and vi of the heading "*In vitro* gene mutation study in bacteria", above, are applicable *mutatis mutandis* to the present heading. In addition to these deficiencies, ECHA shall make the following observations:

i. The Registrant has not provided a credible scientific explanation as to how and why the results of a pre-natal developmental toxicity study in rabbits conducted with the registered substance can be accurately predicted from analogue substance ε-caprolactam (CAS No. 105-60-2);

ii. The Registrant has based the read-across on a common functional group. The common functional group is assumed to determine toxicity. The Registrant has not made this assumption endpoint-specific. For instance explain, he has not justified why the pre-natal developmental toxicity in the rabbit will only depend on this group and not on the steric structure of the rest of the molecule or its metabolites. ECHA considers that the Registrant has failed to address the impact of identified structural differences on the toxicity profiles of the substances. Furthermore, the impact of identified structural differences on the chemical reactivity has not been addressed; and

iii. Signs of reproductive toxicity have been observed in a study performed in the dog with the registered substance; this warrant further investigation for toxicity to reproduction. The Registrant failed to elaborate on this aspect.

Based on the deficiencies listed above ECHA considers that the proposed read-across is not acceptable.

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.

B. Deadline for submitting the required information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 24 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also contained a two-generation reproductive toxicity study (EU B.35, OECD TG 416) or an extended one-generation reproductive toxicity study (EU B.56, OECD TG 443) (Annex X, Section 8.7.3.). As these studies are not addressed in the present decision, ECHA Secretariat considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 12 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 relation to the information required by the present decision, the sample of substance used for the new studies must be suitable for use by all the joint Registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given by the joint Registrants. It is the responsibility of all joint Registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition.

In addition, it is important to ensure that the particular sample of substance tested in the new studies 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 by each Registrant. If the registration of the substance by any Registrant covers different grades, the sample used for the new studies must be suitable to assess these grades.

Finally 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://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[1] by Guilhem de Seze, Head of Unit, Evaluation E1

[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.