ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-0000005159-70-02/F Helsinki, 7 October 2014

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

For cyanoguanidine, CAS No 461-58-5 (EC No 207-312-8), 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 cyanoguanidine, CAS No 461-58-5 (EC No 207-312-8), submitted by [redacted] (Registrant).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 1000 or more tonnes per year. This decision does not take into account any updates submitted after 12 June 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 19 July 2013.

On 16 October 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. That draft decision was based on submission number [redacted]

On 14 November 2013 ECHA received comments from the Registrant on the draft decision.

On 15 January 2014 the Registrant updated his registration dossier with the submission number [redacted]. The ECHA Secretariat considered the Registrant's comments and update.

The information is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

On 12 June 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.

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

II. Information required

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

Pre-natal developmental toxicity study (Annex IX, 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 **14 October 2015**.

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.

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 IX and X of the REACH Regulation.

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

A "pre-natal developmental toxicity study" for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. 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.

The Registrant has provided in the technical dossier a study report entitled: "[redacted]".
The study was indicated as "key study" with reliability score of 2. However, this study does not provide the information required by Annex IX, Section 8.7.2., because this study is only a dose-range finding study and not a definitive one according to test method EU B.31 or OECD 414. For example, the number of pregnant rats per dose group was not sufficiently

high (6 instead of 20) and key parameters of a pre-natal developmental toxicity study like examinations of foetuses for skeletal and visceral alterations were not examined.

In the dossier update provided on 15 January 2014 with the submission number [redacted], the Registrant has proposed to use read-across approach in accordance with Annex XI, 1.5, and to perform the test on another substance than the registered substance. In its evaluation, ECHA has considered the scientific validity of the proposed read-across approach.

Article 13(1) of the REACH Regulation requires information on intrinsic properties of substances on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including information from structurally related substances (grouping or read-across), *"provided that the conditions set out in Annex XI are met".*

According to the Registrant, use of read-across is possible and he proposes to test another substance, guanidinium chloride, to meet the information requirements for the endpoint of prenatal developmental toxicity for the substance registered.

In support of the waiver, the Registrant provides the following justification: *"The similarity between guanidinium chloride and DCD (cyanoguanidine) is based on their structural likeness and their common functional groups. The difference in the structure of both substances is based on the cyanide group that is contained in DCD. However, in contrast to guanidinium chloride, DCD is not classified for (eco-) toxicity, which provides strong evidence that in-vivo DCD does not release the cyanide group when metabolized. Therefore, it can be concluded that the functional cyanide group contained in the DCD molecule is not relevant for the overall toxicity of DCD. Thus, the relevant functional group in the toxicity assessment is the guanidine base which is the same in both molecules, DCD and guanidinium chloride."*

ECHA notes, however, that this hypothesis is not sufficiently substantiated by data and there are too many uncertainties in assuming that the difference in structures (i.e., the presence of the nitrile group) results in similarities in effects with regard to the prenatal developmental toxicity studies. The Registrant has not sufficiently explained that the toxicological properties can be predicted from guanidine to cyanoguanidine.

Furthermore, the Registrant stresses that **"***For human toxicity endpoint studies are available for source and target substance for the following endpoints: acute oral, dermal and inhalation toxicity, in vivo skin and eye irritation, skin sensitization, in-vitro gene mutation in bacteria (Ames test), in-vitro cytogenicity chromosome aberration test, in-vitro gene mutation study in mammalian cells. In addition data regarding sub-acute (28-day) and sub-chronic (90-day) toxicity, toxicity to reproduction, and pre-natal developmental toxicity (range-finding study) are available for DCD"* the Registrant also argues that "*...with human toxicological effects at similar or lower levels for guanidinium chloride. Therefore, the use of guanidinium chloride data is deemed an acceptable worst-case approach that is adequately protective in the assessment of prenatal developmental toxicity of DCD*".

ECHA notes that based on the human toxicity summary data matrix provided by the Registrant, the substances have a different toxicological profiles regarding the acute oral and inhalation toxicity as well as skin and eye irritation, and that, attending at the acute oral toxicity data reported, guanidinium chloride could be considered a worst case example (LD50 773.6 mg/kg bw vs LD50>10000 mg/kg bw for cyanoguanidine). However, there are repeated dose toxicity studies for cyanoguanidine but not for guanidinium chloride. Moreover, there is no data on the toxicokinetics of cyanoguanidine (the registered

substance), thus metabolic divergence for guanidine chloride and cyanoguanidine cannot be excluded. The uncertainties regarding the different toxicological profiles of the substances and lack of data on repeated dose toxicity and toxicokinetics have not been taken into account by the Registrant and therefore the read-across approach is not considered acceptable.

In addition, the range-finding study cited for prenatal developmental toxicity of cyanoguanidine did not examine key parameters like skeletal and visceral alterations of foetuses.

Based on the data submitted, ECHA considers that the Registrant has not demonstrated that the read-across approach from the source substance guanidinium chloride to the target substance cyanoguanidine (the registered substance) can be accepted for the prenatal developmental toxicity endpoint.

Therefore, the criteria of Annex XI, 1.5. are not met, and the read-across approach, as presented by the Registrant, cannot be accepted to meet the information requirements in question.

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.

According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, and the rabbit the preferred non-rodent species. The available information on prenatal developmental toxicity in rats from the range finding prenatal developmental toxicity study – although limited in investigations and statistical power and, therefore, not definitive for prenatal developmental toxicity in rats – together with the information on litter size at birth and on early survival of the pups from the two-generation reproductive toxicity study, suggest that the likelihood for prenatal developmental toxicity in the rat may be low up to the limit oral dose of 1000 mg/kg bw/day. Therefore, and given that there is no indication in the CSR that human exposure above 1000 mg/kg bw/day could occur, ECHA considers it appropriate to use the rabbit as a first species to be tested and the need for a definitive prenatal developmental toxicity study in the rat to be decided based on the results in the rabbit study and all other available information.

According to the test method EU B.31/OECD 414, the test substance is usually administered orally. ECHA considers this default parameter appropriate and testing should be performed by the oral route.

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.

Notes for consideration by the Registrant

In addition, a pre-natal developmental toxicity study on a second species is part of the standard information requirements as laid down in Annex X, Section 8.7.2. for substances registered for 1000 tonnes or more per year (see sentence 2 of introductory paragraph 2 of Annex X).

The Registrant should firstly take into account the outcome of the pre-natal developmental

toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if weight of evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed. If the Registrant considers that testing is necessary to fulfil this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species, which would be the rat in this case. If the Registrant comes to the conclusion that no study on a second species is required, he should update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex X, 8.7.2.

IV. Adequate identification of the composition of the tested material

ECHA stresses that the information submitted by other joint registrants for identifying the substance has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation

In relation to the information required by the present decision, the sample of substance used for the new study 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 study 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 study 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 study 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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