ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114309968-35-01/F Helsinki, 05 November 2015

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

For 2,2'-dimethyl-4,4'-methylenebis(cyclohexylamine), CAS No 6864-37-5 (EC No 229-962-1), 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 2,2'-dimethyl-4,4'-methylenebis(cyclohexylamine), CAS No 6864-37-5 (EC No 229-962-1), submitted by [redacted] (Registrant). The scope of this compliance check is limited to the standard information requirements of Annex VI, Section 2 and Annexes VII to X, Section 8 of the REACH Regulation.

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of [redacted] per year. This decision does not take into account any updates submitted after the deadline for updating (25 March 2015) communicated to the Registrant by ECHA on 16 February 2015.
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 09 January 2013.

On 26 June 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 26 July 2013 ECHA received comments from the Registrant on the draft decision, concerning the information requirements of Annex VI, Sections 2.2.2. and 2.2.7; Annex VII, Section 8.4.1.; and Annex X, Sections, 8.7.2. and 8.7.3.

On 10 March 2015 the Registrant updated his registration dossier with the submission number [redacted].

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 and update(s) concerning the information requirement of Annex X, Section 8.7.3. However, ECHA Secretariat did consider further the Registrant's comments and update(s) concerning the information requirements of Annex VI, Sections 2.2.2. and 2.2.7; Annex VII, Section 8.4.1.;

and Annex X, Section, 8.7.2. On the basis of all this information and change of scope, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 11 June 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.

Subsequently, proposals for amendment to the draft decision were submitted.

On 17 July 2015 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 amended the draft decision.

On 27 July 2015 ECHA referred the draft decision to the Member State Committee.

By 17 August 2015, in accordance to Article 51(5), the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant on the proposals for amendment into account.

After discussion in the Member State Committee meeting on 15-17 September 2015, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 16 September 2015.

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

II. Information required

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

Pursuant to Articles 41(1)(a) and (b), 41(3), 10(a)(vi) and/or (vii), 12(1)(e), 13 and Annexes VII-XI 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 strains *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102; and
2. Pre-natal developmental toxicity study (Annex X, 8.7.2.; test method: EU B.31./OECD 414) in rabbits, oral route.

The Registrant shall determine the appropriate order of the studies taking into account the possible outcome and considering the possibilities for adaptations of the standard information requirements according to the column 2 provisions of the respective Annex and those contained in Annex XI of the REACH Regulation.

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.

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 November 2016**.

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) and 12(1)(e) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities of [redacted] 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.)

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.

Article 13(4) of the REACH Regulation provides that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP).

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA. Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

ECHA notes that the Registrant has provided a non-GLP test from 1986 claimed to equivalent or similar to the relevant study guideline (Bacterial reverse mutation test, OECD 471). The test has been conducted using four different strains of *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100.

According to paragraph 13 of the current OECD 471 test guideline 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. ECHA observes 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.

Therefore, ECHA views that the study provided does not adequately and reliably cover the key parameters of the corresponding test method OECD 471, as required by Annex XI, section 1.1.2. Accordingly, the information requirement of Annex VII, Section 8.4.1.has not been met and that a test using one of the above bacteria is required to conclude on *in vitro* gene mutation in bacteria.

In his comments on the draft decision, the Registrant confirms that the requested *E. coli* or *S. typhimurium* strains are missing in the available OECD 471 mutagenicity test. However, the Registrant highlighted that the 5th strain was not obligatory according to the guideline (OECD 471) at the times the testing was done. Furthermore, the Registrants states '*Mutagenicity testing in mammalian cell cultures is generally accepted to reflect the complexity of eukaryotic DNA-damage appropriately*'. ECHA points out that for a substance a tonnage band above 10 tonnes per year three different negative *in vitro* tests are required (Annex VII, Section 8.4.1.; and Annex VIII, Sections 8.4.2. and 8.4.3.).
Moreover, the Registrant argues that no hints of '*mutagenic effects or even tumorigenic effects*' are seen in the available sub-chronic toxicity studies. ECHA notes that neither the OECD 408 nor the OECD 413 guidelines states that these tests are designed to detect mutagenicity.

Finally, the Registrant argues that additional testing would not add significant information as the other available *in vitro* tests gene mutation in mammalian cells (OECD 476) and chromosome aberration in mammalian cells (OECD 473) are negative. ECHA notes that neither the OECD 473 nor the OECD 476 guidelines states that these tests are designed to detect gene mutations in bacteria.

The Registrant is reminded that this decision does not take into account any updates submitted after 25 March 2015. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

Therefore, pursuant to Article 41(1)(a) 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 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 study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation for substances registered for 100 to 1000 tonnes or more per annum. According to Annex X, Section 8.7.2. of the REACH Regulation, a further pre-natal developmental toxicity study performed in a second species is required to fulfil the standard information requirements for substances registered for 1000 tonnes or more per annum. The test method to be used is EU B.31/OECD 414.

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. Both information requirements are subject to all appropriate column 2 or Annex XI data adaptations. 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."

ECHA notes that in the present case there is information available on this endpoint for a pre-natal developmental toxicity study in a first species by the oral route. More specifically, the Registrant has provided a pre-natal developmental toxicity study (OECD 414) performed in the first species (rat) by the oral route (gavage) using the registered substance. The doses used in this study were 0, 5, 15 and 45 mg/kg body weight/day; the NOAEL for maternal toxicity was determined to be 5 mg/kg body weight/day (based on reduced body weight at 15 and 45 mg/kg body weight/day); the NOAEL for developmental toxicity was determined to be 45 mg/kg body weight/day (no adverse effects observed; no detailed results provided by the Registrant). The Registrant concludes: "*There were no substance-induced, dose-related influences on the gestational parameters and no signs of prenatal developmental toxicity, especially no substance induced indications of teratogenicity, up to and including the high dose-level (45 mg/kg bw/day)*". The study result is negative for teratogenicity, but the Registrant has provided no justification to omit the study in a second species.

However, there is no information available for a pre-natal developmental toxicity study in a second species for the registered substance in the technical dossier. Accordingly, and also in the absence of any justification in line with respective column 2 or Annex XI not to conduct the study in a second species, 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, the rabbit 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.

In the updated dossier the Registrant provided the following waiver for a pre-natal developmental toxicity study in a second species: "*The overall conclusion for the endpoint teratogenicity was that only slight fetotoxicity (retardation of ossification of skull bones) without teratogenicity was observed at 45 mg/kg bw/day, together with severely reduced body weights of the dams.*

Rabbits have been reported to react more sensitive to DMDC and oral LD50 values are significantly lower in rabbits than observed for rats. The mentioned rabbit LD50 values are reported to be below 100 mg/kg bw (see also endpoint acute oral toxicity; < 100 mg/kg bw and 320-460 mg/kg bw, respectively). As the documentation is insufficient and the rabbit is not the appropriate species for the evaluation of the acute oral toxicity hazard, these studies were considered being inadequate for classification and labeling (Klimisch Code 3, not reliable). However, they may provide some information on the dose setting for a teratogenicity study in the second species rabbit. In this case the dosing would have to be significantly lower than the doses having been applied in the available teratogenicity study in the rat. This information makes the arguments for waiving the teratogenicity study in the second species rabbit more robust.
Developmental toxicity testing in the second species would not significantly contribute to the endpoint evaluation as the doses would be expected to be rather low. In combination, DMDC is a corrosive substance, showing a distinctive toxicological profile after repeated exposure with a rather low NOAEL and specific target organ toxicity as observed in the repeated dose toxicity study (OECD 408, rat; NOAEL = 2.5 mg/kg bw).
Due to animal welfare reasons according to Article 25 of the REACH Regulation, the conduction of a prenatal developmental toxicity study (OECD 414) on a second species is scientifically unjustified and will most probably not contribute to the overall risk assessment."

In his comment on the draft decision and updated dossier, the Registrant has provided a waiver and argues that additional testing for pre-natal developmental toxicity in *"a second species is scientifically unjustified and will most probably not contribute to the overall risk assessment."* The reasoning for this is that the outcome of the pre-natal developmental study in the first species (rat) was negative; the substance is corrosive; the substance has a low NOAEL in the repeated dose toxicity study (2.5 mg/kg/day; OECD 408); and the substance is classified for specific target organ toxicity (STOT RE 2; target organs: liver, kidney, adrenal gland, heart, blood). Furthermore, the Registrant argues that rabbits are more sensitive than rats and therefore doses *"would have to be significantly lower than the doses having been applied in the available teratogenicity study in the rat. This information makes the arguments for waiving the teratogenicity study in the second species rabbit more robust."* Moreover, the Registrant raises animal welfare arguments .

ECHA notes that for a substance registered under REACH in the tonnage band above [redacted] per year, a pre-natal developmental toxicity study in a second species is a standard information requirement. The arguments brought forward by the Registrant do not meet the specific rules for adaptation in Column 2, Annex X, Section 8.7 or in Annex XI. Therefore, ECHA has not amended the draft decision.

The Registrant is reminded that this decision does not take into account any updates submitted after 25 March 2015. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

Therefore, pursuant to Article 41(1)(a) 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 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 the request for this study 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 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://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.

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.