~~CONFIDENTIAL~~

European Chemicals Agency

Decision number: TPE-D-0000001364-79-06/F
Date for the decision: 1 July 2011

Helsinki, 1 July 2011

DECISION ON A TESTING PROPOSAL SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For VULCUREN VERSUCHSPRODUKT *KA 9188*, CAS: 151900-44-6 (EC No 429-280-6), 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 (the REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined the testing proposal set out in the registration dossier for **Vulcuren Versuchsprodukt KA 9188, CAS: 151900-44-6 (EC No 429-280-6)**, Registration Number: [redacted] submitted by [redacted] (the "Registrant"), latest submission number [redacted] for the tonnage band 100 - 1000 tonnes per year.

In accordance with Article 12(1)(d) of the REACH Regulation, the Registrant submitted the following testing proposal as part of the registration dossier for the provision of the information requirements set out in Annex IX:

- Pre-natal developmental toxicity study (OECD Test Guideline 414) to fulfil the information requirement of section 8.7.2. of Annex IX

The examination of the testing proposal was initiated on 21 June 2010.

ECHA held a public consultation for the testing proposal from 1 September 2010 until 15 October 2010. ECHA received 2 comments (see section III).

ECHA examined the testing proposal and the information received from third parties and prepared a draft decision in accordance with Article 40(3) of the REACH Regulation.

On 16 December 2010 ECHA notified the Registrant of its draft decision and invited him pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

On 14 January 2011 ECHA received comments from the Registrant on the draft decision. ECHA reviewed the comments received and amended the draft decision accordingly.

European Chemicals Agency
Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland
Tel.: +358 9 6861 80 | Fax +358 9 6861 8210 | http://echa.europa.eu

On 18 February 2011 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 to amend the draft decision within 30 days. Subsequently, one Competent Authority of the Member States submitted a proposal for amendment to the draft decision.

On 23 March 2011 ECHA notified the Registrant of the proposal for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments within 30 days of the receipt of the notification. ECHA reviewed the proposal for amendment received and decided not to amend its draft decision.

On 4 April 2011, the draft decision was referred to the Member State Committee.

On 12 April 2011, the Registrant provided to ECHA comments on the proposed amendment. The Member State Committee took the comments of the Registrant into account.

The Member State Committee reached a unanimous agreement on the draft decision, on 10 May 2011 in a written procedure launched on 28 April 2011.

This decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the present dossier at a later stage.

II. Testing required

Pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant shall carry out the following tests:

- Pre-natal developmental toxicity study in rats, oral route (method B.31 of Regulation (EC) No 440/2008; OECD Test Guideline 414)

Pursuant to Articles 40(4) and 22 of the REACH Regulation the Registrant shall submit to ECHA by ***1 October 2012 - 15 months from the date of the decision*** an update of the registration containing the information required by this decision.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposal of the Registrant for the registered substance and the information submitted by the third parties during the public consultation.

According to section 8.7.2 of Annex IX of the REACH Regulation a pre-natal developmental toxicity study in one species is required to fulfil the standard information requirements.

No information on developmental toxicity was provided in the registration dossier. During the public consultation, ECHA received information related to developmental toxicity from third parties.

- Results from a QSAR model "Nonlinear classification ANN QSAR Model for Combined 28-Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test" and QMRF (QSAR Model Reporting Format).

European Chemicals Agency
Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland
Tel.: +358 9 6861 80 | Fax +358 9 6861 8210 | http://echa.europa.eu

- A proposal to use developmental toxicity data of thioperoxydicarbonic diamide ($[(H_2N)C(S)]_2S_2$), tetramethyl- (synonyms: tetramethylthiuram disulfide, thiram, thiuram), CAS:137-26-8, EC No. 205-286-2 in a read-across approach.

ECHA has examined this information in order to determine whether the scientifically valid information that addresses the relevant substance and hazard endpoint is already available.

1. Information related to the submitted QSAR model:

A third party submitted a prediction of developmental toxicity of the registered substance generated by a QSAR model and provided additional information on the model in a QSAR Model Reporting Format.

Results from QSAR models can be used instead of testing when the conditions set out under Annex XI, section 1.3 of the REACH Regulation are met. These conditions require that the scientific validity of the model used to derive the results is established, the registered substance falls within the applicability domain of the model, the results provided by the model are adequate for the purpose of classification and labelling and/or risk assessment and that the method applied is adequately and reliably documented.

ECHA has identified several deficiencies in the information provided by the third party with regard to the fulfilment of the conditions laid down under Annex XI, section 1.3 of the REACH Regulation, as follows:

- The prediction from the model is in the form "toxic/non-toxic". In the absence of additional information on the meaning of these terms, the predicted result cannot be directly used or extrapolated to fill a data gap according to the information requirements of REACH and is not considered as adequate for classification and labelling and/or risk assessment.
- Based on the information provided in the QMRF, the possibility that the registered substance does not fall within the structural applicability domain of the model cannot be ruled out. The prediction is not reported in a form of a QSAR Prediction Reporting Format (QPRF) and hence no further assessment of the accuracy of the prediction can be made.
- The level of detail in the documentation regarding the algorithm used in the model is not considered sufficient to transparently describe the model and thus, to assess its certainty. Information is needed on how the descriptors were selected, on the algorithm and the method (approach) used to generate each of the descriptors, and on the algorithm as an output of formalised mathematical approach. Therefore, the method applied is not adequately and reliably documented.
- The model is developed to predict the outcome from the combined 28-day repeated dose study/reproductive/developmental toxicity screening test (OECD TG 422). This study does not provide an adequate coverage of key parameters addressed in the pre-natal developmental toxicity study and is not considered sufficient to fulfil the information requirements for pre-natal developmental toxicity laid down in Annex IX of the REACH Regulation.

Therefore, ECHA concludes that the prediction obtained from the above-mentioned QSAR model does not meet the conditions of Annex XI, 1.3 for adapting the standard requirement for the developmental toxicity endpoint of the registered substance and can therefore not be used to fulfil the information requirement.

European Chemicals Agency
Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland
Tel.: +358 9 6861 80 | Fax +358 9 6861 8210 | http://echa.europa.eu

2. Information related to the proposal for read-across

A third party submitted a summary of a developmental toxicity study for the substance thioperoxydicarbonic diamide ($[(H_2N)C(S)]_2S_2$), tetramethyl- (hereafter 'tetramethylthiuram disulfide'), CAS:137-26-8, EC No. 205-286-2 and a proposal to use the developmental toxicity data from the above-mentioned substance for the registered substance, in a read-across approach. The third party submitted also additional information on the properties of tetramethylthiuram disulfide and two other substances: tetramethylthiuram monosulfide (CAS: 97-74-5) and tetraethylthiuram disulfide (CAS 97-77-8).

According to section 1.5 of Annex XI of the REACH Regulation, grouping of substances and read-across approach can be applied for substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity, and when the conditions in section 1.5 of Annex XI are met.

ECHA has identified several deficiencies in the information provided by the third party with regard to the fulfilment of the conditions laid down in section 1.5 of Annex XI of the REACH Regulation and in particular that:

- One of the conditions laid down in section 1.5 of Annex XI of the REACH Regulation is that adequate and reliable information of the applied method is provided. The justification provided by the third party for read-across is limited to a comparison of the structures and physicochemical properties of the substances and summary of available data on developmental toxicity for tetramethylthiuram disulfide, tetramethylthiuram monosulfide and tetraethylthiuram disulfide. The documentation of the applied method provided is not considered adequate to justify the read-across.
- Based on the information submitted by the third party and information in the registration dossier of the registered substance the physico-chemical properties of tetramethylthiuram disulfide are different from those of the registered substance. The registered substance has a considerably higher molecular weight and LogKow and considerably lower water solubility than tetramethylthiuram disulfide. These differences are considered likely to result in differences in the toxicokinetic profiles of the substances.
- Based on the available information, the toxicological profile of tetramethylthiuram disulfide is very different from the registered substance. Tetramethylthiuram disulfide is classified for skin and eye irritation, acute toxicity and skin sensitisation. Based on the information provided in the registration dossier the registered substance is not classified for any of these endpoints. Furthermore, tetramethylthiuram disulfide is also classified for effects after repeated oral exposure. Based on the available information, it appears that with regard to repeated dose toxicity there is at least about a two order of magnitude difference in potency between tetramethylthiuram disulfide and the registered substance. The classifications applied show no similarities in the toxicological profile between the registered substance and the substance from which the read-across approach is suggested.
- Available data related to environmental fate and ecotoxicological properties also show differences between the two substances. With regard to environmental fate, tetramethylthiuram disulfide is considered to be readily biodegradable, while the registered substance is not. With regard to toxicity to aquatic organisms, tetramethylthiuram disulfide shows a higher potential for acute hazard, compared to the registered substance.

European Chemicals Agency
Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland
Tel.: +358 9 6861 80 | Fax +358 9 6861 8210 | http://echa.europa.eu

Based on the observations listed above ECHA concludes that the differences between the registered substance and tetramethylthiuram disulfide are such that the application of read-across between the two substances would not be reliable and appropriate to fulfil the information requirement for developmental toxicity of the registered substance.

Pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is thus requested to carry out the following test: Pre-natal developmental toxicity study in rats, oral route (method B.31 of Regulation (EC) No 440/2008; OECD test guideline 414).

The Registrant commented that the time to complete the study requested is 15 months. In light of this comment ECHA considered that the Registrant should provide the study within 15 months from the date of the decision.

IV. General requirements for the generation of information and Good Laboratory Practice

ECHA always reminds Registrants of the requirements of Article 13(4) of the REACH Regulation that reads:

> "*Ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or the Agency and with the provisions of Directive 86/609/EEC, if applicable.*"

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as adapted to technical progress and use the applicable test methods to generate the information on the endpoints indicated above.

National authorities monitoring good laboratory practice (GLP) maintain lists of test facilities indicating the relevant areas of expertise of each facility.

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 appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the 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.

Done at Helsinki,

[redacted]

Jukka Malm
Director of Regulatory Affairs

European Chemicals Agency
Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland
Tel.: +358 9 6861 80 | Fax +358 9 6861 8210 | http://echa.europa.eu