ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000001786-65-04/F Helsinki, 3 February 2012

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

For 3-[(diisoalkyloxyphosphorothioyl)thio]-2-methylalkanoic acid [redacted], 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 40(1) of the REACH Regulation, ECHA has examined a testing proposal set out in the registration dossier for 3-[(diisoalkyloxyphosphorothioyl)thio]-2-methylalkanoic acid [redacted], submitted by [redacted] (Registrant), latest submission number [redacted], for 10-100 tonnes per year.

The Registrant submitted the following testing proposal as part of the registration dossier to fulfil the information requirements set out in the REACH legislation:

Annex IX, 8.7.2: Pre-natal developmental toxicity study in rats, oral route, according to OECD Guideline 414.

The examination of the testing proposal was initiated on 13 December 2010.

ECHA held a third party consultation for the testing proposal from 15 March 2011 until 29 April 2011. ECHA received the following comments from third parties (also see Section III) that address the hazard endpoint concerned:

- A comment regarding the need to conduct the pre-natal developmental toxicity study (OECD Guideline 414) in light of the results of the existing oral 28-day study and other toxicological data;
- A comment suggesting in vitro (pre-) validated tests for the evaluation of the embryotoxic and endocrine disruption potential and apply QSAR classification models for developmental toxicity. Use the results to waive developmental toxicity study (pre-natal developmental toxicity study, OECD Guideline 414);
- A comment based on exposure considerations: use the TTC for reproduction toxicity endpoint.

ECHA examined the testing proposal and the information received from third parties and drafted a decision in accordance with Article 40 of REACH. On 10 June 2011 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 24 June 2011 ECHA received comments from the Registrant on the draft decision indicating that the Registrant agrees with ECHA's draft decision. However, ECHA amended the draft decision by clarifying the statement of reasons.

On 29 July 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 one proposal for amendment to the draft decision.

On 31 August 2011 ECHA notified the Registrant of proposals 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.

On 12 September 2011, the draft decision was referred to the Member State Committee.

On 22 September 2011 the Registrant provided comments on the proposal for amendment. The Member State Committee took the comments of the Registrant into account.

A unanimous agreement of the Member State Committee on the draft decision was reached on 14 October 2011 in a written procedure launched on 3 October 2011.

This decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the requirements of the REACH Regulation. The decision does not prevent ECHA to initiate 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 test using the indicated test method:

- Pre-natal developmental toxicity study (EU test method B.31; OECD Guideline 414) in rat by the oral route.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by 3 February 2013 an update of the registration dossier containing the information required by this decision.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other registrants.

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 scientific information submitted by third parties.

According to Article 40(1) of the REACH Regulation, ECHA shall examine a testing proposal set out in a registration dossier for provision of information specified in Annexes IX and X.

The examination and decision on the testing proposal are based on the standard information requirements for the registered tonnage band (10-100 tones per year), as specified in Articles 10(a)(vii) and 12(1)(c) and Annexes VII and VIII of the REACH Regulation.

Annex VIII, section 8.7.1., requires the Registrant to provide a screening for reproductive/ developmental toxicity, one species. According to column 2 of Annex VIII, Section 8.7.1, in cases where there are serious concerns for adverse effects on fertility or development, either a pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) or a two generation reproductive study (Annex IX, Section 8.7.3) may be proposed by the Registrant instead of the screening study.

In the registration dossier the Registrant indicated that he has a specific concern as regards possible developmental toxicity associated with the sensitizing properties, the in-vitro clastogenicity and presumed alkylating properties. On this basis the Registrant, pursuant to the second column of Annex VIII, 8.7.1, submitted the testing proposal for the pre-natal developmental toxicity study.

ECHA considers that the Registrant has provided a valid reason for proposing the test. Furthermore, the results of the public consultation did not yield scientifically relevant information that addresses the registered substance and the hazard end-point addressed in the testing proposal.

Therefore, ECHA accepts the testing proposal, and the Registrant is requested to carry out the pre-natal developmental toxicity study (EU test method B.31; OECD Guideline 414) in rat by the oral route.

The comments received by third parties on the proposed testing were not capable to omit the proposed testing as follows:

1. Comments regarding the need to conduct the pre-natal developmental toxicity study (OECD Guideline 414) in light of the results of the existing oral 28-day study and other toxicological data:

One comment from third parties suggests that the findings of the available toxicity studies, including the 28-day study, can be extrapolated to longer exposure duration, and suggests the use of different assessment factors.

The existing oral 28-day study, however, does not address pre-natal developmental toxicity and therefore it cannot be used to adapt the standard information requirement for this endpoint.

2. Comments suggesting in vitro (pre-) validated tests for the evaluation of the embryotoxic and endocrine disruption potential and apply QSAR classification models for developmental toxicity. Use the results to waive developmental toxicity study (pre-natal developmental toxicity study, OECD Guideline 414).

The third party has proposed a testing strategy for ECHA to consider. However, ECHA invited submission of "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal", as specified by Article 40(2), and the proposal for a strategy cannot be considered as such information.

Concerning scientifically validated in vitro methods such as the embryonic stem cell test, the limb bud micromass culture and the whole embryo culture such methods may provide additional information which can be assessed together with existing in vivo data in a weight of evidence approach. However, ECHA notes that the mentioned in vitro tests only cover some of the reproductive toxicity endpoints, modes of action and mechanisms covered by

the in vivo pre-natal developmental toxicity tests and therefore cannot be used as stand alone replacements tests. Furthermore these alternative methods are not part of the information requirements laid down in Annex VII to X of REACH and can therefore not be requested by ECHA in the context of a testing proposal examination.

Concerning QSAR classification model, a prediction using QSAR model (CAESAR prediction) for pre-natal developmental toxicity study giving the result non-toxic was provided. The dependent variable of the model is in the form "toxic/non-toxic". Annex XI, 1.3 governing QSAR models requires that information concerning the validity, applicability domain (in this case, it is clearly stated that "the compound could be out of the model Applicability Domain), adequacy for classification & labelling and documentation of the method be provided. As this information was not provided, ECHA considers that the model fails to meet the requirements of Annex XI, 1.3. The predicted result can therefore not be directly used or extrapolated to fill the information requirements in question.

Consequently, ECHA concludes that this is not a sufficient basis to rejecting the testing proposed.

3. Comments based on exposure considerations: use the TTC for reproduction toxicity endpoint.

The third party states that since testing can be exempted based on the negligible exposure, exposure should be thoroughly analysed before conducting the test. In addition, they suggest that the Threshold of Toxicological Concern (TCC) should be adopted and cut-off values: 1.0 µg/kg bw/day for oral and 0.5 µg/kg bw/day for inhalation exposure should be used.

According to Annex XI, Section 3 of REACH Regulation, the testing can be omitted if it can be demonstrated that there is no or no significant exposure. The Registrant did not use substance-tailored exposure-driving testing according to Annex XI, Section 3. The exposure values are not considered to be non-significant.

Therefore, ECHA concludes that testing cannot be omitted based on negligible exposure.

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 ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

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 or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

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.

[redacted]

Jukka Malm
Director of Regulatory Affairs