European Chemicals Agency

Decision number: CCH-D-0000001329-73-04/F Helsinki, 25 March 2011

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

For [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 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration dossier for [redacted] the "Registrant"), latest submission number [redacted]

The compliance check was initiated on 17 February 2010.

On 25 August 2010 the draft decision was sent to the Registrant for comments. By 27 September 2010 ECHA did not receive any comments from the Registrant on the draft decision.

On 29 October 2010, ECHA notified the Member State Competent Authorities of its draft decision and invited them to provide proposals for amendment.

After receiving one proposal for amendment from a Member State Competent Authority, ECHA forwarded the proposal for amendment to the Registrant on 1 December 2010 and did not amend its draft decision.

On 13 December 2010, the draft decision was referred to the Member State Committee.

On 31 December 2010, the Registrant provided comments not leading ECHA to change its draft decision.

The Member State Committee took the comments of the Registrant into account. After discussion in the Member State Committee meeting on 1-3 February 2011, a unanimous agreement of the Member State Committee on the draft decision was reached on 1 February 2011. Following Article 51(6) of the REACH Regulation, ECHA has therefore taken the decision concerning the present compliance check as notified to the Member State Competent Authorities.

This compliance check decision does not prevent ECHA to initiate further compliance checks on the present dossier at a later stage.

II. Information required

ECHA has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of the REACH Regulation. Pursuant to Articles 41(1)(a), 41(3), 10(a)(vii) and 12(1)(c) and Annexes VII and VIII and XI of the REACH Regulation, the Registrant shall submit the following missing information using the test method as indicated:

- Skin sensitisation (Annex VII, 8.3.; recommended test method is OECD 429 or EU Method B.42)
- Eye irritation (Annex VII, 8.2.; recommended test method is OECD 405 or as outlined in the Appendix to EU Method B5)
- Short-term repeated dose toxicity via the dermal route in the rat (Annex VIII, 8.6.1.; recommended test method is OECD 410 or EU Method B.9)
- Screening for reproductive/developmental toxicity in the rat (Annex VIII, 8.7.1.; test method OECD 421 or 422).

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated IUCLID dossier to ECHA by 26 March 2012.

III. Statement of reasons

Based on the examination of the technical dossier, ECHA concludes that the information therein, submitted by the Registrant for registration of the above mentioned substance in accordance with Article 6 of the REACH Regulation, does not comply with the requirements of Articles **10, 12 and 13 and with Annexes VII, VIII and XI** thereof. Consequently, the Registrant is requested to submit the information mentioned above that is needed to bring the registration into compliance with the relevant information requirements.

Pursuant to Articles 10(a)(vii) and 12(1)(c) of the REACH Regulation, [redacted]

a. The technical dossier submitted by the Registrant contains statements for the use of a weight of evidence approach according to Annex XI, 1.2. on the following endpoints:

   - Skin sensitisation (Annex VII, 8.3.)

The weight of evidence includes three read-across studies with [redacted] one read-across *in vivo* study with [redacted], as well as two QSAR simulations and three literature studies with electrophilicity for the registered substance. The Registrant claims that [redacted] are analogous to the registered substance.

ECHA concludes that the **read-across from two analogues** [redacted] suggested by the Registrant is not acceptable because there is a structural difference between the suggested analogues and the registered substance. More notably, the registered substance has ester bonds whereas the suggested analogues do not. The suggested analogues are break-down products of the registered substance but not structurally similar to it. Moreover, the Registrant has not provided the rate of hydrolysis via the dermal route in order to justify the use of the two break-down products for read-across purposes. Therefore, the criteria set out in REACH Regulation Annex XI, 1.5. for grouping and read-across are not met.

The **QSAR studies** do not meet the Annex XI, 1.3. criteria for adequate and reliable documentation, nor is there proof for the models' scientific validity and applicability domain. None of the used QSAR models is currently accepted as predictive.

The **studies on** the registered substance that refer to **electrophilicity** are relevant but do not sufficiently address the sensitisation potential of the substance. Electrophilicity is only one parameter that can be used in a preliminary assessment of sensitisation.

For these reasons, the weight of evidence analysis is considered to be insufficient, and cannot fully replace the experimental data obtained with the registered substance.

The Registrant is accordingly requested to submit the missing information for skin sensitisation for the registered substance. ECHA recommends the use of test method EU B.42 or OECD 429.

- Eye irritation (Annex VII, 8.2)

The Registrant suggests omitting the information requirement for eye irritation under Annex VII, 8.2. on the basis of an *in vitro* HET-CAM test with the registered substance, as well as on the basis of the results of a cytotoxicity assay and a read-across from [redacted] based on a material safety data sheet. [redacted]

The Registrant has provided the results of the *in vitro* HET-CAM test. According to the rules of adaptation in Column 2 of Annex VIII, 8.2.1, an *in vivo* study does not need to be conducted if the substance is classified. However, according to the protocol of the *in vitro* HET-CAM test, it detects severe irritants, whereas the test has not been formally validated for non-irritants. Moreover, according to the test

result, the substance is not an irritant, and thus the result is neither considered definite nor sufficient for classification.

Furthermore, Annex XI, 1.4 concerning *in vitro* methods lays down that '*if the results obtained from the use of in vitro methods (which are ready for prevalidation, but not formally approved) do not indicate a certain dangerous property, the relevant test shall nevertheless be carried out at the appropriate tonnage level to confirm the negative result...*'. As explained in the paragraph above, the second of the three waiving conditions given in Annex XI 1.4, concerning classification and labelling does not apply and, in this case, the relevant test according to Annex VIII, 8.2.1 would be OECD test 405.

Regarding the results of a cytotoxicity assay and a read-across from [redacted] based on a material safety datasheet, the support to the weight of evidence is considered to be insufficient because:

- The cytotoxicity test provided did not replace or significantly contribute to the assessment of eye irritation potential of the substance. As noted in the Expert Statement provided by the Registrant: "*This test was not investigated by ECVAM. It onlyk addresses toxicity to cornea cells whereas the in vivo study also requires assessment of effects to iris and conjunctivae*", and
- Read-across from [redacted] has not been justified using the criteria given in Annex XI, 1.5. Moreover, a material safety data sheet is not an adequate source of toxicity data, because it does not contain information, which is necessary for the preparation of a study summary or robust study summary as defined in Art. 3 of the REACH Regulation. In the Registrant's own words "*The validity of information given on the material safety datasheets cannot be assessed*".

Accordingly, the Registrant is requested to submit information on eye irritation of the registered substance following the testing strategy set out in Column 1 of Annex VII, 8.2.; recommended test method is OECD 405 or as outlined in the Appendix to EU Method B5.

b. <u>The Registrant suggests to omit the information requirement for the following endpoints:</u>

- Repeated dose toxicity via the dermal route (Annex VIII, 8.6.1)

The Registrant suggests omitting the information requirement for repeated dose toxicity via the dermal route because "*the oral exposure is the likely route of exposure*". The dossier contains a NOEL value for [redacted] values for [redacted] and [redacted]. No toxicological information was provided on the oral route for the registered substance.

Annex VIII, 8.6.1. of the REACH Regulation requires the performance of a short-term repeated dose toxicity study (28 days) via the most appropriate route of administration having regard to the likely route of human exposure. When evaluating the relevant information contained in the dossier against the criteria given in Column 2 of Annex VIII, 8.6.1, the following observations were made:

1. Inhalation exposure is unlikely because of the vapour pressure of the registered substance is [redacted]
2. Skin contact with the substance is likely [redacted] Furthermore, skin contact in production and use is likely, in "PROC 5, Mixing or blending in batch processed, multistage and/or significant contact." Additionally, the dermal route of exposure was the only route of human exposure as indicated by the Registrant in IUCLID section 3.5. Identified uses; and
3. In the section of toxicokinetics of the dossier, it is indicated that skin permeability of [redacted] is moderate, and thus there is potential for significant rate of dermal absorption.

Having considered the relevant criteria above, ECHA does not consider that the omission proposed by the Registrant is acceptable, because the dermal route is the most appropriate route for human exposure.

Therefore, the Registrant is requested to submit the missing information on repeated dose toxicity of the registered substance via the dermal route for the rat. ECHA recommends the use of test method EU B.9. or OECD 410.

- Screening for reproductive/developmental toxicity (Annex VIII, 8.7.1)

The Registrant suggests to omit the information requirement for screening for reproductive/developmental toxicity because the "*screening study for reproductive/developmental toxicity does not need to be performed if a valid pre-natal developmental toxicity study is available. In the case of* [redacted] *, a valid pre-natal developmental toxicity study is available for* [redacted] *This study is considered suitable for read-across because* [redacted] *is the only metabolite that is relevant for hazard assessment*".

ECHA points out that while the claim as such of the Registrant is correct pursuant to Column 2 of Annex VIII, 8.7.1, it is notable that the pre-natal developmental toxicity study was performed with the break-down product of the registered substance [redacted] where read-across within the meaning of Annex XI, 1.5 should be established. However, Annex XI, 1.5 criteria have not been met, because [redacted] is not structurally similar to the registered substance. More notably, the registered substance has ester bonds whereas [redacted] does not. Furthermore, while the Registrant suggests that the registered substance breaks down by hydrolysis to [redacted] and [redacted], he has failed to give sufficient data on in the hydrolysis rate of the registered substance.

For these reasons, the omission of the present information requirement cannot be accepted and the Registrant is accordingly requested to submit the missing information for the registered substance using the test method OECD 421 or 422 on the rat.

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."

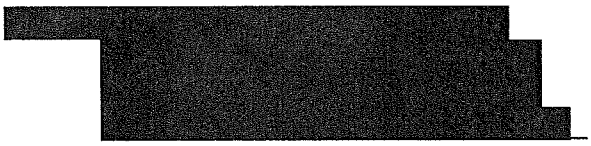
According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the 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 adapted to the technical progress by Commission Regulation (EC) No 761/2009 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 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.

Done at Helsinki,



Jukka Malm
Director of Regulatory Affairs