~~CONFIDENTIAL~~

European Chemicals Agency

Decision number: CCH-D-0000001299-68-04/F Helsinki, 12/08/2011

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

For [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 (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] submitted by [redacted] (Registrant), latest submission number [redacted], for [redacted]

The Registrant notified the substance pursuant to the national legislation implementing Directive 67/548/EEC relating to the classification, packaging and labelling of dangerous substances (as amended) by submitting a notification to the German competent authority in accordance with Article 7 of Directive 67/548/EEC. The notification number allocated was [redacted].

Article 24(1) of the REACH Regulation provides that the notification is regarded as a registration and ECHA has assigned a registration number.

The national competent authority did not finalise its assessment of the testing programme before Article 135 of the REACH Regulation entered into force on 1 August 2008. Thus, the dossier may not include some relevant legally required information. For that reason, ECHA invited the Registrant by letter of 27 August 2009 to update the dossier and submit testing proposals if necessary to bring the registration into compliance with the information requirements of the REACH Regulation. However, no

testing proposal or updated dossier has been received by the date the compliance check was initiated.

The compliance check of this dossier was therefore initiated on 28 January 2010.

On 3 September 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 1 October 2010 and 14 October 2010 the Registrant provided to ECHA comments on the draft decision.

ECHA has taken into account the information received and amended the Statement of Reasons of the draft decision accordingly.

On 18 February 2011, ECHA notified the Member State Competent Authorities 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.

After receiving a proposal for amendment from one Member State Competent Authority, ECHA forwarded the proposal for amendment to the Registrant on 23 March 2011 and decided not to amend the draft decision.

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

On 26 April 2011, the Registrant provided to ECHA comments on the proposed amendment. The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 25-27 May 2011, a unanimous agreement of the Member State Committee on the draft decision was reached on 26 May 2011.

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

II. Information required

Pursuant to Articles 41(1)(a), 41(3), 10(a)(vi) and (vii), 12(1)(d) and Annexes VIII and IX of the REACH Regulation, the Registrant shall submit the information using the test method as indicated below.

- *In vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3. of the REACH Regulation; Annex VIII, level 1 of Directive 67/548/EC, EU test method B.17)
- Prenatal developmental toxicity (Annex IX, 8.7.2. of the REACH Regulation; Annex VIII, level 1 of Directive 67/548/EC), one species, oral (EU test method B.31)
- Sub-chronic toxicity study (90-day) (Annex IX, 8.6.2. of the REACH Regulation; Annex VIII, level 1 of Directive 67/548/EC), one species, oral (EU test method B.27)

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 12 February 2013 - 18 months from date of decision**.

III. Statement of reasons

The registration was formerly a notification made in accordance with Directive 67/548/EEC. It follows from Article 24(2) of the REACH Regulation that a registration originating from a previous notification, in cases other than a tonnage band update, needs to comply with the information requirements of the REACH Regulation for the registered tonnage band or in case the requirements of the REACH Regulation for that tonnage band are stricter than those set out in Directive 67/548/EEC, the registration needs to comply with the requirements of Directive 67/548/EEC for that tonnage band.

Based on the examination of the technical dossier, ECHA concludes that the information therein, does not comply with the requirements of Articles **10 and 12 and Annexes VIII and IX** of the REACH Regulation.

The technical dossier for the registered substance does not contain any information for the endpoints listed in Section II of this decision. This information would have also been required for the same tonnage band under Directive 67/548/EEC. Consequently ECHA indicated in its draft decision of 3 September 2010 that this information was missing.

In response to ECHA's draft decision sent on 3 September 2010 the Registrant provided additional justification, Chemical Safety Report of the read-across substances [redacted] and robust study summaries of studies conducted with [redacted], to support read-across to fulfil the required information requirements under the REACH Regulation. The read-across substances include [redacted] The read-across justification submitted by the Registrant is based on similarities regarding chemical structures and metabolism. For the relevant end-points the Registrant further provided specific comments why read-across should be possible. ECHA has examined the possibility for filling the data gaps with the read-across proposed by the Registrant.

The Registrant has therefore proposed to adapt the required standard information according to Annex XI 1.5 (Grouping of substances and read-across approach) of the REACH Regulation. Registrants are generally obliged to clearly state the reasons for such adaptations to the standard testing regime and refer to the appropriate specific rule(s). For read-across, Annex XI 1.5 sets out rules on which similarities may be based on. ECHA however considers that the Registrant has failed to adequately justify why the rules on similarities set out in Annex XI 1.5 can be applied to the registered substance for the reasons set out below.

For the purposes of the present decision ECHA only needs to make a detailed evaluation of the proposed read-across with substances [redacted] as experimental study results were available only for these substances. Accordingly, due to lack of information, ECHA could not assess whether the registered substance can be read-across with [redacted], and therefore on this basis read-across can not be accepted with those three substances.

Chemical structure

Pursuant to Annex XI 1.5 read-across may be based on a common functional group. The Registrant claims that the only variability between the registered substance and the read-across substances is related to the [redacted] (R): [redacted] has the shortest carbon chain of the [redacted] whereas the chain length for the read-across substances range from [redacted]

ECHA concluded that although the basic structure is similar, the presence of [redacted] of the registered substance indicates that there will be different toxicological profile between the registered substance and the read-across substances. This is due to the fact that the functional group [redacted] gives a toxicological alert for liver toxicity and is classified as Repr. Cat.2; R61. Therefore, the registered substance and the read-across substances contain different functional groups which do not support structural similarity.

Metabolism

Pursuant to Annex XI 1.5 read-across is possible between substances that are likely to have common breakdown products via physical and biological processes. The Registrant states that although no metabolism studies are available for the registered and read-across substances, a cleavage of the peptide bond of [redacted] with liberation of the carboxylic moiety and the [redacted] is very likely based on theoretical considerations of bond strengths and enzymatic metabolism. Both higher [redacted] and the shortest one, [redacted] proposed to be formed from the [redacted], are claimed to be natural constituents of the human body, which are not expected to have an effect on the intrinsic systemic toxicity or genotoxicity. The [redacted] which is closely related to the [redacted] and to the physiological derivates of this [redacted] would be identical in [redacted]. The Registrant claims that there is no indication on an intrinsic toxicity of these structures.

ECHA concluded that the proposed metabolism is in line with known biochemical pathways, but not excluding other possibilities. Information from the public domain ([redacted]) indicates that the registered substance and the read-across substances will not necessarily break down completely to the same [redacted]. Therefore, the registered substance and the read-across substances will not break down to similar breakdown products. On this basis ECHA considers that neither the registration dossier nor the Registrant's comments to the draft decision contain sufficient evidence on common breakdown products.

Genetic toxicity: *in vitro* gene mutation in mammalian cells

The Registrant has submitted mutagenicity studies conducted with the registered substance (Ames test and *in vitro* cytogenicity study in mammalian cells) and the proposed read-across substances (Ames test, *in vitro* gene mutation test in mammalian cells and *in vivo* micronucleus test). The Registrant claims that there was no evidence of mutagenic or clastogenic intrinsic properties in any of the studies. The carboxylic acid moiety would be independently from the chain length and degree of unsaturation considered not to be genotoxic, and therefore the genotoxic potential of the whole group of [redacted] is assumed to be similar.

Pursuant to Annex VIII, section 8.4.3., an *in vitro* gene mutation study in mammalian cells must be provided in case of a negative result of the *in vitro* cytogenicity study and the *in vitro* gene mutation study in bacteria. ECHA

concluded that the registered substance contains a toxicological alert for genotoxicity, resulting from one of the potential breakdown products ([redacted]), which is not present in the proposed read-across substances. This alert together with dissimilarities with the proposed read-across substances does not allow drawing firm conclusions for the genotoxic potential of the registered substance. Therefore, an *in vitro* gene mutation test in mammalian cells is missing and is necessary to fulfill the REACH information requirement in section 8.4.3, Annex VIII of the REACH Regulation.

Pre-natal developmental toxicity and sub-chronic toxicity studies

The Registrant has provided a prenatal developmental toxicity study conducted with the proposed read-across substance [redacted], three oral repeated dose toxicity studies (28-day and two 90-day studies) conducted with the proposed read-across substances, and 28-day dermal study conducted with the registered substance. The Registrant concludes that there is no evidence for an intrinsic developmental toxicity/teratogenicity and systemic repeated dose toxicity for long chain [redacted].

ECHA concluded that maternal toxicity (e.g. decreased body weight change, reduced food consumption, effects in stomach mucosa and reduced gravid uterus weight) and fetal toxicity (e.g. increased number of resorptions, reduced fetal weight and number of viable fetuses) was observed in the developmental toxicity study at the highest dose tested (1000 mg/kg bw/day). No effects were seen in the oral 28-day and 90-day studies with the proposed read-across substances, and in the dermal 28-day study with the registered substance. In the oral repeated dose toxicity studies, the highest dose tested was 300 mg/kg bw/day. Therefore, there is remaining uncertainty for possible effects at higher concentrations.

It can be concluded that the toxicological profile concerning systemic and reproductive toxicity and genotoxicity of the registered substance, although it is similar to the read-across substances regarding the [redacted], can be different from that of the read-across substances due to:

(i) the presence of the [redacted] moiety in the registered substance,
(ii) the potential of formation of [redacted] from the registered substance,
(iii) the incomplete breakdown of the [redacted] in the long-chain part of the proposed read-across substances.

Therefore, the read-across justifications provided by the Registrant do not meet the similarities as set out in Annex XI, 1.5 of the REACH Regulation. The Registrant is requested to submit the information listed in Section II above to bring the registration dossier into compliance with the relevant REACH information requirements.

IV. General instruction on the update of dossiers of previously notified substances

Pursuant to Article 111 of the REACH Regulation, the requested information should be submitted to ECHA in the form of an IUCLID dossier update. You can find instructions on the submission of the dossier update in the Question and Answers document for the registrants of previous notified substances published on the ECHA website on the following link: http://echa.europa.eu/doc/reachit/prev_not_sub_Registrants_qa.pdf. In addition we also advise you to consult the Data Submission Manual No 5, Annex 4, "Minimum information required for updating a registration under previous directive", in the section "Other updates", available at: http://echa.europa.eu/reachit/registration-it_en.asp.

These reference documents include information on possible alternative means that can be used in place of robust study summaries, i.e. that under certain circumstances study summaries can be sufficient when submitting a dossier update.

V. 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 1907/2008 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.

VI. 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. The procedure is described in the Board of Appeal's "Preliminary instructions to Appellants" that can be found at the ECHA website. 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,

[redacted]

Jukka Malm
Director of Regulatory Affairs