EUROPEAN CHEMICALS AGENCY

Helsinki, 13 June 2012

Decision number: CCH-D-0000002254-81-04/F

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

For 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 the ECHA has performed a compliance check of the registration dossier for [redacted] submitted by [redacted] (Registrant), latest submission number [redacted] for 100 – 1000 tonnes per year.

The compliance check was initiated on 29 June 2011.

On 25 August 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. The draft decision referred to submission number [redacted].

On 23 September 2011 the Registrant provided to ECHA comments on the draft decision. On 24 October 2011 the Registrant updated his registration dossier (submission number [redacted]).

ECHA reviewed the further information received and amended the draft decision accordingly.

On 20 January 2012 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 of the receipt of the notification. Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision.

ECHA reviewed the proposals for amendment received and amended the draft decision accordingly.

On 23 February 2012 ECHA communicated the proposals for amendment to the Registrant and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

The Registrant did not provide comments on the proposals for amendment within 30 days (i.e., by 26 March 2012). Comments were provided after the deadline, on 27 March 2012, and could therefore not be taken into account by the Member State Committee.

On 5 March 2012, the draft decision was referred to the Member State Committee.

A unanimous agreement of the Member State Committee on the draft decision was reached on 11 April 2012 in a written procedure launched on 28 March 2012.

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

II. Information required

1) Pursuant to Articles 41(1)(a), 41(3) and 10(a)(ii) as well as Annex VI, section 2 of the REACH Regulation, the Registrant shall submit for the registered substance:

   a. The name of the substance (Annex VI, 2.1.1) as specified under section III.1)(a) below;
   b. The structural formula (Annex VI, 2.2.1), as specified under section III.1)(b) below; and
   c. The composition (Annex VI, 2.3): Any information which is suitable and necessary to allow ECHA to establish and verify the composition and the name of the registered substance, as specified under section III.1)(c) below.

2) Pursuant to Articles 41(1)(a) and (b), 41(3), 10(a)(vii), 12(1)(d), 13 and Annexes VII, VIII and IX of the REACH Regulation the Registrant shall submit the information using the test method as indicated on:

   a. Mutagenicity, *in vitro* gene mutation study in bacteria (Annex VII, 8.4.1; EU test method B.13/14. or OECD guideline 471);
   b. Mutagenicity, *in vitro* cytogenicity study in mammalian cells (Annex VIII, 8.4.2, EU method B.10 or OECD guideline 473) or in vitro micronucleus study (Annex VIII, 8.4.2.; OECD guideline 487);
   c. Mutagenicity, *in vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3; EU test method B.17 or OECD guideline 476), provided that there is a negative result in the studies requested under 2)a. and 2)b;
   d. Screening for reproductive/developmental toxicity in rats, oral route (Annex VIII, 8.7.1, OECD guideline 421); and
   e. Pre-natal developmental toxicity, one species, oral (Annex IX, 8.7.2, EU test method B.31 or OECD guideline 414).

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 **13 December 2013**.

The Registrant shall determine the appropriate order of the studies taking into account the possible outcomes and considering the possibilities for adaptations of the standard information requirements according to column 1 or 2 provisions of the relevant Annexes of the REACH Regulation. The Registrant shall consult the Guidance on information requirements and chemical safety assessment (Version 1.1, May 2008, Chapter R.7.A, Section R.7.6.6.3, page 365) to follow the integrated testing strategy for reproductive toxicity testing. In general, it should be noted that the OECD TG 414 (EU B.31) study does

not incorporate post-natal parameters and therefore it is advisable not to bypass the screening study when a prenatal developmental toxicity study is triggered.

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

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 VI, VII, VIII, IX 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.

1) Missing information related to substance identity

Pursuant to Article 10(a)(ii) and Annex VI, section 2 of the REACH Regulation, the technical dossier of the registration shall include information on the identity of the substance. Annex VI, section 2 lists information requirements that shall be sufficient to identify the registered substance.

a) Name of the substance (Annex VI, 2.1.1):

ECHA notes that the Registrant identified the registered substance as of Unknown or Variable composition, Complex reaction products or Biological materials (UVCB). ECHA observes that the chemical name assigned to the substance, as required under Annex VI section 2.1.1 of the REACH Regulation, is not representative of the structural information derived from the analytical data attached to the dossier.

More specifically, the Registrant has provided a chemical name which indicates that the registered substance predominantly consists of [redacted] having a [redacted] substituent at an undefined position on the [redacted]. However, ECHA observes that the Registrant has also provided a gas chromatography-mass spectrometry (GC-MS) and nuclear magnetic resonance (NMR) analysis of the [redacted] precursor, which clearly indicates that the [redacted] are in para position one to each other in the [redacted]. Therefore, considering also the indicated manufacturing process description reported in IUCLID section 3.1, it is expected that the relative position of the [redacted] groups in the constituents of the registered substance will be maintained. Nevertheless there is uncertainty related to the position of the [redacted] group which can be found either in meta or ortho position with respect to the [redacted] ECHA therefore concludes that the provided chemical name does not correctly represent the registered substance.

The Registrant is requested to amend the name of the registered substance in order to take into account the information on the position of the [redacted] groups in the [redacted] The Registrant shall ensure that the chemical name is representative of the composition. For this purpose, the predominance of the [redacted] and the carbon number distribution of the [redacted] substituents shall be taken into account.

As for the reporting of the information in IUCLID, the amended chemical name of the registered substance shall be provided in the IUPAC name field in IUCLID section 1.1. Any

available CAS entry specifically corresponding to the registered substance shall be reported under the CAS information header of the reference substance in IUCLID section 1.1.

The updated information on name of the substance and other identifiers should be taken into account also in other relevant sections of the technical dossier as well as the chemical safety report.

b) Structural formula (Annex VI, 2.2.1):

ECHA notes that the structural information specified by the registrant is not representative of the registered substance.

More specifically, the Registrant has provided structural information of the registered substance "[redacted]" showing the [redacted] group in position 2 with respect to the [redacted] substituent. Moreover, the structural formula indicates an undefined position of the [redacted]. As already described under point III.1)(a) above, the information on the starting material indicates that the [redacted] are in para position in the [redacted] and that the [redacted] group can lay in up to two possible positions. ECHA therefore concludes that the indicated structural information does not provide an appropriate representation of the registered substance.

The Registrant is accordingly requested to amend the structural formula in order to take into account the relative position of the different substituents in the benzene ring.

As for the reporting of the information in IUCLID, the structural representation of the registered substance shall be reported in the appropriate field of the reference substance in IUCLID section 1.1.

c) Composition of the registered substance (Annex VI, 2.3):

The substance composition corresponds to the chemical representation of what the substance consists of and is therefore an essential part of substance identification and the corner stone of all the REACH obligations.

ECHA notes that the registration dossier does not contain appropriate and sufficient information for establishing the composition of the registered substance and therefore its identity, as required under Annex VI, Section 2.3 of the REACH Regulation.

More specifically, the Registrant has specified that the registered UVCB substance predominantly consists of [redacted] presenting a branched [redacted] substituent at an undefined position in the [redacted]. As already described under point III.1)(a) above, the information on the starting material indicates that, for this group of constituents, the relative position of the substituents on the [redacted] is not correctly represented.

In addition, ECHA notes that the GC-MS analysis, attached in the dossier, indicates that the [redacted] substituent of the [redacted] presents a carbon number distribution from at least [redacted]. However, ECHA points out that the dossier does not include verifiable quantitative information on the distribution of the carbon number range. In particular, the description of the GC-MS analysis used by the registrant to determine that distribution in the starting material is not sufficiently detailed as it is unclear how the registrant differentiated between the constituents having different carbon numbers. Moreover, the

dossier does not include information on the concentration ranges of the constituents presenting the same carbon number. ECHA points out that this information is necessary to understand the variability of the composition in the substance.
Furthermore, ECHA observes that the registrant has not provided any quantitative information on the relative content of the [redacted] regioisomers with the [redacted] substituent in ortho or meta position relative to the [redacted] group. ECHA points out that the behaviour/response of such regioisomers, including the [redacted] constituents present in the registered substance or the aldehyde precursors, is expected to differ to such extent that quantitative information on the relative regioisomeric content can be determined, using techniques such as NMR spectroscopy or chromatography.
ECHA therefore concludes that the compositional information reported in the dossier is neither appropriate nor sufficiently detailed.

Following section 4.3 of the Guidance for identification and naming of substances under REACH (version 1.1)[1], the Registrant should note that, for UVCB substances such as the registered substance, the following applies:

- All constituents present in the substance with a concentration of ≥ 10 % shall be identified and reported individually;
- All constituents relevant for the classification and/or PBT assessment of the registered substance shall be identified and reported individually; and
- Other constituents shall be identified as far as possible by a generic description of their chemical nature. The identification of these other constituents must be provided in order to allow ECHA to establish the composition of the substance as manufactured and to use the compositional information as one identifier for the registered substance.

For the substance which is the subject of this registration, the reporting of the [redacted] groups of constituents and any other appropriate group of constituents according to the carbon number of the branched [redacted] substituent is necessary. For each group of [redacted] constituents, the relative ratio of regioisomers (i.e. the "[redacted]" ratio) shall be indicated.

For each constituent and group of constituents required to be reported, the typical, minimum and maximum concentration level shall be specified.

In line with the above, the Registrant is requested to provide any information which is suitable and necessary to allow ECHA to establish and verify the composition and the name of the registered substance.

Regarding how to report the composition of the registered substance in IUCLID, further technical details are available in paragraphs 2.1 and 2.2.2 of the Data Submission Manual 18 (1. version 06/2010) on the ECHA website.[2]

The registrant shall also ensure that the compositional information is verifiable and therefore supported by qualitative and quantitative analytical data, as required under Annex VI section 2.3.7. The description shall be sufficient for the methods to be reproduced and shall therefore include details of the experimental protocol followed, any calculation made and the results obtained.

2) Missing information related to endpoints

[1] http://echa.europa.eu/web/guest/guidance-documents/guidance-on-the-different-methods-under-reach
[2] http://echa.europa.eu/web/guest/support/dossier-submission-tools/reach-it/registration

Pursuant to Articles 10(a)(vii) and 12(1)(d) of the REACH Regulation, a registration for a substance produced in quantities of 100 – 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

2.1. The technical dossier provided information originating from another substance ([redacted]) than the registered substance on the following endpoints:

a) Mutagenicity, *in vitro* gene mutation study in bacteria (Annex VII, 8.4.1.; and

b) Mutagenicity, *in vitro* cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, 8.4.2.).

c) Mutagenicity, *in vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3.)

a) Mutagenicity, in vitro gene mutation study in bacteria and
b) Mutagenicity, in vitro cytogenicity study in mammalian cells or in vitro micronucleus study.

Article 13(1), the fourth introductory paragraph of Annex VII and the second introductory paragraph of Annex VIII require to clearly state reasons for adapting the standard information according to the rules in Annex XI. More specifically, Annex XI, section 1.5. provides that substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances. Application of the group approach requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) by interpolation to other substances in the group (read-across approach).

The Registrant has justified the structural similarity with comparison of the analytical reports for the registered substance which is subject to this decision with the substance that has been tested in the in vitro mutagenicity tests. In addition he has stated that the chemical syntheses to produce these two UVCB substances are identical. ECHA notes that the Registrant has not supported the read across with any comparison of the toxicological properties for the registered substance and the substance that has been tested. Furthermore, there is no genetic toxicity data for the registered substance allowing comparison of the genotoxic properties of the two substances. These justifications do not allow ECHA to conclude that the genotoxic properties of the registered substance can be reliably predicted from the data available for the analogue substance. Therefore the requirements of Annex XI, section 1.5. in conjunction with Annex VII, fourth introductory paragraph, and Annex VIII second introductory paragraph, of the REACH Regulation are not met.

The Registrant is accordingly requested to submit the information for those endpoints on the registered substance.

c) Mutagenicity, in vitro gene mutation study in mammalian cells.

No information on an *in vitro* or *in vivo* gene mutation study in mammalian cells has been submitted with the registered substance. According to Annex VIII, section 8.4.3 of the REACH Regulation, the *in vitro* gene mutation study in mammalian cells is required if there is a negative result in the *in vitro* studies specified under Annex VII, section 8.4.1 and

Annex VIII, section 8.4.2, and if adequate and reliable data from an *in vivo* mammalian gene mutation test are not available.

For this endpoint the technical dossier provided information originating from another substance [redacted] than the registered substance. For the reasons explained under points 2 a) and b) above, ECHA concludes that the requirements of Annex XI, section 1.5. in conjunction with Annex VIII second introductory paragraph, of the REACH Regulation are not met.

The Registrant is accordingly requested to submit the information for those endpoints on the registered substance, provided there is a negative result in the studies requested under II. 2)a. and II. 2)b.

2.2. The technical dossier contained adaptations to the standard information requirements for the endpoints on:

d) Screening for reproductive/developmental toxicity, one species, rat (Annex VIII, 8.7.1)
e) Pre-natal developmental toxicity (Annex IX, 8.7.2.).

d) Screening for reproductive/developmental toxicity, in rats oral route (Annex VIII, 8.7.1)

The Registrant is justifying the omission of this information requirement with the fact that the registered substance contains as impurity [redacted], a potential toxicant to reproduction, and therefore the outcome of a study would be predictable. The Registrant has therefore by way of precaution classified the registered substance as R 62 (Repro Cat 3 according to Annex VI of Directive 67/548/EEC and Repr. 2 according to Annex I of Regulation (EC) No 1272/2008).

The justification for waiving provided by the Registrant does not meet the conditions of Annex VIII, Column 2, 8.7.1 or those of Annex XI. The Registrant is accordingly requested to submit the missing information for the screening study on reproductive/developmental toxicity (rat, oral route) for the registered substance by using OECD TG 421

e) Pre-natal developmental toxicity (Annex IX, 8.7.2).

The Registrant is justifying this adaptation of the standard information requirements with a weight of evidence argument based on the following facts: (1) The registered substance contains as impurity [redacted] a close homologue of [redacted] which has a harmonised classification as Repro Cat 3, R62/R63 according to Annex VI of Directive 67/548/EEC (and Repr. 2 H361d according to Annex I of Regulation (EC) No 1272/2008) and therefore the outcome of pre-natal developmental toxicity study would be predictable. The Registrant has therefore classified the registered substance by way of precaution as R62. (2) Any further test results from a pre-natal developmental toxicity study would not have consequences beyond classification as R62/R63. (3) The registered substance is used only in two sites both having strict risk management measures in place and indirect exposure via environment being well below the threshold of toxicological concern.

ECHA notes that according to column 2 of Annex IX section 8.7., the following classification and labelling based adaptations apply for not conducting the pre-natal developmental toxicity study:

The substance is known to have adverse effect on fertility, meeting the criteria for classification as Repr Cat 1 or 2; R60 (category 1A or 1B: May damage fertility (H360F) under CLP Regulation), and the available data are adequate to support robust risk assessment. However, testing for developmental toxicity must be considered.

The substance is known to cause developmental toxicity, meeting the criteria for classification as Repr Cat 1 or 2; R61 (category 1A or 1B: May damage the unborn child (H360D) under CLP Regulation), and the available data are adequate to support robust risk assessment. However, testing for effects on fertility must be considered.

ECHA notes further that [redacted] of the registered substance and the registrant has provided no evidence that in a pre-natal developmental toxicity study, the remaining constituents could not have toxicological properties leading to a classification more severe than R62/R63.

ECHA notes that the exposure considerations meet neither the conditions of Annex XI section 3.2(a) nor those of Annex XI section 3.2(b). Annex XI section 3.2 (a)(ii) conditions concerning the derivation of a no-effect level (DNEL) are not met because there are no appropriate data available to derive the DNEL covering the pre-natal developmental toxicity for the registered substance. Conditions of Annex XI section 3.2 (b) are not met because the Registrant has not demonstrated and documented strictly controlled conditions for all relevant scenarios as set out in Article 18(4) of the REACH Regulation. The highest risk characterisation ratios (RCR) reported are of the order of 0.6, and the Registrant has not demonstrated rigorous containment by technical means for such exposure scenarios.

Due to the lack of several individual sources indicating certain substance properties as stipulated by Annex XI, 1.2 of the REACH Regulation, ECHA concludes that the above arguments do not constitute a weight of evidence that sufficiently covers the end-point of pre-natal developmental toxicity study. Therefore the Registrant is requested to submit the information for this endpoint on the registered substance.

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 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.

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