ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000001733-76-05/F Helsinki, 31 January 2012

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

For Reaction products of benzeneamine, N-phenyl- with nonene (branched), 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 testing proposals set out in the registration dossier for Reaction products of benzeneamine, N-phenyl- with nonene (branched), submitted by [redacted] latest submission number [redacted] for > 1000 tonnes per year.

In accordance with Articles 10(a)(ix) and 12(1)(e) of the REACH Regulation, the Registrant submitted the following testing proposals as part of the registration dossier to fulfil the information requirements set out in Annex IX and X:

> Repeated Dose 90-Day Oral Toxicity Study in Rodents (OECD 408)
> adjusted by additionally testing methemoglobin formation in dosed, recovery and control group animals. Testing material proposed is *benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene*.
>
> AND
>
> One-Generation Reproduction Toxicity Study (OECD 415)
> in rodents using oral application. If there are serious findings in the first generation prolongation to a second generation is considered. Testing material proposed is *benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene*.

The present decision relates solely to the examination of the testing proposal for the Repeated Dose 90-Day Oral Toxicity Study in Rodents. The testing proposal for a One-Generation Reproductive Toxicity Study will be addressed in a separate decision although both testing proposals were initially addressed together in the same draft decision.

The examination of the testing proposals was initiated upon the date when receipt of the complete registration dossier was confirmed on 8 October 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 2 March 2011 until 14 April 2011. ECHA received the following information from third parties (TPI):

Before an oral sub-chronic toxicity study (OECD Guideline 408), and a Two-Generation Reproduction Toxicity Study (OECD Guideline 416) is conducted, consideration should be given to the following alternative testing strategies:

a. *Evaluate the need to conduct an oral sub-chronic toxicity study (OECD Guideline 408) and a Two-Generation Reproduction Toxicity Study (OECD Guideline 416) in light of the results of the existing combined repeated dose and reproduction/developmental screening tests with related substances (read-across) and other toxicological data.*
b. *Perform in vitro (pre-) validated tests for the evaluation of the endocrine disruption potential.*
c. *Conduct a sub-chronic toxicity study (90-day oral Toxicity Study, OECD Guideline 408) with additional reproduction toxicity parameters instead of a two-generation reproductive toxicity study (OECD Guideline 416).*
d. *Conduct an Extended One Generation Reproductive Toxicity Study (EOGRTS) and use results to waive a Two-Generation Reproduction Toxicity Study (OECD 416).*
e. *Exposure considerations: use the TTC for repeated dose and reproduction toxicity end points.*

ECHA examined the testing proposal and the information received from third parties and drafted a decision in accordance with Article 40 of REACH.

On 5 July 2011 ECHA notified the Registrant of its draft decision and invited him pursuant to Article 50(1) of the REACH Regulation to provide comment on the draft decision.

On 4 August 2011 the Registrant provided to ECHA comments on the draft decision. ECHA reviewed the further information received and amended the draft decision accordingly.

On 2 September 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, Competent Authorities of the Member States submitted proposals for amendment to the draft decision. ECHA reviewed the proposals for amendment received and decided to amend the draft decision accordingly.

On 5 October 2011 ECHA notified the Registrant of the proposals for amendment to the draft decision 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.

On 17 October 2011 ECHA referred the draft decision to the Member State Committee.

On 4 November 2011 the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 7-9 December 2011, the draft decision was split into two draft decisions, one relating to the testing proposal for a One-Generation Reproduction Toxicity Study and another relating to the testing proposal for a Repeated Dose 90-Day Oral Toxicity Study in Rodents.

Unanimous agreement of the Member State Committee on the draft decision relating to the testing proposal for a Repeated Dose 90-Day Oral Toxicity Study in Rodents was reached on 9 December.

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)(c) of the REACH Regulation, the Registrant shall carry out the following tests on the registered substance concerned by the present decision *"reaction products of Benzeneamine, N-phenyl- with nonene (branched)"* using the indicated test method:

> Sub-chronic toxicity study (90-day) (Annex IX, 8.6.2, EU Method B.26) in rat by the oral route additionally testing methemoglobin formation in dosed, recovery and control group animals;

while the originally proposed test on *"benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene"* is rejected.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by 31/07/2013 an update of the registration dossier containing the information required by this decision.

In the draft decisions communicated to the Registrant the time indicated to provide the requested information was 24 months from the date of adoption of the decision. This period of time took into account the fact that the draft decisions also requested a 2-generation reproductive toxicity study. As the testing proposal for this study is not addressed in the present draft decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 18 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

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 concerned by the present decision and scientific information submitted by third parties.

A sub-chronic toxicity study (90-day) is a standard information requirement of Annex IX, 8.6.2 at the present tonnage level. ECHA notes that this standard information is not available in the present registration dossier, but a testing proposal concerning a sub-chronic toxicity study (90-day) additionally testing methemoglobin formation in dosed, recovery and control group animals using *"benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene"* as test material has been made.

ECHA has examined the information submitted by third parties, as follows:

> The third party has proposed five testing strategies (a, b, c, d, and e, as referred to under section I above) 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) of the REACH Regulation,

and the proposal for a strategy cannot be considered as such information. Consequently, ECHA concludes that this is not a sufficient basis for rejecting the testing proposed.

ECHA observes that in his testing proposal the Registrant has suggested an adaptation of the need to test the registered substance as concerned by the present decision, by using *"benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene"* as test material according to Annex XI, 1.5. Taking into consideration the comments provided, the Registrant has failed to provide adequate and reliable documentation of the applied method (see ECHA Guidance R.6.2 and particularly R.6.2.6) and has failed to demonstrate that the human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group, as required by Annex XI, Section 1.5. governing grouping of substances and read-across approach.

The possibility to predict the results of a sub-chronic toxicity study (90-day) for the registered substance as concerned by the present decision from the results of such a study performed with the reference substance is essentially based by the registrant on the following, as interpreted by ECHA from the documentation provided by the registrant. Differences in toxicity between the registered substance and the reference substance are assumed to be only the result of differences in absorption and thus, systemic exposure. The differences in absorption are in their turn assumed to be the result of the differences between the alkyl chains attached to the phenyl rings. The toxicity of the two substances is further assumed to be entirely determined by the diphenylamine moiety of the substances and not to be influenced by the differences between the alkyl side chains attached to the phenyl rings. The reference substance is assumed to represent a worst-case because its absorption is assumed to be higher than the absorption of the registered substance.
In the documentation provided by the registrant ECHA does not find scientific data or scientific argumentations that allow ECHA to agree with these assumptions to the extent that the proposal to test the reference substance in stead of the registered substance for sub-chronic toxicity (90-day) can be accepted. Other differences in the toxicokinetics or toxicodynamics between the two compounds have not been addressed.

Consequently, the adaptation according to Annex XI, 1.5, fails.
In addition, ECHA notes that the Registrant has not presented any justifications referred to in Column 2 of Annex IX, 8.6.2 to omit the information requirement with the registered substance concerned by the present decision. ECHA considers therefore that testing *benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene* would be insufficient to meet the information requirement concerning sub-chronic toxicity of Annex IX, 8.6.2 for the registered substance.

As evidence for effects on hematology has been presented in the dossier and the proposed parameter is integral part of EU Method B.26, the proposal for inclusion of testing of the methemoglobin formation in dosed, recovery and control group animals is accepted.

Accordingly, the Registrant is requested to provide information on the Annex IX, 8.6.2 endpoint by carrying out a sub-chronic toxicity study (90-day) in rat by the oral route by using EU Method B.26. with the registered substance *"reaction products of benzeneamine, N-phenyl- with nonene (branched)"* as test material additionally testing methemoglobin formation in dosed, recovery and control group animals.

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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]
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