ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 23 March 2017

Addressee: [redacted]

Decision number: CCH-D-2114354729-36-01/F
Substance name: N-1,3-DIMETHYLBUTYL-N'-PHENYL-P-PHENYLENEDIAMINE
EC number: 212-344-0
CAS number: 793-24-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 02.03.2016
Registered tonnage band: 1000+T

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA requests you to submit information on

1. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit), oral route with the registered substance;**

2. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **30 March 2020**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[1] by Claudio Carlon, Head of Unit, Evaluation E2

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

ECHA's evaluation and conclusion of the information in the technical dossier

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material.

In the technical dossier you have also provided a study record for a pre-natal developmental toxicity study in rabbits by the oral route with the registered substance ("[redacted] 1976b"). However, this study does not provide the information required by Annex X, Section 8.7.2., because the study is to be considered as inadequate under Article 13(3) of the REACH Regulation since it is not 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 Agency as being appropriate, specifically OECD test guideline 414/ EU B.31. More specifically, the health of the animals was poor and mortality occurred in all groups, resulting in 10 to 13 surviving pregnant animals per group (mortality was 5/17 in controls and 3/17 or 6/23 in low-and high-dosed animals, respectively). The OECD 414 guideline states "Maternal mortality does not necessarily invalidate the study providing it does not exceed approximately 10 percent." This level has been exceeded and the study is invalid. Also the numbers of pregnant females were lower than 16 per group, which is recommended in the OECD 414 guideline. Annex XI, 1.1.2 describes conditions for the use of "Data on human health and environmental properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3)". ECHA considers that the two deficiencies listed above mean that there is not adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), as required under Annex XI, 1.1.2. Furthermore, this study has been performed by [redacted] in 1976, before GLP was introduced as requested under Article 13(4) of REACH. A routine inspection by FDA in 1976 uncovered numerous discrepancies between raw data and study reports, and gross deficiencies in study conduct. Problems were uncovered in studies conducted during the 1960's and until 1978. According to an OECD "*Guidance for determining the Quality of Data for SIDS Dossiers*", for studies conducted during the suspected period, the assumption should be that they are potentially invalid and the findings are unreliable. Expert judgement is required on a case by case basis to judge how those data should be used. Furthermore, information should be provided if and by whom the study has been audited (see http://www.oecd.org/chemicalsafety/risk-assessment/36045203.pdf).

ECHA notes that you did not provide any information on the validity of this study. ECHA considers that there is therefore a failure to satisfy the requirement of Annex XI, 1.1.2 that adequate and reliable documentation of the study is provided. Considering the failure to meet the requirements of Annex XI, 1.1.2, ECHA cannot accept the provided information as appropriate to fulfil the standard information requirement.

ECHA's evaluation and conclusion of the comments on the draft decision

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you indicated that "*As outlined in the dossier there is no indication of developmental toxicity in the available limited rabbit study even at dose levels exceeding the Maximum Tolerated Dose. Since the comprehensive available data in rats and the limited data in rabbits do not indictate developmental toxicity, the registrant believes that the requested study is likely to have no impact on the human risk assessment and, consequently, should be of low priority for vertabrate testing taking into account animal welfare considerations. We therefore request the ECHA to consider removing this requirement from the Decision, awaiting the outcome of the OECD 433 test. If then required, a testing proposal can be submitted by the lead registrant.*"

ECHA notes that, as explained above, the provided study in rabbits is invalid, especially due to the high mortality in this study, it is not appropriate to conclude that "*there is no indication of developmental toxicity*". Hence, it is not possible to judge on the impact of a valid pre-natal developmental toxicity study in rabbits on human risk assessment. Hence, there is a data gap for standard information and as you are already requested to perform the study, there is no need to submit a testing proposal.

ECHA further notes that the timeline provided allows for sequential testing and that it is your responsibility to decide on the order of testing. If you consider that based on the results of the first test no further testing is required, you need to provide a scientific justification, referring and conforming to the appropriate rules in the respective Annex of the REACH Regulation, including an adequate and reliable documentation.

Conclusion

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement of Annex X, Section 8.7.2. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The test in the first species was carried out by using a rodent species (rats). According to the test method EU B.31./OECD 414, the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbits as a second species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.
Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rabbit) by the oral route.

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information requirement

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

You have sought to adapt this information requirement according to Annex XI, Section 1.2., on weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this adaptation.

Information you provided as weight of evidence in the technical dossier

You have provided in the IUCLID section 7.8.1. the following information:

- Reproduction/developmental toxicity screening test in rats (OECD TG 421; GLP), [redacted]. 2001 (publication), Rel. 1, NOAEL mat/dev 100 mg/kg bw/d (highest dose tested);
- Three generation reproduction study in rats (non-guideline, non-GLP), [redacted] 1980 (IBT study), Rel. 2, NOAEL 75 mg/kg bw/d (highest dose tested);
- Chronic toxicity study chronic oral study in rats (OECD TG 452; non-GLP) [redacted] 1993 (Bio/dynamics study), Rel. 2, NOAEL 84-110 mg/kg bw/d (highest dose tested), limited reporting;
- Chronic toxicity and reproduction studies on rubber antiozonants (no guidelines mentioned), [redacted] (undated) / Stevens et al. 1981 (published abstract); Rel. 2, insufficient reporting;
- Reproduction/developmental toxicity screening test (OECD TG 421), [redacted] 2009 (study report), Rel. 4 ("*The overall assessment of the study is that the study has deficits in retrieval, presentation and interpretation of data which render reliability of data debatable*").

ECHA notes that you have not provided a conclusion of your weight of evidence adaptation. ECHA understands that you conclude that the substance does not have a dangerous property with respect to reproductive toxicity.
ECHA's evaluation and conclusion of the provided information as weight of evidence in the technical dossier

ECHA has evaluated your weight of evidence information according to REACH Annex XI, Section 1.2., and assessed whether you have provided "*sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that the substance has or has not a particular dangrous property*" with respect to the information requirement of Annex X, Section 8.7.3. for the registered substance (see 'specification of the study design').

ECHA has further evaluated the information according to ECHA Guidance R.4.4. by considering whether the criteria given in that guidance i.e. relevance, reliability and adequacy for the purpose apply to the information you have provided. ECHA has also evaluated whether the provided information is consistent and covers the relevant aspects of information on "sexual function and fertility" in parental P0 and F1 generation and on "developmental toxicity" observable peri- and postnatally in F1 generation as specified at Annex X, Section 8.7.3.

ECHA notes that the three-generation reproduction toxicity study [redacted] 1980) cannot be regarded as reliable and adequate. More specifically, you indicated that "*Mortality of parental animals was excessively high throughout the study. However, these mortalities occurred in all study groups and were not considered related to treatment.*" ECHA notes that you did not report the incidences of mortalities and incidences of effects.

Since the study was performed with a relatively low number of 8 male and 16 female animals per group (compared to sufficient number of mating pairs to yield at least 20 pregnant females per dose group in an extended one-generation reproductive toxicity study), and the number of animals that died or were of poor health were not reported, it is not possible to evaluate those effects independently. ECHA further notes that reduced fertility indices (F1b male fertility and F2a female fertility) and reduced pup survival indices (F1b, F2a, F3a, and F3b litters) were reported in the mid dose group. Those effects were reported to be attributed to the poor health of the parent animals. No tables on these observations were provided. Furthermore, this study has been performed by [redacted] According to the number of this study ([redacted]), it can be assumed that this test was performed in the year 1976 prior to the introduction of GLP as requested under Article 13(4) of REACH. As mentioned above for studies conducted during the suspected period (1960 - 1978), the assumption should be that they are potentially invalid and the findings are unreliable. Expert judgement is required on a case by case basis to judge how those data should be used. ECHA notes that you have scored the reliability of the study as 2 but you do not provide any information on the auditing of this study (see request 1) to support the reliability scoring. Considering the high mortality, the low number of animals used for this test and high uncertainty of the validity of this study, it cannot be regarded as reliable and adequate source of weight of evidence information. Therefore, this study is considered invalid and the findings unreliable and not accepted as a piece of information in a weight of evidence adaptation.

ECHA notes that the information you provided on "Chronic toxicity and reproduction studies on rubber antiozonants" is insufficiently reported. More specifically, no details on the method of the performed test and the results were provided. Therefore, this information cannot be accepted as a piece of information in a weight of evidence adaptation.

ECHA also notes that you have provided information on an Reproduction/developmental toxicity screening test (OECD TG 421; [redacted] 2009) for which you assigned reliability 4 and commented that "*the study has deficits in retrieval, presentation and interpretation of data which render reliability of data debatable.*" ECHA acknowledges that you have provided information on another OECD TG 421 screening study for which you assigned reliability 1. ECHA has taken this information into consideration below.

With respect to the aspect of "sexual function and fertility" of P and F1 generation, you have provided information on histopathological changes in major reproductive organs from a reliable OECD TG 421 screening study and information from a non-GLP chronic toxicity study of limited reporting (OECD TG 452). You have also provided reliable information on male and female reproductive performance such as gonadal function, mating behaviour, conception, development of the conceptus and parturition (OECD TG 421 screening study). However, ECHA notes that the statistical power of this study is lower than that of the extended one-generation reproductive toxicity study, the premating exposure duration is shorter, not covering the spermatogenesis and folliculogenesis before mating, and certain investigations are not included, such as histopathology of the reproductive organs in F1 animals in adulthood, precoital interval, thyroid hormone and oestrous cycle measurements in F1 animals. Furthermore, you did not provide information on sperm parameters in P and F1 generations. Hence, while the provided information gives some indication that the substance might not have a dangerous property with respect to sexual function and fertility, it does not give sufficient confidence for a conclusion.

With respect to "developmental toxicity" observable during peri- and postnatal period, you provided very limited reliable information. The OECD TG 421 screening study investigates developmental toxicity only until postnatal day 4. An extended one-generation reproductive toxicity study provides extensive information on developmental toxicity observable during pre- and postnatal period until adulthood. This information includes growth, survival/mortality, certain external malformations, investigations related to hormonal modes of action (anogenital distance, nipple retention, thyroid hormone measurements) and sexual maturation. Hence, you did not provide reliable information to support your assumption/conclusion that the substance does not have a dangerous property with respect to developmental toxicity observable during peri- and postnatal period.

ECHA concludes that the evidence you provided to adapt the information requirement for an extended one-generation reproductive toxicity study based on Annex XI, Section 1.2., either alone or together, does not sufficiently cover the aspects of the reproductive toxicity, which are relevant for addressing information requirement of Annex X, Section 8.7.3, the extended one-generation reproductive toxicity study.

Therefore, to conclude on the weight of evidence adaptation you have proposed, ECHA considers that you did not provide enough information which is reliable and give confidence to support your assumption/conclusion that the substance does not have a dangerous (hazardous) property with respect to the information requirement of Annex X, Section 8.7.3. for the registered substance (see 'specification of the study design'). Therefore, your adaptation of the information requirement is rejected.

ECHA's evaluation and conclusion of the provided information as weight of evidence in your comments

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you provided the following arguments: *"A chemically similar substance N-(1,4-dimethylpentyl)-N'-phenylbenzene-1,4-diamine (7PPD, CAS 3081-01-4) was evaluated by Austria in the CoRAP in 2012 (final Decision issued on 10 April 2014). This dossier described a comprehensive read-across to 6PPD in particular for the endpoints fertility and developmental toxicity.*

Based on the available data on 6PPD the evaluating member state did not request any human toxicity study for 7PPD. This is in line with our conclusion that the available information is sufficient to conclude that 6PPD is not toxic to fertility or development and the requested study is likely to have no impact on the human risk assessment and, consequently, should be of low priority for vertebrate testing taking also into account animal welfare considerations." Furthermore, you indicated that *"We therefore agree with the study design being limited to the basic study as proposed by ECHA".*

ECHA refers to the discussion on the "available information" above and acknowledges your agreement on an extended-one-generation reproductive toxicity study limited to the basic study design.

ECHA notes your comment on the substance evaluation outcome of the substance 7PPD. ECHA would like to clarify that in a substance evaluation process, the evaluating Member State identifies a concern based on available information. However, in a compliance check, the compliance of the provided information with the legal provisions of Article 41(1)(a) of the REACH Regulation has to be considered, i.e., the information needs to fulfil the standard information requirements of the Annexes III and VI to X.

Conclusion

For the process of dossier evaluation, ECHA considers that the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement of Annex X, Section 8.7.3. Consequently there is an information gap and it is necessary to provide information for this endpoint. Thus, an extended one-generation reproductive toxicity study is required. The following refers to the specifications, *i.e.* the study design, of this required study.

b) The specifications for the study design

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.
If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Species and route selection

According to the test method EU B.56./ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

c) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide the requested information was 30 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline to 36 months. You sought to justify this request by difficulties in performing a study with rabbits. ECHA acknowledges the technical difficulties and has granted the request by seting the deadline to 36 months.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 1 June 2016.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and amended the deadline.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

ECHA received proposal(s) for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-52 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new test(s) must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants. It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new test(s) is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.