ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 25 July 2017

Addressee: [redacted]

Decision number: CCH-D-2114367243-51-01/F
Substance name: N,N'-di-sec-butyl-p-phenylenediamine
EC number: 202-992-2
CAS number: 101-96-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 10.11.2016
Registered tonnage band: 100-1000T

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. **Vapour pressure (Annex VII, Section 7.5.; test method: EU A.4./OECD TG 104) with the registered substance;**

2. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421/422) in rats, oral route with the registered substance;**

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

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to IX and/or according to the general rules contained in Annex XI to the REACH Regulation. 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 adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **1 February 2019**. You also have to 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 and 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, has to 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 Kevin Pollard, Head of Unit, Evaluation E1

[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

TOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for several endpoints adaptation arguments in form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints.

Grouping of substances and read-across approach

You have sought to adapt the information requirements for the following endpoints by applying a read-across approach in accordance with Annex XI, Section 1.5.:

- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation.

The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis.

Description of your grouping and read-across approach

You propose read-across from the substance N, N'-bis(1,4-dimethylpentyl) -p-phenylenediamine (EC No 221-375-9) (hereafter the 'source substance' or '77PD') for each of the above-mentioned information requirements. You conclude that this analogue substance can be used to close data-gaps in the health hazard assessment of the registered substance N, N'-di-sec-butylbenzene-1,4-diamine (EC 202-992-2) (hereafter the 'target substance' or '44PD'), as the target and source substances share the following properties:

(i) (Bio-) chemical reactivity
(ii) Physico-chemical properties (molecular weight, pKa, Log Kow and water solubility)
(iii) Similarities in the toxicological effects

You provide the following rationale for your read-across approach

"The main drivers for systemic toxicity of a substance are the (bio-)chemical reactivity of the substance and its bioavailability, which in itself is determined by the substance's molecular weight, pKa, log Kow and water solubility ([redacted], 2008). 77PD is a structural analogue of 44PD (see also Figure 1 below), and is considered to be a valid read-across substance based on a comparison of these main drivers for systemic toxicity."

In your conclusion you further state that *"Nevertheless, the incomplete match of the toxicity profiles of 44PD and 77PD urges for caution. Furthermore, the difference in toxicological thresholds between 44PD and 77PD is to be taken into account when calculating the DNELs for 44PD."*

Information provided for the read-across approach

For the endpoints mentioned above, you have provided the following study summaries in IUCLID with the source substance twice, once flagged as "read-across from supporting substance" and once with information on the source substance:

- Key study: Three-Generation Reproduction Study with Albino Rats with Santoflex 77, [redacted], 1981, Rel. 2 ("*acceptable documented study report, which meets basic scientific principles, but study with limitations (mortality of parental animals in all study groups was excessively high throughout the study; a large number of treated and control F0 animals were reported as possibly having respiratory infection)*"), $NOAEL_{fertility}$ 22.5 mg/kg bw/day (no adverse effects on fertility), $NOAEL_{parental}$ 7.5 mg/kg bw/day (transient and slight body weight gain reduction during the study), $LOAEL_{parental}$ 22.5 mg/kg bw/day (body weight and body weight gain reduction, reduced liver and kidney weights)
- Key study: Teratology study in rats with Santoflex 77 (according to OECD TG 414), [redacted]., 1986, Rel. 1 with $LOAEL_{maternal}$ 75 mg/kg bw/day (mortality, increased incidence of ptyalism, reduced body weight gain), $NOAEL_{maternal}$ 25 mg/kg bw/day (slight ptyalism), $NOAEL_{developmental}$ 150 mg/kg bw/day (no adverse effects observed)
- Supporting study: Range-Finding study in rats with Santoflex 77, [redacted]., 1986, Rel. 2, 4/5 females died between gestation days 12 and 16 at 270 mg/kg/day
- Supporting study: Pilot Teratogenic study- albino rabbits, [redacted]., 1976, Rel. 4, all maternal animals given 100 or 300 mg/kg died
- Supporting study: Teratogenic Study with Santoflex 77 in Albino Rabbits, [redacted] 1978, Rel. 2, $NOAEL_{developmental}$ 10 mg/kg bw/day, $LOAEL_{fetotoxicity\ (24\ h\ viability\ index\ of\ pups)}$ 3 mg/kg bw/day

With respect to the target substance, ECHA notes that you have provided – *inter alia* – information on repeated dose toxicity but you did not provide any information on reproductive toxicity.

You have also provided read-across justifications for adapting the above information requirements under section 5.9.3., 'Summary and discussion of reproductive toxicity' of the Chemical Safety Report (CSR) attached to the IUCLID.

Furthermore, you attached the document '[redacted] to each endpoint study summary of a reproductive toxicity study performed with the source substance.

ECHA analysis of the grouping and read-across approach

ECHA notes that the document '[redacted] addresses the structure, physico-chemical data, biotic and abiotic degradation and ecotoxicity of the source and target substance as well as of other paraphenylenediamine substances. However, since this document does not address read-across with respect to the endpoints on reproductive toxicity, ECHA is using as basis for evaluation the justifications you provided in the CSR on the endpoints on reproductive toxicity.

With regard to the proposed prediction for reproductive toxicity and developmental toxicity endpoints, ECHA has the following observations:

Based on the available toxicological information you consider that "*From this data it can be concluded that there are similarities in the toxicological effects after 44PD and 77PD are administered orally. Both substances tend to the liver to differing degrees (as is shown by the deviating levels of liver enzymes). Nevertheless, the effects of 44PD are more severe, as actual liver damage was observed upon repeated administration of this substance.*" ECHA acknowledges the similarities observed with the target and source substance with respect to repeated dose toxicity. However, ECHA also notes the dissimilarities of source and target substance and the more severe effects on the target substance. More specifically, you explain that the source substance is leading to hematologic changes which you do not report for the target substance and the source substance shows more severe liver toxicity than the target substance. Furthermore, you did not provide any information on reproductive toxicity, namely functional fertility and developmental toxicity, of the target substance (e.g., a screening study for reproductive/developmental toxicity). Hence, in the absence of such supporting information and considering the potential differences of source and target substance with respect to repeated dose toxicity, it is not possible to assume/conclude whether human health effect of the target substance with respect to reproductive and developmental toxicity can be predicted from the information provided on the source substance. Hence, your read-across adaptation does not comply with the general rules of Annex XI, Section 1.5. of the REACH Regulation.

ECHA observations on the study with the source substance

In addition, with regard to the provided three-generation reproduction toxicity study ([redacted], 1981) on the source substance, which you have labelled as 'key study', ECHA notes that this study cannot be regarded as reliable and adequate. More specifically, you indicated that "*mortality of parental animals in all study groups was excessively high throughout the study; a large number of treated and control F0 animals were reported as possibly having respiratory infection.*" Furthermore, you state that "*these mortalities occurred in all study groups and were not considered related to treatment*" and that "*lessions of chronic murine pneumonia were present in most animals of the sacrificed, moribund sacrifice and death groups of animals of the F0, F1 and F2 generations.*" ECHA notes that such incidences of mortalities make the study relevance, reliability and adequacy for the purpose questionable. Furthermore, ECHA notes that incidences of effects indicating pneumonia were not reported and that independent evaluation of the study results is therefore not possible. ECHA notes also that 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). Furthermore, this study has been performed by Industrial Bio-Test Laboratories Inc (date and study period not indicated). A routine inspection of the testing laboratory 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 have scored the reliability of the study as 2 but you do not provide any information on the auditing of this study to support the reliability scoring. Therefore, the provided 'key' study on the source substance cannot be regarded as reliable and adequate source of information to adapt the standard information requirement of Annex IX, Section 8.7.1. according to Annex XI, Section 1.5.

Conclusion on your read-across approach

For the reasons as set out above, and taking into account all of your arguments, ECHA considers that this grouping and read-across approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. Therefore, this adaptation cannot be accepted and there is a data gap for the endpoints on screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) and pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species, which are covered by this read-across approach and further discussed in points 2 and 3 below.

1. Vapour pressure (Annex VII, Section 7.5.)

"Vapour pressure" is a standard information requirement as laid down in Annex VII, Section 7.5 of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

Whilst you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this adaptation.

To support your weight of evidence you have provided the following sources of information:

- ESR1: Key study, (Q)SAR prediction with the registered substance, EPI Suite (v. 4.10), publication, rel. 2. Vapour pressure: 0.207 Pa at 25 °C.
- ESR2: Key study, (Q)SAR prediction with the registered substance, SPARC (v. 4.6), publication, rel. 2. Vapour pressure: 0.04 Pa at 25 °C.
- ESR3: Supporting study, experimental study with the registered substance, method not described, 1995 (publication), rel. 4. Vapour pressure: 160 Pa at 20 °C.
- ESR4: Supporting study, experimental study with the registered substance, method not described, 1993 (publication), rel. 2. Vapour pressure: 1333 Pa at 170 °C.
- ESR5: Supporting study, experimental study with the registered substance, method not described, publication, rel. 4. Vapour pressure: 11372 Pa at 38 °C.
- ESR6: Supporting study, experimental study with the registered substance, method not described, 1995 (publication), rel. 4. Vapour pressure: 4400 Pa at 196 °C.

You have concluded that the key value for the chemical safety assessment is the value predicted with EPI Suite v. 4.10 (i.e. vapour pressure of 0.207 Pa) considering this is the most conservative value among those studies with higher reliability.

However, ECHA notes that although you have assigned reliability 4 to most of the experimental data provided considering there is "*very little detail*", some of them show a high discrepancy with the values obtained by estimation. Thus, ESR3 and ESR5 report much higher values than the estimated vapour pressure by EPI Suite even in the case that the result from ESR5 could be an outlier as indicated by you. In addition, ECHA also notes that estimated values for vapour pressure can be subjected to great uncertainty. This is reflected in the two estimations provided, which are also very different, adding a degree of uncertainty with regard to the estimations.

ECHA notes that on the basis of the information provided there is a too high uncertainty to be able to conclude reliably that the value predicted for vapour pressure is actually conservative enough and representative of the registered substance. Therefore, ECHA concludes that there is not sufficient weight of evidence.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you agreed to perform an experimental test for this endpoint.

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

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: Vapour pressure (test method: EU A.4./OECD TG 104).

2. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a three-generation reproductive toxicity study (no guideline) with the analogue substance(s) N, N'-bis(1,4-dimethylpentyl) -p-phenylenediamine (EC No 221-375-9). However, as explained above in Appendix 1, section 'Grouping of substances and read-across approach' of this decision, your adaptation of the information requirement is rejected.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you propose, for reasons of animal welfare, not to conduct a screening study for reproductive/developmental toxicity while the requested pre-natal developmental toxicity study would allow for adaption of the information requirement according to the rules laid down in Annex VIII of the REACH Regulation. ECHA acknowledges the possibility to adapt the requested testing according to Annex VIII, Section 8.7.1., column 2 and notes that it is

in your responsibility to adapt the testing requested according to the specific rules outlined in Annexes VI to IX and/or according to the general rules contained in Annex XI to the REACH Regulation. ECHA has also added a respective paragraph under "*Notes for your considerations*" below.

Hence, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test methods OECD TG 421 and 422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with 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 6.0, July 2017) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, 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: Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, section R.7.5 and 7.6 (version 6.0, July 2017).

You are invited to consider the order of conducting the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure unnecessary animal testing is avoided paying particular attention to the end point specific guidance (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf) p 461/2.

3. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for a developmental toxicity studies (OECD TG 414) in rats and rabbits with the analogue substance N, N'-bis(1,4-dimethylpentyl) -p-phenylenediamine (EC No 221-375-9). However, as explained above in Appendix 1, section 'Grouping of substances and read-across approach' of this decision, your adaptation of the information requirement is rejected.

Hence, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first 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 6.0, July 2017) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, 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 first species (rat or rabbit) by the oral route.

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 8 November 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 did not amend the request(s).

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) 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 requests in this decision, or to otherwise fulfil the information requirements 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 tests 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 tests 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 tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.