MINISTERSTVO HOSPODÁRSTVA SLOVENSKEJ REPUBLIKY

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Mixture of two components: 1. N-(1,3-dimethylbutyl)-N´-phenyl-p-phenylenediamine 2. N1-(1,3-dimethylbutyl)-N4-(4-(1-methyl-1-phenylethyl)phenyl)benzene-1,4-diamine

EC No 448-020-2

CAS No not available

Evaluating Member State(s): Slovakia

Dated: 06 February 2017

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2013

The evaluating Member State (eMSCA) concludes that more data is indeed required to clarify the initial concern for including this substance in the CoRAP. However, as this substance no longer has any active registrations according to the ECHA dissemination website, the evaluation is terminated with several open concerns.
If in future the currently inactive registration is re-activated, or there are new registrants for the substance, authorities shall consider including the substance again in the CoRAP for obtaining the information which is considered important to clarify the concern related to this substance. In such a situation the potential registrants are recommended to take note of these conclusions and make appropriate testing proposals to ECHA, where relevant under Article 12(1)(d) and (e) of the REACH Regulation.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

The substance, mixture of two components: 1. N-(1,3-dimethylbutyl)-N´-phenyl-p-phenylenediamine 2. N1-(1,3-dimethylbutyl)-N4-(4-(1-methyl-1-phenylethyl)phenyl)benzene-1,4-diamine, was originally selected for substance evaluation in order to clarify concerns about:

- Human health/CMR,
- Environment/Suspected PBT,
- Exposure/High RCR.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Not applicable.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluating Member State (eMSCA) concludes that more data is indeed required to clarify the initial concerns for including this substance in the CoRAP. However, as this substance no longer has any active registrations according to the ECHA's register/dissemination website, the evaluation is terminated with several open concerns.

If in future the currently inactive registration is re-activated, or there are new registrants for the substance, authorities shall consider including the substance again in the CoRAP for obtaining the information which is considered important to clarify the concern related to this substance. In such a situation the potential registrants are recommended to take note of these conclusions and make appropriate testing proposals to ECHA, where relevant[2] under Article 12(1)(d) and (e) of the REACH Regulation.

In this report the evaluation performed is based on information on the ECHA dissemination website as well as other publically available information on the mixture of two components: 1. N-(1,3-dimethylbutyl)-N´-phenyl-p-phenylenediamine 2. N1-(1,3-dimethylbutyl)-N4-(4-(1-methyl-1-phenylethyl)phenyl)benzene-1,4-diamine.
The report includes specifications on what data would clarify the identified concern. The report includes also some additional data that was published after the initial evaluation was performed (2013). The possible high risk characterization ratios, as mentioned in the initial concern, were not further evaluated due to the inactivation of the registration.

[2] Dissociation constant, soil degradation simulation testing

The eMSCA would like to note that the name of the substance: mixture of two components: 1. N-(1,3-dimethylbutyl)-N´-phenyl-p-phenylenediamine 2. N1-(1,3-dimethylbutyl)-N4-(4-(1-methyl-1-phenylethyl)phenyl)benzene-1,4-diamine is not in line with the ECHA Guidance for identification and naming of substances under REACH and CLP (Version 2.0 - December 2016).
The substance was previously notified in accordance with Directive 67/548/EEC and was, thus, listed in ELINCS. In the latest edition of ELINCS (EUR 23923 EN – 2009) this substance is listed under EC No 448-020-2, registration number 04-26-0001 and trade name "Dusantox L".
The substance is a reaction product consisting of two constituents. It is a multi–constituent substance. The naming convention for multi-constituent substances is given in Chapter 4.2.2 of the Guidance for identification and naming of substances under REACH and CLP (Version 2.0 - December 2016) is as follows:

"Naming convention
A multi-constituent substance is named as a reaction mass of the main constituents of the substance as such i.e. not the starting materials needed to produce the substance .The generic format is: "Reaction mass of [names of the main constituents]". It is recommended that the names of the constituents are presented in alphabetical order and they are separated by the conjunction "and". Only main constituents typically ≥ 10% contribute to the name. In principle, the names should be given in English language according to the IUPAC nomenclature rules. Other internationally accepted designations can be given in addition."

To prevent the misinterpretation of the name of the substance as "mixture" (Article 3 (2) of REACH) the eMSCA would like to recommend to the registrant(s) of this substance to change the name as follows:
Reaction mass of N-(1,3-dimethylbutyl)-N´-phenyl-p-phenylenediamine and N1-(1,3-dimethylbutyl)-N4-(4-(1-methyl-1-phenylethyl)phenyl)benzene-1,4-diamine.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION **Conclusions**	**Tick box**
Need for follow-up regulatory action at EU level *[if a specific regulatory action is already identified then, please, select one or more of the specific follow-up actions mentioned below]*	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	X

4. FOLLOW-UP AT EU LEVEL

See section 5 below.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

The substance evaluation of mixture of two components: 1. N-(1,3-dimethylbutyl)-N´-phenyl-p-phenylenediamine 2. N1-(1,3-dimethylbutyl)-N4-(4-(1-methyl-1-

phenylethyl)phenyl)benzene-1,4-diamine was terminated as this substance no longer has any active registrations. The eMSCA concluded that further information would have been necessary to clarify the concerns regarding Environment/Suspected PBT.

The eMSCA is of the opinion that as the above mentioned hazards remain unverified, a further assessment should be undertaken if in future the currently inactive registration is re-activated, or there are new registrants for the substance.

Although the classification criteria for some endpoints are met (as explained later in the report), the substance is not a priority for making an official classification proposal/dossier.

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/exposure	
Actions by the registrants to ensure safety, as reflected in the registration dossiers i.e. manufacture was ceased and the registrations were revoked/inactivated.	X

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

See section 3 and 5.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

See section 1 for the concerns subject to evaluation. An overview of the outcome of the evaluation is summarised in Table 3.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Reprotoxicity	No further action eMSCA considered the initial concern for reproduction toxicity as clarified and does not require an additional information. If changes in the current circumstances occur (such as e.g. new Registrants appear with different self-classifications of this substance than Repr. 1B, the PNDT study in a second species (rabbit) may be required for possible clarification of the remaining unclear concerns and possible preparation of an Annex VI dossier for harmonised classification and labelling either by a MSCA, or by the Registrant according to the CLP Regulation.
Repeat dose toxicity	No further action. The eMSCA agrees with Registrant´s self-classification STOT RE Cat 1 (H372 – Caused damage to organs, targeted organ: liver) according CLP Regulation No 1272/2008.
Sensitisation	No further action. The eMSCA agrees with Registrant´s self-classification Skin Sens 1 (H317 May cause an allergic skin reaction) according CLP Regulation No 1272/2008.
Environmental hazard assessment	No conclusion reached. To enable assessment of the substance behaviour in the environment the eMSCA recommended to carry out: - Dissociation constant (test method: calculation for both constituents according to ECHA guidance for information requirement and chemical safety report, Chapter R7.1.1) - Water solubility (test method: EU A.6/OECD 105). Reliable analytical protocol to measure and quantify both constituents of the substance in water shall be used. The test shall be performed under conditions that ensure that abiotic degradation does not occur during the study. See also section 7.4

	To clarify the concern for microorganisms in sewage treatment plant the eMSCA recommended to carry out Activated sludge respiration inhibition testing (test method: Activated sludge, respiration inhibition test (carbon and ammonium oxidation), OECD 209); The respiration rate regarding carbon oxidation and ammonium oxidation shall be measured. One test performed with freshly prepared test item concentrations of the registered substance. Another test performed with five days old test item concentration to allow the generation of hydrolysis products. See section 7.8.3. The eMSCA does not agree with registrant´s self-classification on aquatic toxicity of the substance as Aquatic Chronic 2; H411 and recommends to classify the substance as Aquatic Chronic 1 (H410) with an M-factor of 10 (0.001 < NOEC ≤ 0.01). See section 7.8.6. However, as this substance no longer has any active registrations according to the ECHA's register/dissemination website, the evaluation is terminated with open concern for Environment.
Persistency	To clarify the potential of persistency the eMSCA recommended at the first step to repeat ready biodegradability study (Closed Bottle Test C.4-E) with request for specific chemical analysis to determine and assess the main degradation products. Based on the outcome of the closed bottle ready biodegradability study (i.e. giving that the study indicates that the substance is not ready biodegradable) soil simulation testing (OECD 307 Aerobic and Anaerobic transformation in Soil) with request for identification of transformation products would be considered to reach conclusion on persistency. However, as this substance no longer has any active registrations according to the ECHA's register/dissemination website, the evaluation is terminated with open concern for Persistency.

7.2. Procedure

The evaluation of the mixture of two components: 1. N-(1,3-dimethylbutyl)-N´-phenyl-p-phenylenediamine 2. N1-(1,3-dimethylbutyl)-N4-(4-(1-methyl-1-phenylethyl)phenyl)benzene-1,4-diamine was primarily targeted on possible reprotoxicity and PBT properties. Other parts of the registration dossier were screened for inconsistencies, however were not evaluated in–depth.

A summary of the substance evaluation procedural history:

- 20 March 2013 - 19 March 2014: The initial evaluation was performed. During this period there were informal interactions with the Registrant. The eMSCA identified that more data was required to confirm the initial concern for including this substance in the CoRAP.
- 19 March 2014: A draft decision to require more information from the registrant(s) was submitted to ECHA. This draft decision reflected the registration status at that point of time and that registered tonnage was 100 - 1000 tonnes per year.
- 29 April 2014: The registrant(s) were notified by ECHA of the draft decision.
- By 5 June 2014: ECHA received the registrant´s comments.
- 5 March 2015 the evaluating MSCA notified the Competent Authorities of the other Member States and ECHA of its draft decision and invited them to submit proposals to amend the draft decision
- 10 April 2015 ECHA notified the registrant(s) of the proposals for amendment to the draft decision
- On 20 April 2015 ECHA referred the draft decision to the Member State Committee.
- By 11 May 2015 ECHA did not receive any comments from the registrant(s) to the proposals for amendment to the draft decision.
- On 9 June 2015 agreement of modified draft decision was reached by the Member State Committee.
- 01 October 2015 Final ECHA decision sent to the registrant(s).
- In late September 2016 the registration was inactivated according to information available on the ECHA dissemination website. There are currently no active registrations for the substance and the volume of the substance manufactured/imported is put to zero.
- 06 February 2017: The evaluation performed was reported as required by REACH Article 48, based on information available on the ECHA dissemination website as well as other publically available information on mixture of two components: 1. N-(1,3-dimethylbutyl)-N´-phenyl-p-phenylenediamine 2. N1-(1,3-dimethylbutyl)-N4-(4-(1-methyl-1-phenylethyl)phenyl)benzene-1,4-diamine.

The source of information was:

- ECHA dissemination website: https://echa.europa.eu ; https://echa.europa.eu/substance-information/-/substanceinfo/100.104.136
- Other publically available information.

7.3. Identity of the substance

Table 5

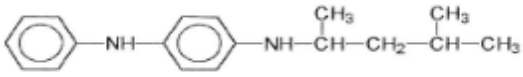
SUBSTANCE IDENTITY	
Public name:	mixture of two components: 1. N-(1,3-dimethylbutyl)-N´-phenyl-p-phenylenediamine 2. N1-(1,3-dimethylbutyl)-N4-(4-(1-methyl-1-phenylethyl)phenyl)benzene-1,4-diamine
EC number:	448-020-2
CAS number:	Not available
Index number in Annex VI of the CLP Regulation:	Not applicable
Molecular formula:	Constituent 1: C18H24N2 Constituent 2: C27H34N2

Molecular weight range:	268,4 – 386,6
Synonyms:	N-1,3-dimethylbutyl-N'-phenyl-p-phenylenediamine, reaction products with 2-phenylpropene Trade name: Dusantox L Constituent 1: 6PPD Constituent 2: p-cumyl-6PPD

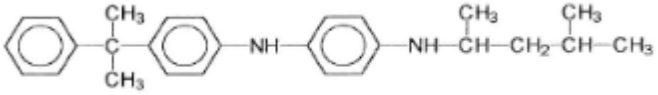
Type of substance ☐ Mono-constituent x Multi-constituent ☐ UVCB

Structural formula:

1. N-(1,3-dimethylbutyl)-N´-phenyl-p-phenylenediamine



2. N1-(1,3-dimethylbutyl)-N4-(4-(1-methyl-1-phenylethyl)phenyl)benzene-1,4-diamine



Multiconstituent/UVCB substance/others

The substance is multi-constituent substance. There is no information on impurities, on the ECHA dissemination website.

Table 6

Constituent			
Name	**Typical concentration**	**Concentration range**	**Remarks**
N-1,3-dimethylbutyl-N'-phenyl-p-phenylenediamine EC number: 212-344-0 CAS number: 793-24-8	no data available on the ECHA dissemination website	no data available on the ECHA dissemination website	Abbreviation "6PPD" is also used in this report
N1-(1,3-dimethylbutyl)-N4-[4-(1-methyl-1-phenylethyl)phenyl]benzene-1,4-diamine EC number: - CAS number: 194478-84-7	no data available on the ECHA dissemination website	no data available on the ECHA dissemination website	Abbreviation "p-cumyl 6PPD" is also used in this report

7.4. Physico-chemical properties

Table 7

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid Form: viscous Colour: dark brown to black Odour: characteristic of aromatic compounds Experimental study (other company data) 2001, not GLP, reliability 2,
Vapour pressure	340 Pa at 25° Test method: OECD Guideline No.104, EEC directive 92/69/EEC, A.4 Type of method: static Experimental study 2001, reliability 1
Water solubility	< 1 mg/L at 20°C, pH 6 Test method: EEC directive 92/69/EEC, A.6., OECD Guideline No.105 Column elution method 2001 WSKOW(v. 1.42) estimates: 6PPD: **2.2 mg/L (log Kow = 4.6)** 1.879 mg/L (log Kow = 4.68) 2.8262 mg/L (from fragments) p-cumyl-6PPD: **0.0104 mg/L (log Kow = 6.5)** 0.0022 mg/L (log Kow=7.29) 0.0009 mg/L (from fragments) See section 7.4.2.
Partition coefficient n-octanol/water (Log Kow)	< 6.5 at 23°C and pH ca. 7.5 EEC Directive 92/69 EEC, A.8 Partition coefficient, OECD Guideline No.117 Type of method: HPLC 2001, reliability 1 The estimation based on the atom/fragment contribution by Kow Win v. 1.68 (US EPA): logKow = 4.68 for 6PPD logKow = 7.29 for p-cumyl-6PPD
Flammability	No data available. Not evaluated by the eMSCA
Explosive properties	No data available. Not evaluated by the eMSCA
Oxidising properties	No data available. Not evaluated by the eMSCA
Granulometry	Not evaluated by the eMSCA
Stability in organic solvents and identity of relevant degradation products	No data available. Not evaluated by the eMSCA
Dissociation constant	Data waiving: study technically not feasible See section 7.4.1.
Koa	EPI Suite estimation (KOAWIN v1.10) Log KoA: 11.542 for 6PPD Log KoA::14.956 for p-cumyl-6PPD

Viscosity	325-338 mm2/s (static) at 40°C Method: OECD TG 114 , 2006, reliability 1

7.4.1. Dissociation constant

No data is available on ECHA dissemination website. The registrant(s) provided waiving with justification that study was technically not feasible.

The calculations of pKa values separately for the constituent 1: 1. N-(1,3-dimethylbutyl)-N´-phenyl-p-phenylenediamine (CAS No 793-24-8) and for the constituent 2: N1-(1,3-dimethylbutyl)-N4-(4-(1-methyl-1-phenylethyl)phenyl)benzene-1,4-diamine (CAS No 194478-84-7) of the substance are possible and shall be provided instead of measured values.

According to publicly available data on ECHA dissemination website from registration for constituent 1 of the substance (CAS No 793-24-8), the dissociation constants (calculated by using ACD/Labs, v. 7.00) are pKa (HL/H+L) = 6.73±0.32 and pKa (H2L/H+HL) = -0.71±0.40 at 25 °C (ECHA, 2013)[3]. The calculation shows that both the neutral and the mono-protonated forms are present at environmental relevant pH.

According to Column 2 of the REACH Annex IX a study does not need to be conducted if the substance is hydrolytically unstable (Half-life less than 12 hours).

According to the study of hydrolysis as function of pH available on ECHA dissemination website (2007) the registered substance undergoes significant abiotic degradation. The values of DT50 less than 12 hours are at pH 7, temperature 15°C and 25°C for both components of the substance and at pH 10, temperature 25°C for component 1. Therefore, the calculations of pKa values separately for the both components of the substance according to the ECHA Guidance for information requirement and chemical safety report, Chapter R7.1.17) should be provided instead of measured values.

7.4.2. Water solubility:

Water solubility study (OECD TG No. 105, Column elution method, 2001) for the mixture of two components: 1. N-(1,3-dimethylbutyl)-N´-phenyl-p-phenylenediamine 2. N1-(1,3-dimethylbutyl)-N4-(4-(1-methyl-1-phenylethyl)phenyl)benzene-1,4-diamine is available on ECHA dissemination website.

Despite of the reliability 1 (reliable without restriction) assigned by the registrant(s) the eMSCA considers that study has several limitation and is not satisfactory according to OECD TG 105. Based on the data given in the original study report, the equilibrium could not be established for the lower flow rate – the concentrations differ by more than ±30% in a random fashion. In addition, the data shows that the measured solubility was higher with the lower flow rate but the test with halving of the flow rate was not conducted. The mean concentration values obtained from two tests with different flows differ by far more than 30%. There is no mention whether hydrolytic stability and acid dissociation constant of the substance had been considered in this study. The value of water solubility of the substance is stated to be < 1 mg/L for both constituents (below the limit of detection) at 20°C, pH 6, the exact value of water solubility of the substance is not determined. The study could be considered as limit test performed up to the detection limit of analytical method used. It is necessary to underline that the value of < 1 mg/L for both constituents was determined only based on the detection of constituent 1 (CAS No 793-

[3] http://echa.europa.eu/

8) as in the performed study the problem with detection of constituent 2 (CAS No 194478-84-7) was reported.

Considering the hydrolytical instability of the substance, the eMSCA used EPI Suite v4.1 (WSKOW v1.42) for estimation of water solubility. Water solubility for constituent 1 (CAS No 793-24-8) is 1.879 mg/L and for constituent 2 (CAS No 194478-84-7) is 0.0022 mg/L at 25°C (based on estimated log Kow values). Estimated values at 25°C based on measured/user entered log Kow value are 2.2 mg/L for constituent 1 (CAS No 793-24-8) and 0.0104 mg/L for constituent 2 (CAS No 194478-84-7).

According to data available on ECHA dissemination website for registration of constituent 1 (CAS No 793-24-8) the water solubility is 1.1 mg/L at ambient temperature, pH was not reported and water solubility at 50°C is circa 1 mg/L, pH was not reported (ECHA, 2013).

The estimations show that the values of water solubility of the constituents differ considerably (by two and more orders), which was not considered in the water solubility test. The analytical method used was not optimised for as low concentration as needed for identification and quantification of constituent 2. Developing new analytical method (reliable analytical protocol) is required to measure and quantify both components of the substance in water.

The water solubility is an essential parameter in ecotoxicological testing and evaluation. The determination of reliable value of water solubility (for both components of the substance) is essential for the proper risk assessment of the substance.

As the value of water solubility is the crucial parameter for the environmental part of evaluation, reliable value of water solubility of the substance shall be determined by using integrated testing strategy for water solubility according to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7.1.7. Reliable analytical protocol to measure and quantify both components of substance in water shall be used. The test shall be performed under conditions that ensure that abiotic degradation does not occur during the study. The registrant(s) shall refer to the difficult substances guidance. For example, pH adjustment may be necessary.

7.5. Manufacture and uses

7.5.1. Quantities

At the start of the evaluation in 2013 the aggregated tonnage was 100-1000t/year. After notification of ECHA decision to require more information from the registrant(s) in October 2015 the registrant(s) ceased the production and on late September 2016 the registration of the substance was inactivated. According to the ECHA dissemination website there are no active registrations of the mixture of two components: 1. N-(1,3-dimethylbutyl)-N´-phenyl-p-phenylenediamine 2. N1-(1,3-dimethylbutyl)-N4-(4-(1-methyl-1-phenylethyl)phenyl)benzene-1,4-diamine until January 2017. For more details on the procedure see Section 7.2.

7.5.2. Overview of uses

At the time of finalising this report, there were no active registrations for this substance.

Table 8 Previous uses according to ECHA dissemination website January 2017

PREVIOUS USES (BEFORE REGISTRATION BECAME INACTIVE)	
	Use(s)
Manufacture	Manufacture of Dusantox L Environmental release category: ERC1: Manufacture of the substance Process category: PROC 3: Use in closed batch process (synthesis or formulation)
Uses as intermediate	No data
Formulation	No data
Uses at industrial sites	Identified use name: Industrial use of Dusantox L in Polymer Industry Environmental release category (ERC):ERC6d: Use of reactive process regulators in polymerisation processes at industrial site (inclusion or not into/onto article) Process category(PROC): • PROC 2: Use in closed, continuous process with occasional controlled exposure • PROC 3: Use in closed batch process (synthesis or formulation) • PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities • PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities Product category used: PC 32: Polymer preparations and compounds Sector of end use: • SU 8: Manufacture of bulk, large scale chemicals (including petroleum products), • SU 0: Other: C20 - manufacturing: manufacture of chemicals and chemical products
Uses by professional workers	No data
Consumer Uses	No data
Article service life	No data

Information on uses from other publicly available sources: The mixture of two components: 1. N-(1,3-dimethylbutyl)-N´-phenyl-p-phenylenediamine 2. N1-(1,3-dimethylbutyl)-N4-(4-(1-methyl-1-phenylethyl)phenyl)benzene-1,4-diamine (Dusantox L) is an effective stabilizer of synthetic styrene-butadiene and polyisoprene rubber and also an antidegradant for dry rubber compounds.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Mixture of two components: 1. N-(1,3-dimethylbutyl)-N´-phenyl-p-phenylenediamine 2. N1-(1,3-dimethylbutyl)-N4-(4-(1-methyl-1-phenylethyl)phenyl)benzene-1,4-diamine has no harmonised classification in Annex VI of CLP Regulation.

7.6.2. Self-classification

- According to the ECHA dissemination website:

Skin Sens. 1 H317: May cause an allergic skin reaction.
Repr. 1B H360: May damage fertility or the unborn child.
STOT RE. 1 H372: Causes damage to liver through prolonged or repeated exposure by oral route.
Aquatic Chronic 2 H411: Toxic to aquatic life with long lasting effects.

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory*:* no data available.

7.7. Environmental fate properties

7.7.1. Degradation

7.7.1.1. Hydrolysis

According to the study of hydrolysis as function of pH available on ECHA dissemination website (2007) the registered substance undergoes significant abiotic degradation. Its intensity depends on temperature and pH. The study results show that component 2 (CAS No 194478-84-7) undergoes abiotic degradation more slowly compared to component 1 (CAS No 793-24-8) of the registered substance. The components of registered substance are the most stable at pH 4 and 15°C, hydrolysis half-life is 43.4 h for component 1 and 53.8 h for component 2.The values of DT50 less than 12 hours are at pH 7, temperature 15°C and 25°C for both components of the substance and at pH 10, temperature 25°C for component 1.

In the study possible hydrolysis products were identified as 4-hydroxydiphenylamine, p-benzoquinone / p- hydroquinone, acetophenone, aniline, benzoquinone-monoimine and benzophenone.

According to the key experimental study for 6PPD (2003, reliability 2) available on ECHA dissemination website the hydrolysis half-life is 14 h at 26°C, pH 7; 4-Hydroxydiphenylamine (CAS 122-37-2) was identified as the major hydrolysis product.

7.7.1.2. Phototransformation / photolysis

7.7.1.2.1. Phototransformation in air

No information is available on this endpoint on ECHA dissemination website.

Based on information available in OECD SIDS profile for 6PPD (OECD, 2004), 6PPD entering into the atmosphere is expected to be photodegraded rapidly by OH-radicals. The calculated half-life of 6PPD in air due to indirect photodegradation is 1 h. Since 6PPD absorbs UV-B radiation, it is expected that 6PPD will undergo direct photolysis due to absorbance of environmental UV light.

7.7.1.2.2. Phototransformation in water

No information is available on this endpoint on ECHA dissemination website.

7.7.1.2.3. *Phototransformation in soil*

No information is available on this endpoint on ECHA dissemination website.

7.7.1.3. **Biodegradation**

7.7.1.3.1. **Biodegradation in water**

Estimated data

ECHA dissemination website does not contain any estimation on biodegradation. BIOWIN estimations (EPI Suite v. 4.10) were performed for prediction of persistency potential of both components of the registered substance; results are summarized in tables below:

Table 9 BIOWIN estimation for component 1

Persistence	**Criterion**	**Conclusion**	**Probability of Rapid Biodegradation:**
Biowin 2 (non-linear model prediction) and Biowin 3 (ultimate biodegradation time) or Biowin 6 (MITI non-linear model prediction) and Biowin 3 (ultimate biodegradation time)	Does not biodegrade fast (probability <0.5), and ultimate biodegradation timeframe prediction: ≥months (value < 2.2 to 2.75)** or Does not biodegrade fast (probability <0.5) and ultimate biodegradation timeframe prediction: ≥months (value < 2.2 to 2.75)**	Potentially P or vP Potentially P or vP	Biowin 2: 0.0564 Biowin 3: 2.3581 Biowin 6: 0.0018

Table 10 BIOWIN estimation for component 2

Persistence	**Criterion**	**Conclusion**	**Probability of Rapid Biodegradation:**
Biowin 2 (non-linear model prediction) and Biowin 3 (ultimate biodegradation time) or Biowin 6 (MITI non-linear model prediction) and Biowin 3 (ultimate biodegradation time)	Does not biodegrade fast (probability <0.5), and ultimate biodegradation timeframe prediction: ≥months (value < 2.2 to 2.75)** or Does not biodegrade fast (probability <0.5) and ultimate biodegradation timeframe prediction: ≥months (value < 2.2 to 2.75)**	Potentially P or vP Potentially P or vP	Biowin 2: 0.0020 Biowin 3: 1.8849 Biowin 6: 0.0002

** *For substances fulfilling this but BIOWIN indicates a value between 2.25 and 2.75 more degradation relevant information is generally warranted.*
Biowin Models used are only recommended for "negative" screening, concluding on the non-biodegradability (P).

The overall prediction of the ready biodegradability for both components is not ready biodegradable.

Screening tests

Results from three studies on ready biodegradability (OECD TG 301B, 301 D, 301 F) available on ECHA dissemination website indicate 46%, 33% and 9% degradation after 28 days, respectively. A modified MITI (II) inherent biodegradation study indicates 18% degradation after 28 days.
However, the biodegradability (ready and inherent biodegradability) studies are of low quality with the exception of the Modified Sturm Test (OECD 301 B) which indicates 46% degradation. This study is of the best quality from among the submitted biodegradability studies.
A clear trend is observed in used test concentrations and biodegradability percentage in the biodegradability studies i.e. the higher the test concentrations, the less the percentage of biodegradability. A possible explanation of the low biodegradation is the formation of degradation products p-benzoquinone/p-hydroquinone which is very toxic to bacteria.

In an OECD TG 301C test on ready biodegradability for 6PPD available on ECHA dissemination website only ca. 2 % of 6PPD was biodegraded. The following transformation products were identified: 4-hydroxydiphenylamine, phenylbenzoquinone imine, 1, 3-dimethylbutylamine, aniline and p-benzoquinone.

Simulation tests (water and sediment)

No data available for the registered substance.

Based on the study available in OECD SIDS profile for 6PPD (OECD, 2004) the degradation of 6PPD was studied in River die-away assay using Mississippi river water (biologically active river water, controls with sterile river water and with deionized water). During 2h (22 h), the concentration of 6PPD decreased by 57 % (97 %) in the active river water, by 30 % (96 %) in the sterile river water, and by 12 % (88 %) in the deionized water. The estimated half-lives are 2.9 h in active river water, 3.9 h in sterile river water, and 6.8 h in sterile deionized water.

7.7.1.3.2. **Biodegradation in soil.**

No data available for the registered substance. The registrant(s) provided waiving with justification that exposure of soil is not probable.

Based on information available on ECHA dissemination website a read-across approach is applied for soil biodegradation data of 6PPD using data from 7PPD; the study Aerobic and Anaerobic Transformation in Soil, OECD 307 was performed for 7 PPD in 2015. The read-across is applied using the justification that both substances are members of the paraphenylene diamine family. 7PPD has a similar structure as 6PPD; the difference is that 7PPD has a C7 branched aliphatic chain, whereas 6PPD has C6 branched aliphatic chain.

7.7.1.3.3. **Summary and discussion on degradation.**

Both components of the registered substance undergo significant abiotic degradation; its intensity depends on temperature and pH. The study results show that component 2 (CAS No 194478-84-7) undergoes abiotic degradation more slowly compared to component 1 (CAS No 793-24-8). The components of the registered substance are the most stable at pH 4 and 15°C, hydrolysis half-life is 43.4 h for component 1 and 53.8 h

for component 2 .The values of DT50 less than 12 hours are at pH 7, temperature 15°C and 25°C for both components of the substance and at pH 10, temperature 25°C for component 1.

In hydrolysis study possible hydrolysis products were identified: 4-hydroxydiphenylamine, p-benzoquinone / p- hydroquinone, acetophenone, aniline, benzoquinone-monoimine and benzophenone.

BIOWIN estimation (v4.10) predicts no ready biodegradability for both components.

Results from three studies on ready biodegradability indicate 46%, 33% and 9% degradation after 28 days, respectively. A modified MITI (II) inherent biodegradability test indicates 18% degradation after 28 days.

However, the biodegradability (ready and inherent biodegradability) studies are of low quality with the exception of the Modified Sturm Test which indicates 46% degradation. This study is of the best quality from among the submitted biodegradability studies.

The results from aerobic biodegradation studies indicate that Dusantox L does not biodegrade rapidly in water compartment; the substance is neither readily nor inherently biodegradable and fulfils screening P criterion.

To clarify the potential of persistency it is recommended at the first step to repeat ready biodegradability study (Closed Bottle Test C.4-E) as the basic respiration in this study is the lowest. As no data on degradation products of the substance is provided (only possible hydrolysis products have been identified) the study should be performed with request for specific chemical analysis to determine and assess main degradation products.

Based on the outcome of the closed bottle ready biodegradability study (i.e. giving that the study indicates that the substance is not ready biodegradable) soil simulation testing with request for identification of transformation products (OECD 307 Aerobic and Anaerobic transformation in Soil) would be considered to reach conclusion on persistency.

7.7.2. Environmental distribution

7.7.2.1. Adsorption/desorption

ECHA dissemination website reports the results of adsorption/desorption screening test (OECD TG 121) of the registered substance: Koc = 3200 (log Koc = 3,5) for component 1 and Koc= 25000 (log Koc = 4,4) for component 2.

7.7.2.2. Volatilization

No information available on ECHA dissemination website.

7.7.2.3. Distribution modelling

Based on information obtained from ECHA dissemination website the eMSCA's estimation of the environmental distribution using Level III Fugacity model (EPI Suite v4.1) indicates that the main target environmental compartments for the components of the registered substance are sediment (14% for component 1, 60% for component 2) and, predominantly, soil (76% for component 1 , 38% for component 2).

7.7.2.4. Summary and discussion of environmental distribution

Considering the physical and chemical properties of the substance (likely very low value of water solubility < 1 mg/L, log Kow < 6.5, vapour pressure 340 Pa at 25°C) once it is released to the environment transport of the substance from water to soil/sediment is expected; transport from water to air is of low relevance. The values of log Koc indicate high adsorptive potential of the both components of the substance; this is also supported by the estimation of the environmental distribution i.e. the main target environmental compartments for the substance are sediment and soil.

7.7.3. Bioaccumulation

7.7.3.1. Estimated data

EPI Suite (v4.1) estimations of log Kow (KOWWIN v1.68) and BCF values (BCFBAF v3.01) for both components of Dusantox L are presented in table below.

Table 11 Log Kow and BCF estimations for Dusantox L

CAS Nr	Name	log Kow (e)	BCF (e)
793-24-8	6PPD	4.68	568.8[1] 348.5[2]
194478-84-7	p-cumyl-6PPD	7.29	9586[1] 1322[2]

[1] BCF from regression-based method
[2] BCF from Arnot-Gobas method (upper trophic level)

The estimation for both components of the parent compound indicates fulfilling of screening B-criterion as well as higher potential for bioaccumulation of p-cumyl-6PPD.

7.7.3.2. Bioaccumulation in aquatic organisms

The measured value of an octanol water partition coefficient available on ECHA dissemination website resulted in a log Kow of < 6.5 which indicates that Dusantox L has a potential to bioconcentrate in aquatic organisms.

ECHA dissemination website contains a semi-static study with Dusantox L on bioconcentration in fish (2007, reliability assigned by the registrant(s) is 1) with reported BCF results: BCF of 110 (c = 0, 25 mg/l) and BCF of 47 (c = 0,025 mg/l).

7.7.3.3. Bioaccumulation in terrestrial organisms

No information available on ECHA dissemination website.

An octanol-air partition coefficient KoA is a crucial physical-chemical property controlling the potential of organic chemicals to biomagnify in terrestrial mammalian food-chains.

EPI Suite estimation (KOAWIN v1.10) of log KoA values for both component of Dusantox L are reported in table below:

Table 12 Log KoA estimation for both components of Dusantox L

CAS Nr	Name	log KoA (e)
793-24-8	6PPD	11.542
194478-84-7	p-cumyl-6PPD	14.956

Substances with log Kow between 2 and 5 and log KoA > 5 were identified as a group of potentially bioaccumulative substances in terrestrial mammalian food-chains (A. Gobas et al, 2003); according to this presumption the components of parent substance (especially 6PPD) have potential to biomagnify in terrestrial mammalian food-chains.

7.7.3.4. **Summary and discussion of bioaccumulation**

The value of measured log Kow <6.5 indicates that Dusantox L has a potential to bioconcentrate in aquatic organisms and fulfils the screening B criterion.

Based on the results of the bioconcentration fish study reported BCF values of 110 (c=0,25 mg/l) and of 47 (c=0,025 mg/l) do not indicate fulfilling of bioaccumulation criterion. However, the quality of the study and the reliability assigned by the registrant(s) are controversial. The study was performed in semi-static mode (not in flow-through mode as registrant stated). However, the study should be performed at flow through mode to guarantee the test substance concentration in satisfied range with regard to the character of the substance (abiotic degradation / hydrolytical instability). The measured concentration for both components differed considerably from the nominal concentrations (200% and more). BCFs for main components of Dusantox L (6PPD and p-cumyl-6PPD) were calculated based on the steady-state concentrations and kinetic constants but steady state was not reached for both components during the uptake phase. In addition the lipid content of the test fish was not reported. No information was provided on the accuracy, sensitivity, and detection limit of analytical method used.
The eMSCA is of the opinion that the study doesn't fulfil validity criteria given by C.13 / OECD TG 305 test method and the quality of the study and the reliability assigned by the registrant are controversial. The eMSCA considers the study as not reliable as a key study for bioaccumulation.

Considering the physical and chemical properties of the substance once it is released to the environment transport of the substance from water to soil/sediment is expected and substance is immobile in soil/sediment.
The values of log Koc indicate high adsorptive potential of the both components of the substance; in addition estimated log KoA values indicate that biomagnification in terrestrial mammalian food chains may occur.
Bioaccumulation criterion should be examined further considering the potential for bioaccumulation (especially terrestrial bioaccumulation) and biomagnification to be able to conclude on bioaccumulation of the substance.

7.8. Environmental hazard assessment

All data presented is available on ECHA dissemination website.

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

7.8.1.1.1. Short-term toxicity to fish

Table 13 Summary of the short-term effects of Dusantox L on fish

Method	Species	Results	Reliability assigned in registration
Fish. Acute toxicity test (C.1; OECD TG 203) Freshwater Semi-static	Cyprinus carpio	LC50 (24 h): > 1.9 mg/L LC50 (48 h): 1.9 mg/L LC50 (72 h): 1.5 mg/L LC50 (96 h): 1.1 mg/L LC100(96h): 2,7 mg/L NOEC (96h): ≤ 0,73 mg/L (nominal)	1 (reliable without restriction)

LC50 (96 h) for fish (Oryzias latipes) based on geometric means of measured concentrations was determined to be 0.028 mg/l for 6PPD.

7.8.1.1.2. Long-term toxicity to fish

Table 14 Summary of the long-term effects of Dusantox L on fish

Method	Species	Results	Reliability assigned in registration
Fish juvenile growth test (C.14; OECD TG 215): Semi-static Freshwater	Oncorhynchus mykiss	EC50(28d) = 0,05 mg/L <0,03 - 0,10> p=0,05 EC100(28d) - 0.39 mg/L <0,10 - 0,53> p=0,05 LOEC = 0,022 mg/L NOEC = 0, 01 mg/L (nominal)	1 (reliable without restriction)

The chronic toxicity of 6PPD to fish (Oryzias latipes) was tested with in an Early-Life Stage Toxicity Test according OECD TG 210 (reliability 1). Effect values are based on analytical monitoring; the 30d NOEC is of 0.0037 mg/l.

7.8.1.2. **Aquatic invertebrates**

7.8.1.2.1. **Short-term toxicity to aquatic invertebrates**

Table 15 Summary of the short-term effects of Dusantox L on aquatic invertebrates

Method	**Species**	**Results**	**Reliability assigned in registration**
Daphnia sp. Acute Immobilisation Test and reproduction Test part I: 24 h (C.2; OECD TG: 202-I) freshwater static	Daphnia magna	EC50 (24 h): 2.3 mg/L EC50 (48 h): 1.3 mg/L NOEC (48 h) = ca 0,6 mg/L % concentration loss over test: 0-27	1 (reliable without restriction)

The acute toxicity of 6PPD to invertebrates (Daphnia magna) was conducted under Flow-through immobilisation test according OECD TG 202; the EC50 (48 h) of 0.23 mg/l was determined based on geometric mean of measured concentrations.

7.8.1.2.2. **Long-term toxicity to aquatic invertebrates**

Table 16 Summary of the long-term effects of Dusantox L on aquatic invertebrates

Method	**Species**	**Results**	**Reliability assigned in registration**
Daphnia Magna reproduction test (C.20; OECD TG 211) freshwater semi-static	Daphnia magna	EC50 (21d):0.28 mg/L NOEC (21 d): 0.01 mg/L (nominal)	1 (reliable without restriction)

The chronic toxicity study of 4–Hydroxydiphenylamine (the main hydrolysis product of the PPD) to Daphnia magna is reported as the key chronic toxicity study for 6PPD to Daphnia magna; the NOEC (21 d) of 0.028 mg/l was determined in the study.

7.8.1.3. **Algae and aquatic plants**

Table 17 Summary of the toxic effects of Dusantox L on algae

Method	**Species**	**Result**	**Reliability assigned in registration**
Static test corresponding to EEC specification 92/69/EEC C.3 and OECD TG 201	Scenedesmus subspicatus (new name: Desmodesmus subspicatus)	EC50 (72 h): 3.8 mg/L based on: biomass EC50 (72 h): > 5.3 mg/L based on: growth rate NOEC (72 h): 2.5 mg/L	1 (reliable without restriction)

The chronic toxicity study of 4–Hydroxydiphenylamine (the main hydrolysis product of the PPD) to Desmodesmus subspicatus is reported as the key toxicity study for 6PPD to algae. ErC50 (72 h) of 2.6 mg/l and ErC10 (72 h) of 0.58 mg/l was measured and a NOEC (72 h) of 0.23 mg/l was calculated.

7.8.1.4. Sediment organisms

No data available for the substance on ECHA dissemination website.

7.8.1.5. Other aquatic organisms

No data available.

7.8.1.6. Summary and discussion on aquatic toxicity

Prior to assessing the effects of aquatic toxicity it is important to stress that the exact value of water solubility of Dusantox L is not determined; w_s of < 1 mg/l at 20°C for both components (the value is below the limit of detection).

Short-term aquatic toxicity studies with algae, daphnia and fish are available for Dusantox L. The EC50 and LC50 values of the substance were found to be 5.3, 1.3 and 1.1 mg/l for algae, daphnia and fish respectively.

It is important to underline that all effect values reported are based on nominal concentrations and exceed assumed water solubility of the substance. Thus the actual effect values are likely to be lower; that is also supported by the value of fish toxicity for 6PPD: the LC50 (96 h) = 0.028 mg/l based on geometric means of measured concentrations.

Both available chronic toxicity studies, Daphnia Magna Reproduction Test and Fish Juvenile Growth Test report NOEC of 0.01 mg/l which indicates that fulfilling toxicity criterion for the substance is borderline case. In addition reported NOEC values are based on nominal concentrations.

The value of NOEC (30d) of 0.0037 mg/l for 6PPD based on analytical monitoring implies that the value of chronic aquatic toxicity for Dusantox L is expected to be lower. Thus the toxicity criterion based on the values of aquatic chronic toxicity for Dusantox L can be regarded as fulfilled. Due to significant abiotic degradation of Dusantox L toxicity can be caused by parent substance as well as by the degradation products.

7.8.2. Terrestrial compartment

7.8.2.1. Toxicity to soil macro organisms

Table 18 Summary of toxic effects of Dusantox L on earthworms

Method	Species	Result	Reliability assigned in registration
Toxicity to earthworms : artificial soil test (C.8; OECD TG 207) Substrate: defined artificial soil	Eisenia foetida	LC0 (14 d) = 800 mg/kg dw LC50 (14 d) = 1463 mg/kg dw LC100 (14 d) > 2000 mg/kg dw LC50 (7 d) =1735 mg/kg dw basis for effects: mortality	1 (reliable without restriction)

The results of the long-term toxicity to earthworm (Eisenia fetida) tested according OECD TG 222 (Earthworm Reproduction Test) is available for 6 PPD using the read-across from supporting substance (structural analogue or surrogate). NOEC (56d) for reproduction was determined to be 100 mg/kg dw.

7.8.2.2. Toxicity to terrestrial plants

No data available for the substance on ECHA dissemination website; waiving provided.

7.8.2.3. Toxicity to soil micro-organisms

No data available for the substance on ECHA dissemination website; waiving provided.

7.8.2.4. Toxicity to other terrestrial organisms

No data available for the substance on ECHA dissemination website.

7.8.2.5. Summary and discussion on terrestrial toxicity

Terrestrial toxicity of the substance can be assumed only based on the result of the toxicity on earthworms (LC50 (14 d) = 1463 mg/kg dw which indicates low terrestrial toxicity potential. However result of the long-term toxicity to earthworm for structural analogue to 6 PPD (NOEC (56d) of 100 mg/kg dw) is not consistent with this assumption.

7.8.3. Microbiological activity in sewage treatment systems

7.8.3.1. Toxicity to aquatic micro-organisms

Table 19 Summary of effects of Dusantox L on micro-organisms

Method	Results	Reliability assigned in registration
"Activated Sludge, Respiration inhibition test" (OECD TG 209); activated sludge from STP, predominantly domestic sewage	EC50 (3 h): > 2000 mg/L EC20= 189-745 mg/l pH: 7.9 – 8.3; t: 18 – 21°C	1 (reliable without restriction)

Despite the reliability 1 assigned by the registrant(s) the study has several limitations: the test concentration is far above the water solubility of the registered substance (< 1mg/L) and it can be assumed that due to short test duration, the major amount of the registered substance will be insolubilized and thus not available to micro-organisms. No data on inhibition of nitrification are presented in the study report. However, the inhibitory effect on nitrification might be a sensitive endpoint, as the possible products of hydrolysis (hydroquinone and other quinone-like compounds) might be toxic to aquatic microorganisms. The data from literature show that nitrification was progressively inhibited as quinone-like compounds concentration was increased, with IC50 values at 1hr of exposure time of 3.1 ± 0.5 mg/L for hydroquinone and 2.8 ± 0.4 mg/L for p-benzoquinone (as reported by Suárez-Ojeda et al, 2010).

The results of Activated Sludge, Respiration Inhibition Test for 6 PPD are available (2016, OECD TG 209, reliability 1). An EC10 and an EC50 of > 100 mg/L are to be determined; study duration was 3 hours.
The toxicity of hydroquinone to Microcystis aeruginosa was investigated by determining the cell multiplication inhibition threshold concentration. A toxicity threshold (TT) EC3 (8 d) = 1 mg/l nominal was found (Bringmann G., Kuhn R., 1978).

The micro-organisms in the sewage treatment plant should be protected to ensure proper waste water treatment. Reliable data on inhibition of nitrification as a probably sensitive endpoint are missing in the registration dossier which results in concern regarding the

hazard and risk assessment of sewage treatment plant and its microorganisms. Therefore, toxicity tests on aquatic microorganisms for the registered substance and its hydrolysis products is recommended. The testing of hydrolysis products is needed as the registered substance undergoes significant abiotic degradation in water compartment under aerobic conditions, leading to the generation of compounds potentially toxic to micro-organisms. The eMSCA recommends that one test shall be performed with five days old test item to allow generation of hydrolysis products.

Therefore, if the registration becomes active again, the eMSCA recommends to registrant(s) of this substance to carry out Activated sludge respiration inhibition testing (test method: Activated sludge, respiration inhibition test (carbon and ammonium oxidation), OECD 209). The respiration rate regarding carbon oxidation and ammonium oxidation shall be measured. One test shall be performed with freshly prepared test item concentration of the registered substance. Another test shall be performed with five days old test item concentration to allow the generation of hydrolysis products.

7.8.4. Non compartment specific effects relevant for the food chain (secondary poisoning)

7.8.4.1. Toxicity to birds

No data available for the substance on ECHA dissemination website.

7.8.4.2. Toxicity to mammals

The substance has been self- classified by the registrant as Reprotox 1B and STOT RE 1.

7.8.5. PNEC derivation and other hazard conclusions

Table 20

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks/Justification**
Freshwater	NOEC value 0.01 mg/L PNEC: 0,0002 mg/L	Assessment factor: 50 The lowest long-term NOEC value of 0.01 mg/L (Oncorhynchus mykiss), 2 long-term results from species representing two trophic levels (fish and Daphnia) are available, an assessment factor (50) taken from Table R.10-4 of the ECHA guidance document (2008)
Marine water	NOEC value 0.01 mg/L PNEC: 0,00002 mg/L	Assessment factor: 500 The lowest long-term NOEC value available 0.01 mg/L (Oncorhynchus mykiss), 2 long-term results from species

		representing two trophic levels (fish and Daphnia) are available, an assessment factor (500) taken from Table R.10-5 of the ECHA guidance document (2008)
Intermittent releases to water	PNEC: 0.011 mg/L	Assessment factor: 100 The lowest L(E)C50 of three short-term tests from three trophic levels was found for the fish species *Cyprinus carpio*. Since results of all acute toxicity studies are above water solubility, estimation of PNEC value is therefore only indicative.
Sediments (freshwater)	PNEC: 0.011 mg/kg sediment dw	Extrapolation method: partition coefficient Absence of well reported ecotoxicological data for sediment-dwelling organisms, the PNECsed was calculated using the equilibrium partitioning method
Sediments (marine water)	PNEC: 0.0011 mg/kg sediment dw	Extrapolation method: partition coefficient Absence of well reported ecotoxicological data for sediment-dwelling organisms, the PNECsed was calculated using the equilibrium partitioning method
Sewage treatment plant	No reliable data	
Soil	PNEC: 1.463 mg/kg soil dw	Assessment factor: 1000 PNECsoil based upon earthworms (Eisenia foetida) acute toxicity test: 14 days L(E)C50=1463 mg/kg dried matter and the assessment factor (1000) for short-term toxicity tests taken from Table R.10-10 of the ECHA guidance
Air	Not evaluated	
Secondary poisoning	PNEC: 1.33 mg/kg	PNECoral has been derived from the 28d NOAEL (40mg/kg/day) in rats and applying a conversion factor of 10 (*Rattus norvegicus _ 6 weeks)* and assessment factor for extrapolation of 300

7.8.6. Conclusions for classification and labelling

The self-classification on aquatic toxicity as "Aquatic Chronic 2 H411: Toxic to aquatic life with long lasting effects" does not reflect changes according to CLP regulation regarding M-factor and changes according to the 2nd Adaptation to Technical Progress to the CLP Regulation (Commission Regulation (EU) No 286/2011). The second ATP introduced the principle that classification for chronic aquatic toxicity shall be based on chronic studies if those are available.
Therefore, based on available data the eMSCA reassessed and proposed the classification on aquatic toxicity.

Degradation

As the three tests on ready biodegradation (OECD TG 301 B, 301 D, 301 F) indicate 46%, 33% and 9% degradation after 28 days. A modified MITI (II) test (OECD TG 302C) shows 18% degradation after 28 days. Based on these results Dusantox L is considered as not readily and not inherently biodegradable.
Although based on the results of hydrolysis test the substance undergoes significant primary abiotic degradation, the relevant information on degradation products is not available. As it cannot be demonstrated that degradation products of Dusantox L do not fulfil the criteria for classification as hazardous to the aquatic environment, Dusantox L is considered as not rapidly degradable.

Bioaccumulation

The measured value of log Kow <6.5 indicates that Dusantox L has a potential to bioaccumulate.

Based on the results of the bioconcentration fish study reported BCF values of 110 (c=0,25 mg/l) and of 47 (c=0,025 mg/l) don´t indicate fulfilling of bioaccumulation criterion (BCF ≥ 500). However, the quality of the study and the reliability assigned by the registrant(s) are controversial.

Toxicity:

Table 21 The experimental results on acute and chronic aquatic toxicity of Dusantox L including the key studies highlighted in bold are as follows:

Trophic level	**Species**	**Short-term result**	**Long-term result**
Fish	*Cyprinus carpio*	**96h LC_{50}= 1.1 mg/L**	
	Oncorhynchus mykiss		**28d NOEC=0.01 mg/L growth**
Aquatic invertebrates	*Daphnia magna*	48h EC_{50}=1.3 mg/L	**21d NOEC=0.01 mg/L reproduction**
Aquatic algae and plants	*Scenedesmus subcapitata* *(Desmodesmus subcpitatus)*	72h ErC_{50}> 5.3 mg/L	72h NOEC=2.5 mg/L

All available acute aquatic toxicity studies are based on nominal concentrations. Due to the low and not precise value of water solubility (<1mg/L) and high viscosity (325-338 mm2/s at 40°C) of the test substance, the nominal concentrations do not reflect the actual test concentrations which might have been significantly lower. Regarding hydrolytical instability of parent substance in water, it cannot be excluded that the observed aquatic toxicity is due to the parent substance and the degradation products.

The eMSCA proposal for classification on aquatic toxicity

Acute aquatic hazard:
Aquatic acute toxicity studies are available for all trophic levels. The L(E)C50 values of the substance are 5.3, 1.3 and 1.1 mg/L for algae, daphnia and fish, respectively. This data is based on nominal concentrations in the suspension and the reported L(E)C50 values are above the water solubility.
The values of $L(E)C_{50}$ are > 1 mg/L, Dusantox L does not fulfil the criteria for classification as Aquatic Acute 1.

Chronic aquatic hazard:
Dusantox L is considered not rapidly degradable in the environment. Adequate long-term data are available from Daphnia Magna Reproduction Test and Fish Juvenile Growth Test. The lowest NOEC value of 0.01 mg/L is reported for invertebrates *Daphnia magna* and for fish *Oncorhynchus mykiss.*
This value is equal to classification threshold value of ≤ 0.01 mg/L for no-rapidly degradable substances, Dusantox L therefore fulfils criteria for classification as **Aquatic Chronic 1 (H410) with an M-factor of 10 (0.001 < NOEC ≤ 0.01).**

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

7.9.1.1. Summary and discussion on toxicokinetics

The key study according EC 92/69/EEC, Method B.36 Toxicokinetics OECD No.417 (GLP, reliability 1) is reported on the ECHA dissemination website. The eMSCA agree with the registrant that complete toxicokinetic profile of the substance cannot be relevantly assessed. The study was performed in two experiments (2008). In experiment I, Dusantox L was orally administered to male rats (Wistar) and the parent compound and the metabolites were analysed by HPLC and LC-MS. In experiment II Dusantox L spiked with 14C - Dusantox 6PPD was administered and the distribution of 14C Dusantox 6PPD in biological materials (plasma, bile, urine and faeces) was studied by TLC followed by radiometry. As only one of the components was radio labelled, the toxicokinetic information is available only for that component (6PPD). Very limited toxicokinetic data for the second component are presented. Identification of metabolites in biological samples is missing. For the HPLC method with MS/UV detection no detection and quantification limits are given. The justification by an inadequately sensitive detector is understandable but not acceptable. Identification of metabolites based on the mass spectra would be very important as there is a possibility of degradation to primary and secondary amines, which can react in vivo to form nitrosamines.

This endpoint is not targeted and no further evaluation has been performed by the eMSCA.

7.9.2. Acute toxicity and Corrosion/Irritation

7.9.2.1. Summary and discussion of acute toxicity

The following studies are reported on the ECHA dissemination website:

The acute oral toxicity of Dusantox L was evaluated in acute oral gavage study with Wistar rats performed according to OECD401 and GLP. The oral LD50 was >2000 mg/kg bw (2000).

The acute dermal toxicity of Dusantox L in Wistar rats after occlusive application performed according to OECD 402 (GLP) indicated low toxicity with LD50>2000 mg/kg bw (2ml/kg i.e. 2037 mg/kg bw) (2000).

No classification is required according CLP Regulation No 1272/2008.

This endpoint is not targeted and no further evaluation has been performed by the eMSCA.

7.9.2.2. Summary and discussion of irritation

The following studies are reported on the ECHA dissemination website:

The skin irritation potential of the test substance Dusantox L was evaluated in skin irritation study with 3 New Zeeland White rabbits according to OECD 404 and GLP. The

substance is slight skin irritant (Irritation Index: 1.16); changes fully reversible within 14 days (2000).

The eye irritation potential of the test substance Dusantox L was evaluated in eye irritation study with 3 New Zeeland White rabbits according to OECD 405 and GLP.
In 1 hour after exposure a slight redness was observed at the first and third animals and slight ophthalmorrhoea was observed at first animal. In all animals no observable changes were noted during the observation period - in 24, 48 and 72 hours after application. Changes were fully reversible within 1 day (2000).

No classification is required according CLP Regulation No 1272/2008.

This endpoint is not targeted and no further evaluation has been performed by the eMSCA.

7.9.3. Sensitisation

The skin sensitizing potential of Dusantox L was evaluated in the guinea pig maximisation test according to OECD 406 method (GLP, reliability 1) is reported on the ECHA dissemination website.
Maximum concentration not causing irritating effects in preliminary test: 20%.
For induction twenty guinea pigs were intradermally injected with 1% Dusantox L in olive oil with complete FCA, followed one week later by dermal induction with 50% Dusantox L in olive oil. Animals were treated for 48 hours under occlusive conditions. Pre-treated and control animals were challenged two weeks later with 20% test substance in olive oil under occlusive conditions for 24 hours. In 48 hours after application seven animals had the positive skin reactions: two of the animals had the middle repletion and the mild oedema, five of the animals had the mild or the dappled repletion and the mild or the very mild oedema. In 72 hours after application the reaction was expressed as the repletion, the oedema and the separating of skin surface coats. The sensitivity and reliability control results of the test: Applied substance - Benzocain (CAS No.94-09-7) - intradermal induction 5% conc. in olive oil, epicutan exposition: 25% concentration in vaseline alba, challenge 5% concentration in vaseline alba. Test results: 60% positive dermal reaction. The test reliability was confirmed.
Overall, it can be concluded, that 35% (7/20) of the animals are sensitized at an intradermal induction of 1% Dusantox L in olive oil in this study. The skin sensitisation potency of the test substance Dusantox L is considered to be a moderate

It is improbable that Dusantox L may meet classification criteria as Skin Sens. 1A. For such classification this substance should sensitise at least 30 % of guinea pigs at intradermal induction concentration ≤ 0,1% or should sensitise at least 60 % of guinea pigs at intradermal induction concentration being in the range> 0,1 % to ≤ 1 %.

Although it is not probable that at intradermal induction concentration ≤ 1% the percentage of skin sensitised pigs will be equal or higher than 60, there are no other data to exclude it. Therefore, in case classification in Category 1A cannot be excluded the general Category 1 classification must be chosen.

Therefore, the eMSCA agrees with Registrant´s self-classification Skin Sens 1 (H317 May cause an allergic skin reaction) according CLP Regulation No 1272/2008.

7.9.4. Repeated dose toxicity

7.9.4.1. Summary and discussion of repeated dose toxicity

The following studies are reported on the ECHA dissemination website:

- *28-day oral toxicity study (OECD 407, 2000).* Rats (6 per sex per dose) received doses of 0, 40, 80, 120 mg/kg bw/day Dusantox L by oral gavage. Administration of the substance caused reduced body weight and food and water consumption in both sexes, alterations of clinical chemistry and haematological parameters, changes in organ weights and histopathological findings.
The eMSCA comment: registrant(s) in his registration dossier stated the NOAEL as ca. 40 mg/kg bw/ day and NOEL ≤ 40 mg/kg bw/day. Since at the dose of 40 mg/kg bw/day statistically significant changes in haematological and biochemical parameters were observed, eMSCA proposes to modify these values as follows: NOAEL: < 40 mg/kg bw/ day, NOEL: < 40 mg/kg bw/day.

– *two 90 days oral studies (OECD 408)* (one of them was not reliable)

In valid 90 day RDT study (2009), Wistar rats (10 per sex per dose) received doses of 0, 10, 30, 60 mg/kg bw/day Dusantox L by oral gavage for 90 days. Based on the results of the 90 RDT study it can be concluded that the main targets identified after repeated oral intake of Dusantox L by rats are liver (vacuolar dystrophy of hepatocytes, increased absolute and relative weights, changes of values of ALP and cholesterol), blood (anaemia, affected haemocoagulation), stomach (irritation) and metabolism of ions of animals.

Reduced food intake and body weight (both sexes) is associated with stomach erosions and haemorrhages on mucosa. The influence of administration of tested substance on body weight was reversible.

Treatment related irregular vacuolar dystrophy (vacuolated cell foci with colourless vacuoles of various sizes in larger hepatocytes) was found in liver of treated males and females. Moreover, this effect was observed at the end of the recovery period indicating irreversibility. Concerning to liver weights, an increase of relative as well as absolute weight showed clear dose-relationship to treatment. In males, the values revealed statistical significance and changes were irreversible. Negative influence of Dusantox L on liver was also confirmed by changes of some biochemical parameters. Hypercholesterolaemia (females) and elevated activity of ALP (both sexes) are probably related to vacuolar dystrophy of liver.

Concerning blood system, decrease in haemoglobin (at mid dose males); at low dose females), haematocrit (at high dose females) and red blood cell counts (at mid dose males) occurred in both sexes of animals. Together with dose dependent decrease of MCV (both sexes), increased presence of rubiginous pigment (prob. haemosiderin) in spleen (females) as well as significantly elevated relative weight of heart (females), Dusantox L appears to cause functional anaemia, probably treatment induced haemolytic anaemia (Cesta, 2006; Suttie, 2006). The presence of bilirubin in urine was not recorded.

Negative effect of Dusantox L on haemocolaguation was reflected in a significant reduction in prothrombin time of animals. This change was dose dependent and irreversible. Significantly decreased protrombin time (both sexes) and changes in APTT (significantly increased in female after recovery) could be associated with hepatopathy (coagulation factors are synthesized in liver).

Alteration of ions metabolism (elevated level of P (both sexes); decreased level of Na (males); increased level of K^+ (females); decreased level of Cl^- (males)), increase of relative weight of kidney (in males at high and females at mid and high dose group) and presence of leukocytes in urine could be caused by kidney dysfunction. Since

histopathological examination did not confirmed the functional disorder, observed changes can be regarded as adaptive.

7.9.4.2. **Conclusion on Repeated dose toxicity**

Taking into account the results of repeated dose toxicity, there is evidence that Dusantox L has negative effect on growth, clinical status, red and white blood component, haemocoagulation, metabolism of ions of animals, affected the structure and function of liver and irritated stomach. High incidence of biologically and statistically significant differences were recorded mainly at the mid and high dose level, but some serious and significant changes were observed also at the low dose level (10 mg/kg bw/day). Based on the above mentioned findings, NOAEL can be set at < 10 mg/kg/day (males/females) and LOAEL at 10 mg/kg bw/day (males/females). The overall discussion of repeat dose toxicity in registration dossier is rated as sufficient, also full study reports were available to eMSCA.

The eMSCA agrees with Registrant´s self-classification STOT RE Cat 1 (H372 – Caused damage to organs, targeted organ: liver) according CLP Regulation No 1272/2008.

7.9.5. Mutagenicity

7.9.5.1. **Summary and discussion of mutagenicity**

Summary of experimental studies on mutagenicity based on studies reported on the ECHA dissemination website:

- Reverse mutation test using Salmonella Typhimurium (TA1537, TA98, TA100 , TA1535) – OECD NO. 471 Ames test:
  Results: gene mutation test in bacteria Salmonella Thyphimurium was negative (2000);
- In vitro mammalian chromosome aberration test (B10)/OECD 473:
  Results: positive without metabolic activation, negative with metabolic activation.
  Dusantox L induces chromosome aberrations in V79 Chinese hamster cells in the absence of a metabolic activation system. The test compound induced a statistically significant increase in the number of phases with aberrations without gaps with several concentrations as compared with the solvent control and indicates clastogenic potential (Hüls Infracor AG (2001));
- In vivo mammalian erythrocyte micronucleus test (B12)/OECD 474:
  Results: Dusantox L does not show any mutagenic effect in the doses applied and does not produce any cytotoxic effect on bone marrow of laboratory rats in this test (2003);

- Mammalian bone marrow chromosome aberrations test (OECD 475, B 11):
  Results: Cytogenic analysis of mouse bone marrow cells which were impacted in vivo with tested substance in doses 125, 250,500 mg/kg body weight during 24 hours showed that none of these doses increased statistically significantly either the percentage of cells with aberrations or the number of aberration per cell (2006).

No classification is required according CLP Regulation No 1272/2008.

7.9.6. Carcinogenicity

Not evaluated, no data available.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Reproductive toxicity was identified as an endpoint of concern in the initial CoRAP justification.

7.9.7.1. Summary and discussion of effects on fertility

Reproductive toxicity of Dusantox L was investigated in a Two generation reproductive toxicity study (PNDT) (OECD 416; 2007) in Wistar rats. Rats (6 per sex per dose) received doses of 0, 5, 25, 50 (75) mg/kg bw/day Dusantox L by oral gavage. In the study plan the highest applicated dose of Dusantox L was 75 mg/kg bw/day, but with respect to impaired health of the parental males after 30 days of application, the highest dose was reduced to 50 mg/kg bw/day. The study was rated by registrant(s) with a Klimisch score of 1. However, eMSCA proposes to reduce Klimisch score of the study to 2 on the ground of deviations from current OECD 416 Guideline (2001)/B.35 (2004) found during evaluation (mating -2 females:1 male, duration 3 weeks; dosing (termination one day prior to mating in P/F1-males); biometrics of all organs specified as well as necropsy and biometrics of pups bodies were not carried out; absence of data on number of implantations, corpora lutea, post-implantation losses, offspring gender (sex ratio); individual pups weights; sperm motility and number; qualitative depletion of the primordial follicle population).

Negative impact of Dusantox L is mostly visible in P generation. Adverse effect of the substance (especially in the high dose group) caused a worsening condition of males and females that manifested in reduced weight and food intake. Moreover, treatment related decrease of reproductive parameters in P - females (fertility index, number of females with live offspring, total number of pups at birth and mean number of pups per litter) was recorded. The evaluation of histopathology results in P-generation indicated the dose related increase of liver weight in females and statistical significance of this parameter in mid dose males. The increase of relative weight of follicles was recorded in males of all dose groups and was dose related in both P- and F1-generation. Direct negative effect of Dusantox L was observed on spermatogenesis in P-males at high dose group. However, as stated in the study report, the strongest degenerative changes in testes observed in the P-generation males could be caused by application of 75 mg/kg/day of Dusantox L within the first month of the study.

The moderated effect of Dusantox L in F1/F2 generation could be explained by the fact that F1- and F2-generation animals were in contact with Dusantox L continuously from the moment of conception through the body of the mother and after birth through breast milk. In F1-females an increase in relative liver weight was not observed and the relative weight of male testes did not differ significantly against control. The values of reproductive parameters in two lower dose groups were consistent with those observed in control animals. Worsening of some reproductive parameters was observed only in the highest dose group (decreased fertility index, number of females with live offspring, total number of pups at birth, mean number of pups per litter).

The incidence of degenerative changes in the seminiferous tubules in F1- males was at high dose level lower than in P-generation males and did not meet statistical significance. Histopathological examination of testes in low and mid dose group of F1 generation was not performed due to the nature of degenerative changes and high female fertility index in the low and medium dose (control/low/medium dose: 90.0/90.0/86.67 %).

Additional analysis of raw data of the male fertility index (MFI=Nr. of males impregnating a female/Nr. of males cohabitated × 100) did not show any statistically significant changes (Fisher's exact test) neither in P-generation nor F1-generation. Since no significant changes in the male fertility were observed, further analysis is not required.

Fetal growth retardation in the F1 and F2 generation (reduced average weights) was correlated with the maternal weight loss. These results are in concordance with the results of the prenatal developmental toxicity study.

Conclusion on fertility: Based on clinical sings, reduced body weight, reduced fertility of animals, mortality of 2 dams in P and F1, reduced total number of pups in F1 and F2, reduced litter weight in F1 and F2 generations, reduced body weight gain of pups per litter in F1 and F2 and histopathological findings (increased of relative weight of liver in P males and females and F1 males, increase of relative weight of follicles in P males, degenerative changes in spermiogenesis in P and F1 males), the values of NOAEL and LOAEL can be set as follows:

NOAEL (P): ≥ 5 mg/kg bw/ day (male/female)
LOAEL (P): ≥ 25 mg/kg bw/ day (male/female)
NOAEL (F1): ≥ 25 mg/kg bw/ day (male/female)
LOAEL (F1): > 25 mg/kg bw/ day (male/female)

In conclusion, the available data indicate a mild effect of the substance on male reproduction as well as on female fertility (Parker, 2006). Based on these findings eMSCA recommend to classify the substance Dusantox L in the category 2 for fertility according to CLP Regulation, Annex 1, 3.7.2.1. Moreover, eMSCA points out that the Registrant currently self-classifies the substance as toxic for reproduction 1B (Repr 1B H360) and appropriate risk management measures have already been put in place with this self-classification.

7.9.7.2. **Summary and discussion of prenatal developmental toxicity**

Developmental toxicity of Dusantox L was investigated in one prenatal developmental toxicity study (OECD 414, 2008; reliability 1) in Wistar Han rats.

The highest dose (100 mg/kg bw/day) induced clear maternal toxicity (clinical signs, marked absolute body weight loss) associated with significant reduction of the absolute weight of the uterus and decreased fetal weights. Number of fetal skeletal variations were noted in all test groups. They consisted mainly of retardation of ossification of the cranial bones, sternum, lumbar and sacral vertebrae with incidence predominantly in the highest dose. Detected skeletal anomalies do not constitute anomalies dangerous for further development of individuals and represents transient variations from development. The eMSCA concluded that the developmental toxicity observed was mainly due to a non-specific maternal toxicity such as unspecific clinical sings and marked absolute body weight loss. The effects of the substance administration on offspring were not biologically significant but rather mild and transient (delayed ossification or decreased fetal weight) Based on above mentioned results, the values of NOAEL can be set as follows:

NOAEL (pregnant females): ca. 50 mg/kg bw/ day.
NOAEL (prenatal development): <25 mg/kg bw/day.

During the decision making process, SEv case was returned from the written procedure due to a need for MSC discussion on whether a proposal for amendment (PfA) requesting a PNDT in a second species should be addressed in the draft decision. The additional information request was based on findings from the available PNDT study in rat indicating some effects on maternal and developmental toxicity and the potential data gap identified for this endpoint. The eMSCA agreed in principle with the arguments of the PfA's submitter, however, as the only Registrant currently self-classifies the substance as toxic for reproduction 1B (Repr. 1B H360), the eMSCA concluded at this point of the evaluation process that there is no need for requesting a further PNDT testing in a second species as appropriate risk management measures have already been put in place with this self-classification.

In the following discussion, members agreed with the eMSCA that the available dataset does not allow drawing a clear conclusion whether the substance should be classified as Repr 1B or Repr 2. However, the current Registrant's self-classification covers the possible concerns and ensures the appropriate risk management measures are in place; thus, MSC agreed with the eMSCA that further PNDT testing may not be fully justified at this point in time and under these circumstances also for animal welfare reasons.
MSC agreed with the outlined approach and concluded that the suspected concern for this endpoint is currently properly managed with this self-classification and unanimously agreed on the draft decision as modified at the meeting based on the above considerations.

7.9.7.3. Conclusion on Toxicity to reproduction

The eMSCA considered the initial concern for reproduction toxicity as clarified and does not require an additional information. If changes in the current circumstances occur (such as e.g. new registrant(s) appear with different self-classifications of this substance than Repr. 1B H360 the PNDT study in a second species (rabbit) may be required for possible clarification of the remaining unclear concerns and possible preparation of an Annex VI dossier for harmonised classification and labelling either by a MSCA, or by the Registrant according to the CLP Regulation.

7.9.8. Hazard assessment of physico-chemical properties

Not applicable.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

The eMSCA agrees with the registrant's selection of critical studies and the DNEL Derivation for workers. It was considered that systemic LOAEL of 10 mg/ kg bw/day from 90-day repeated dose toxicity study and respective DNELs for long-term systemic effects (dermal and inhalation) of Dusantox L also cover reproductive toxicity (parental toxicity and developmental toxicity).

Table 21

CRITICAL DNELS/DMELS. WORKERS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Repeat dose toxicity	Systemic effects - long term (inhalation)	Repeat dose toxicity (90 day study in rats by oral route)	LOAEC: 8.850 mg/m3	0.059 mg/m3	LOAEL: 10 mg/kg bw/d (90 d RDT study by oral route) Overall factor: 150
Repeat dose toxicity	Systemic effects - long term (dermal)	Repeat dose toxicity (90 day study in rats by oral route)	LOAEL: 10 mg/kg bw/d	0.017 mg/m3	LOAEL: 10 mg/kg bw/d (90 d RDT study by oral route) Overall factor: 600

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

Dusantox L was self-classified as follows:

Skin Sens. 1 H317: May cause an allergic skin reaction.
Repr. 1B H360: May damage fertility or the unborn child.
STOT RE. 1 H372: (liver) Causes damage to liver through prolonged or repeated exposure by oral route.

Based on available information the evaluating MSCA can support this conclusion.

As discussed in section 7.9.7, the eMSCA considers the initial concern for reproduction toxicity as clarified and does not require an additional information.
If changes in the current circumstances occur (such as e.g. new Registrants appear with different self-classifications of this substance than Repr. 1B) the PNDT study in a second species (rabbit) may be required for possible clarification of the remaining unclear concerns and for possible preparation of an Annex VI dossier for harmonised classification and labelling.

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

7.11. PBT and VPVB assessment

7.11.1. Persistence

Both components of the registered substance undergo significant abiotic degradation; its intensity depends on temperature and pH. The components of registered substance are the most stable at pH 4 and 15°C, hydrolysis half-life is 43.4 h for component 1 and 53.8 h for component 2.

The results from aerobic biodegradation studies range in 9 – 46% of degradation and indicate that Dusantox L does not biodegrade rapidly in water compartment. The substance is neither readily nor inherently biodegradable and fulfils screening P criterion. This is also supported by BIOWIN estimation which predicts no ready biodegradability for both components of the substance.

To clarify the potential of persistency it is recommended at the first step to repeat the ready biodegradability study (Closed Bottle Test C.4-E) with request for specific chemical analysis to determine and assess the main degradation products.

Based on the outcome of the closed bottle ready biodegradability study (i.e. if the study indicates that the substance is not ready biodegradable) soil simulation testing (OECD 307 Aerobic and Anaerobic transformation in Soil) with request for identification of transformation products would be considered to reach a conclusion on persistency.

7.11.2. Bioaccumulation

The measured log Kow value < 6.5 indicates that Dusantox L has a potential to bioconcentrate in aquatic organisms and fulfils the screening B criterion.

Available results of the bioconcentration fish study - BCF values of 110 (c = 0, 25 mg/l) and of 47 (c = 0,025 mg/l) do not indicate fulfilling of bioaccumulation criterion. However, the quality of the study and the reliability assigned by the registrant(s) are controversial.

The values of log Koc indicate high adsorptive potential of the both components of the substance; in addition estimated log KoA values indicate that biomagnification in terrestrial food chains may occur.

Bioaccumulation criterion should be examined further considering the potential for bioaccumulation (especially terrestrial bioaccumulation) and biomagnification to be able to conclude on bioaccumulation of the substance.

7.11.3. Toxicity

Prior to assessing the effects of aquatic toxicity it is important to stress that the exact value of water solubility of Dusantox L is not determined; w_s < 1 mg/l at 20°C for both components.

Results available from aquatic chronic toxicity studies, Daphnia Magna Reproduction Test and Fish Juvenile Growth Test report NOEC values of 0.01 mg/l and indicate that fulfilling toxicity criterion for the substance is a borderline case. It is important to underline that all effect values reported (including EC50 / LC50 values from short-term aquatic toxicity studies with algae, daphnia and fish) are based on nominal concentrations only and exceed the assumed water solubility of the substance. Thus the actual effect values are likely to be lower. This can be supported by the effect values of fish toxicity for 6PPD: the LC50 (96 h) of 0.028 mg/l based on geometric mean of measured concentrations and the NOEC (30d) value of 0.0037 mg/l based on analytical monitoring.

Accordingly the toxicity criterion based on the long-term NOEC values for freshwater organisms for the substance can be regarded as fulfilled.

Considering the significant abiotic degradation of Dusantox L toxicity can be caused by the parent substance as well as by the degradation products.

In addition the substance has been self- classified by the Registrant as Reprotox 1B and STOT RE 1.

7.11.4. Summary and overall conclusions on the PBT, vPvB properties

Based on available information Dusantox L can be regarded as potentially P and B and fulfilling the screening P and B criteria; T criterion can be regarded as fulfilled. No final overall conclusion on PBT / vPvB properties is possible at this time.

7.12. Exposure assessment

7.12.1. Human health

No data on exposure for workers, consumers or indirect exposure via the environment has been assessed due to lack of data on current manufacture, production, import, export and use volumes in the EU (registrations inactive).

7.12.2. Environment

EUSES exposure modelling for environmental compartments has not been performed due to lack of data on current manufacture, production, import, export and use volumes in the EU (registrations inactive).

7.13. Risk characterisation

There are no data on current manufacture, production, import, export and use volumes in the EU (registrations inactive). Consequently emissions of Dusantox L from current sources and their contribution to human and environment exposures cannot be assessed. No risk characterisation could be performed.

7.14. References

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7.15. Abbreviations

ALP	Alkaline phosphatase
bw	body weight
CLP	Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006
eMSCA	Evaluating Member State Competent Authority
LOAEL	Lowest Observed Adverse Effect Level
MCV	Mean Cell Volume
MFI	Male Fertility Index
MSC	Member State Committee
MSCA	Member State Competent Authority
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Effect Level
PBT	Persistent Bioaccumulative and Toxic
PfA	Proposal for Amendment
PNDT	Prenatal Developmental Toxicity Study
SEv	Substance Evaluation
VPvB	very Bioaccumulative and very Toxic