SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Reaction mass of 4,4'-methylenediphenyl diisocyanate and o-(p-isocyanatobenzyl)phenyl isocyanate / methylene diphenyl diisocyanate

EC No 905-806-4

CAS No N/A

Evaluating Member State(s): Estonia

Dated: 13 July 2019

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2015

Before concluding the substance evaluation a Decision to request further information was issued on: 23 February 2017.

Further information on registered substances here:

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

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

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

Reaction mass of 4,4'-methylenediphenyl diisocyanate and o-(p-isocyanatobenzyl)phenyl isocyanate / methylene diphenyl diisocyanate (MDI mixed isomers) was originally selected for substance evaluation in order to clarify concerns related to:

- respiratory and skin sensitisation,
- potential carcinogenicity, mutagenicity and toxicity for reproduction,
- suspected PBT properties,
- wide dispersive use, including consumer use, and
- high aggregated tonnage.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Regulation (EC) 1906/2006 annex XVII entry no 56 applies if substance is part of mixtures containing ≥0.1% of MDI for supply to the general public.

Additionally, ECHA Committee for Risk Assessment (RAC) on 5 December 2017 and Socio-economic Analysis (SEAC) on 15 March 2018 adopted their opinions on the restriction proposal for the industrial and professional uses of diisocyanates made by Germany, which covers among the others MDI mixed isomers (https://echa.europa.eu/documents/10162/d6794aa4-8e3a-6780-d079-77237244f5f9).

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State (eMSCA) to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	**Tick box**
Need for follow-up regulatory action at EU level	
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

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

Not applicable.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

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

Not applicable.

5.2. Other actions

MDI mixed isomers consists predominantly of 4,4'-methylenediphenyl diisocyanate (4,4'-MDI, EC no 202-966-0) and o-(p-isocyanatobenzyl)phenyl isocyanate (2,4'-MDI, EC no 227-534-9). The constituents of the registered substance have common functional group (NCO-group) and belong to the common chemical class – diisocyanates.

Extensive read-across (mostly from 4,4'-MDI as well as polymeric MDI (CAS 9016-87-9)) has been used by the Registrant(s) to cover human health endpoints including reproductive toxiciy and genotoxicity. Regarding the composition, based on the available data, the main difference between the registered substance and 4,4'-MDI appears to be the relative amount of the two main diisocyanate isomeric constituents 4,4'-MDI and 2,4'-MDI. The molecular formula of the two MDI isomers is the same, they have the same molecular weights and NCO-values. The registered substance and 4,4'-MDI have common precursors in the manufacturing process.

In the provided justification document on the read-across the Registrant(s) states that the local toxicity of the isomers depends on the relative reactivities of different NCO-groups that have been measured during the experiments that were conducted under real use conditions, i.e. during polyurethane manufacturing and the application of products. The differences in the reactivity are caused by sterical hindrance and no mesomerism according to "Hückel-Law" can occur (i.e. none or only very minor electronic effects originating from the other aromatic moieties and their substituents). This experimental evidence is indicating that the most reactive NCO-group is the NCO-group in 4-position since 4,4'-MDI reacts 1.8 times faster than 2,4'-MDI.

There is no specific test data provided on MDI mixed isomers for the mutagenicity endpoint. Taking into account the initial grounds of concern and requested information on genotoxicity during SEv the Registrant(s) has provided further information on read-across. The recently performed *in vitro* study (ECHA, 2018) with 2,2'-, 2,4'- and 4,4'-MDI has been provided in order to strengthen the read-across on specific genotoxicity endpoint and to provide evidence that differences in reactivity of NCO-groups at the 2- and 4-positions of MDI are functionally negligible. The study provides an information on the reactivity of different MDI isomers with glutathione (GSH), the major anti-oxidant of the lower airways, which contains the preferred target (cysteine free thiol) for MDI isomers' reactivity.

Currently there is no specific data on the metabolism of the MDI mixed isomers. The assumption about similarities regarding toxicological endpoints of MDI mixed isomers and 4,4'-MDI is mainly based on the chemical reactivity of the common functional group of 4,4'-MDI and 2,4'-MDI. However, the chemical reactivity differences/similarities do not necessarily translate into the same differences/similarities in reactivity towards a biological molecular target, such as DNA, in a cell nucleus under *in vivo* conditions. In fact, less reactive molecules may be even favoured to reach such target whereas more reactive molecules react already prior to reaching this target. Currently there is no information available to exclude such possibility. Based on the available information, the eMSCA cannot conclusively accept the read-across. Therefore, there is potentially a standard data gap for mutagenicity and due to this uncertainty also a minor residual concern for potential genotoxicity. However, the substance is already classified as respiratory sensitiser and the risk appears to be limited.

In relation to reproductive toxicity there is no specific test data provided on MDI mixed isomers. The eMSCA considers the read-across applied by the registrants not sufficiently justified for this endpoint. Therefore, there is potentially a standard data gap for reproductive toxicity. However, based on the provided data, the eMSCA has not identified a specific concern which would require requesting further information under substance evaluation for this endpoint.

Taking into account the abovementioned the eMSCA decided to conclude the current substance evaluation and invites ECHA to consider the potential standard data gaps of MDI mixed isomers in the prioritisation of dossiers for compliance check.

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

Not applicable.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

MDI mixed isomers was originally selected for substance evaluation in order to clarify concerns about:

- respiratory and skin sensitisation,
- potential carcinogenicity, mutagenicity and toxicity for reproduction,
- suspected PBT properties,
- wide dispersive use, including consumer use, and high aggregated tonnage.

Table 2

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Degradation	- *Not P/vP due to hydrolytical unstability* - *Degradation products are pot. P/vP*
Bioaccumulation	- *Not B/vB* - *Degradation products are not B/vB*
Environmental toxicity	- *Not T for environment*
PBT Assessment	- *Not PBT/vPvB* - *Degradation products are not PBT/vPvB* - *Read-across from structually similar substances for environmental properties is accepted due to the similar fate and ecotoxicological pattern in the environment.*
Respiratory and skin sensitiser	- *Respiratory and skin sensitiser, Cat. 1*
Carcinogenicity	- *Carcinogen, Cat. 2*
Mutagenicity	- *Based on the available data the eMSCA concludes that there is potentially a standard data gap for mutagenicity and due to this uncertainty also a minor residual concern for potential genotoxicity, which however does not justify the need to request further information under this SEv.*
Toxicity for reproduction	- *Based on the available data there is potentially a standard data gap for reproductive toxicity, however no specific concern has been identified which would require requesting further information under this SEv.*
Exposure Assessment	- *Exposure can be cosidered controlled.*

7.2. Procedure

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to human health/CMR, sensitiser; environment/suspected PBT; exposure/wide dispersive use, consumer use, aggregated tonnage, MDI mixed isomers was

included in the Community rolling action plan (CoRAP) for substance evaluation. The Competent Authority of Estonia was appointed to carry out the evaluation starting from 20 March 2015. All available data in the registration dossier(s) and in the Chemical Safety Report (CSR) were evaluated in relation to the specified concerns.

During the evaluation period the PBT concern was discussed in the PBT Expert Group. It was concluded that the substance is not considered as PBT since it does not meet the P and B criteria.

In relation to the other concerns, the eMSCA considered that further information was required to clarify the potential genotoxic properties of the substance, the life cycle of the substance with regards to the consumer uses and the simultaneous use of the registered substance with aprotic polar solvents taking into account possible exposure to transformation products, 2,4'-methylenedianiline (2,4'-MDA, EC no 214-900-8) and 4,4'-methylenedianiline (4,4'-MDA, EC no 202-974-4) of the registered substance. It was noted that the requested vertebrate study on genotoxicity has already been requested in the substance evaluation decision for the read-across substance 4,4'-MDI of 13 April 2016 and that there should be no duplication of vertebrate animal studies with regards to fulfilling the Decision from 23 February 2017. However, it was further elaborated that the read-across approach applicability for this property (test result in the comet assay) shall be determined once the requested information is submitted.

The Registrant submitted an updated MDI mixed isomers dossier on 15 June 2018, including robust study summaries and an updated CSR.

7.3. Identity of the substance

Table 3

SUBSTANCE IDENTITY	
Public name:	Reaction mass of 4,4'-methylenediphenyl diisocyanate and o-(p-isocyanatobenzyl)phenyl isocyanate/methylene diphenyl diisocyanate
EC number:	905-806-4
CAS number:	-
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	C15H10N2O2
Molecular weight range:	250 g/mol
Synonyms:	MDI mixed isomers

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

Structural formula:

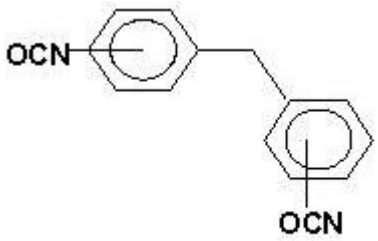


Table 4

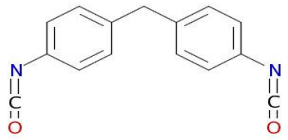
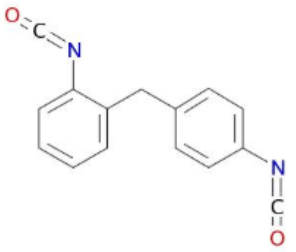
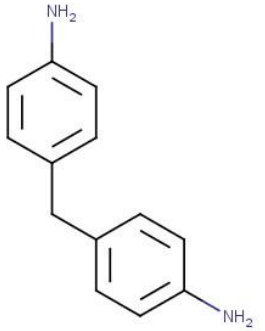
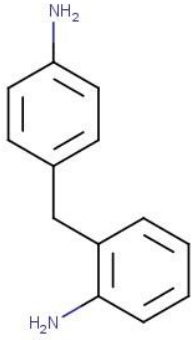
Constituent **Constituents**	**Typical concentration**	**Concentration range**	**Remarks**
4,4'-methylenediphenyl diisocyanate *EC no 202-966-0*	N/A	N/A	
o-(p-isocyanatobenzyl)phenyl isocyanate *EC no 227-534-9*	N/A	N/A	

Table 5

Degradation (transformation) product or metabolite **Constituents**	**Typical concentration**	**Concentration range**	**Remarks**
4,4'-methylenedianiline *EC no 202-974-4*	N/A	N/A	

2,4'-methylenedianiline *EC no 214-900-8*	N/A	N/A	

7.4. Physico-chemical properties

Table 6

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	*Liquid* *Colour: pale* *Odour: slightly musty*
Melting/freezing point	*9.3 to 10.7°C*
Boiling point	*> 300°C*
Vapour pressure	*0.00062 to 0.0014 Pa at 20°C*
Water solubility	*6.8 mg/L at 25°C*
Partition coefficient n-octanol/water (Log Kow)	*4.51 at 22°C*
Flammability	*Non-flammable*
Explosive properties	*Non-explosive*
Oxidising properties	*Non-oxidising*
Stability in organic solvents and identity of relevant degradation products	*Highly unstable in aprotic polar solvents*

7.5. Manufacture and uses

7.5.1. Quantities

Table 7

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☐ 1000- 10,000 t	☒ 10,000-50,000 t
☒ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

Table 8

USES	Use(s)
Uses as intermediate	Not applicable
Formulation	Formulation (including Resin Manufacture), Repackaging and Distribution
Uses at industrial sites	Manufacturing of MDI mixed isomers Manufacturing of other substances Flexible Foam Rigid Foam Coating Adhesives and Sealants Elastomers, TPU, Polyamide, Polyimide and Synthetic Fibres and Manufacturing of other Polymers Composite Material based on Wood/Man-made/Mineral/Natural Fibres Foundry Other Composite Material Cleaning with Aprotic Polar Solvents above 40°C Cleaning with Aprotic Polar Solvents below 40°C Cleaning [no Aprotic Polar Solvents]
Uses by professional workers	Rigid Foam Coating Adhesives and Sealants Composite Material based on Wood/Man-made/Mineral/Natural Fibres Other Composite Material Cleaning [no Aprotic Polar Solvents]
Consumer Uses	Rigid Foam Coating Adhesives and Sealants
Article service life	Not applicable
Uses advised against	Cleaning activities with Aprotic Polar Solvents in combination with MDI for professional uses Consumer spray application Consumer applications that require heating above room temperature before or during use

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

There is no harmonised classification for MDI mixed isomers.

7.6.2. Self-classification

- In the registration(s):

The substance is self-classified by the registrant based on Annex VI CLP entry 615-005-00-9 for methylenediphenyl diisocyanate (EC 247-714-0).

- Carc. 2 H351
- Acute Tox. 4 H332
- STOT RE 2 H373
- STOT SE 3 H335
- Eye Irrit. 2 H319
- Skin Irrit. 2 H315
- Resp. Sens. 1 H334
- Skin Sens. 1 H317

7.7. Environmental fate properties

7.7.1. Degradation

One valid key study (1994) is available in the registration dossier(s) to assess the abiotic degradation of the structurally related analogue polymeric MDI (pMDI). The hydrolysis dependence on pH has not been studied. The hydrolysis half-lives of pMDI constituents were measured in the range of 18 to 24 hours, with average half-life of 20 hours. Hydrolysis is therefore the main removal mechanism of MDI mixed isomers in the environment.

Phototransformation of the main constituent 4,4'-MDI in air has been assessed by the Registrant(s). The rate of gas-phase reaction of 4,4'-MDI with hydroxyl radicals in the atmosphere has been estimated using the AOPWINTM (v1.92) model and the calculated half-life value is 0.92 days (2008).

According to the biodegradation screening test (1986), no biodegradation was observed under the test conditions performed in accordance with OECD 302C, Modified MITI Test (II), using pMDI. The degradation rate of 0% based on the oxygen consumption under aerobic conditions with domestic sewage was observed.

There is no simulation test data on biodegradation in water and sediments for MDI mixed isomers. Due to the hydrolytic behaviour of MDI the biodegradation tests would measure only the biodegradation of hydrolysis products – inert polyurea and methylenedianiline (MDA).

The main hydrolysis products of MDI mixed isomers are inert and insoluble oligo- and polyureas with high molecular weights which yields more than 90% of the parent compound. It is unlikely that the oligomeric urea compounds would meet the P criterion, but polyureas are plausibly persistent in the environment. The other hydrolysis product MDA is not readily biodegradable and is inherently biodegradable only in industrial WWTPs (ECHA, 2018).

The eMSCA concludes that the substance itself is not persistent in the environment due to its hydrolytical unstability, but the hydrolysis products can be considered persistent.

7.7.2. Environmental distribution

The distribution and transport of MDI mixed isomers in the environment are governed by rapid hydrolysis of the substance in the environmental media. The eMSCA can agree that the partitioning parameters like water solubility, octanol-water partition coefficient and soil adsorption coefficients have no real value for risk assessment due to the transient nature of the substance in water.

7.7.3. Bioaccumulation

Although hydrolysing in water, one bioaccumulation test according to OECD 305E (Bioaccumulation: Flow-through Fish Test) has been performed for the main constituent 4,4'-MDI. In the 28 day bioaccumulation study BCFs were determined as 92 and 200 respectively. Those numbers indicate low bioaccumulation potential.

In the mesocosm study in the artificial ponds with pMDI, no MDI nor MDA were found in fish after 112 days confirming a low potential for bioaccumulation in aquatic organisms.

The eMSCA concludes that the substance and its hydrolysis products are not bioaccumulative in the aquatic organisms.

7.8. Environmental hazard assessment

The eMSCA considers that the available information for the environmental compartments is sufficient for the environmental hazard assessment and concludes that the substance does not pose hazard to the environment.

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

Fish acute toxicity study OECD 203 (1986) on *Danio rerio* with pMDI showed no toxic effects at 1000 mg/L after 96 hours. The concentration reported was nominal and the real concentration was probably much lower due to the hydrolysis of the substance in water. In a parallel study the toxicity to fish of the transformation product MDA was determined. LC50 = 65.4 mg/L indicated clearly that MDA is more toxic. However, in the natural environment the interfacial reactions with MDI lead to the formation of a solid crust which restricts ingress of water and egress of amine, and hence, the transformation product MDA cannot be readily available for aquatic organisms. In the other study (1993) where pMDI (up to 10 g/l) was poured into artificial ponds under relatively static conditions which relate closely to environmental spill situation no effects to fish were observed and no MDA was detected in water. Polyureas at the same time are inert materials and should not have toxic effects to aquatic organisms. Therefore eMSCA can conclude that the substance is not acutely toxic to fish.

The Registrant(s) claims that the long term toxicity tests for fish are not available due to substance instability in water environment.

7.8.1.2. Aquatic invertebrates

pMDI effects on *Daphnia magna* have been studied in two tests according to OECD 202 (1986). With nominal concentrations of 1000 mg/L no lethal effects were observed when 1000 rmp stirring method was used. In the other test pMDI was dispersed into the experimental medium by high speed (24000 rpm) shearing and increased toxicity to daphnids was reported - EC50 (24 h) = 129.7 mg/L. This fact has probably been caused by the increased MDA yield in the test medium. The increased toxicity is definitely characteristic to the dispersing method and does not conform to the real environmental situations. The exposure duration in these studies are 24 hours although 48 hours is foreseen by guidelines. Nevertheless, 24 hours values can be considered to be conclusive enough for this endpoint for MDI due to the rapid reaction with water (hydrolysis $T_{1/2}$ = 20 hours).

The lowest value determined for the short term toxicity of degradation product MDA to *Daphnia magna* according to OECD 202 is EC50 (48 h) = 0.35 mg/L (ECHA, 2018). This result indicates that the substance is acutely highly toxic to aquatic invertebrates. However, in the natural environment the interfacial reactions with MDI lead to the formation of a solid crust which restricts ingress of water and egress of amine, and hence MDA is not available for aquatic organisms. This fact is supported by the study (1993) where pMDI (up to 10 g/L) was poured into artificial ponds under relatively static conditions which relate closely to situation of an environmental spill and detected no MDA in water.

There is one long term toxicity study available with *Daphnia magna* (1986) showing no toxicity after 21 days at the highest pMDI concentration of 10 mg/L in semi-static conditions. MDI reacts readily with water to form predominantly insoluble and inert polyurea and traces of MDA, therefore long-term tests are not appropriate to determine the ecotoxicity of MDI.

In conclusion, MDI mixed isomers shows low concern for invertebrates.

7.8.1.3. Algae and aquatic plants

In a limit test according to OECD 201 with *Scenedesmus subspicatus* (1994) no toxicity was observed after 72 hours exposure to pMDI at loading rate of 1640 mg/L based on the growth rate of the algae. Based on this the 72 h NOELR was set as 1640 mg/L and the EC50 (72 h) > 1640 mg/L. The result can be corroborated by the mesocosm study (1993), where no toxic effects were seen in the phytoplankton up to 1000 and 10000 mg/L. Thus, it is expected that MDI mixed isomers is not toxic to freshwater green algae.

The effects of pMDI were also investigated to the pond biota during 112 days. The loadings of 1000 and 10000 mg/L of pMDI were used and the toxic effects were assessed to two macrophytes - *Potamogeton crispus* and *Zannichellia palustris*. Macrophytes abundance was affected at both loadings because of the physical obstruction due to the formation of solid crust of polyurea, but their biomass was significantly higher in the treated ponds compared to the control pond due to increased CO_2 in the water.

The potential indirect hazard due to the formation of degradation product MDA can be described by the EC50 (72 h) of 14.4 mg/L and NOEC of 9.3 mg/L based on the growth rate of *Pseudokirchneriella subcapitata* (ECHA, 2018). These values suggest that MDA has low toxicity to algae.

The eMSCA concludes that the substance is not toxic to algae and aquatic plants.

7.8.1.4. Sediment organisms

No data available.

7.8.1.5. Other aquatic organisms

No data available.

7.8.2. Terrestrial compartment

In the available study (1992) according to OECD 207 guideline no toxic effects of pMDI were observed for the soil macroorganism *Eisenia fetida*. 14 days LC50 > 1000 mg/kg soil (d. w.) was obtained based on the mortality, weight increase, behaviour and appearance of the test organisms. No toxic effects of pMDI were also observed to the terrestrial plants *Avena sativa* and *Lactuca sativa* in OECD 208 study (1992). In this study 14 days EC50 > 1000 mg/kg soil (d.w.) was obtained based on the emergence, mortality, appearance and growth (weight) of the plants. However, in these studies pMDI was in contact with water

in the moistened soil and it is likely that the concentrations of actually bioavailable pMDI were much lower than the nominal concentrations. There is no indication that MDI mixed isomers or its transformation products would show toxicity towards terrestrial organisms.

7.8.3. Microbiological activity in sewage treatment systems

The 3 h EC50 value >100 mg/L have been determined with pMDI based on the respiration rate using activated sludge in OECD 209 study (1986). In parallel study the 3 h EC50 value >100 mg/L has been also determined for MDA (ECHA, 2018), meaning that MDI and MDA are not appreciably toxic to bacteria.

7.8.4. PNEC derivation and other hazard conclusions

Table 9

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks/Justification**
Freshwater	> 1 mg/L	Assessment factor 1000
Marine water	0.1 mg/L	Assessment factor 10000
Intermittent releases to water	10 mg/L	Assessment factor 100
Sewage treatment plant	> 1 mg/L	Assessment factor 100
Soil	> 1 mg/kg soil (d.w.)	Assessment factor 1000

7.8.5. Conclusions for classification and labelling

The available information does not warrant classification for the environment.

7.9. Human Health hazard assessment

One of the main constituents of the registered substance is 4,4'-methylenediphenyl diisocyanate (4,4'-MDI, EC: 202-966-0), for which there was a concern related to carcinogenicity and possible genotoxic mode of action for tumour induction. Based on the provided data it was possible to conclude that the read-across substance is not genotoxic under the testing conditions and do not pose risk to human health due to limited exposure. However, it is not possible to come to a conclusion on this endpoint regarding the registered substance as there is a data gap. The issue is further elaborated below in section 7.9.5.

Reproductive toxicity was assessed during the evaluation process taking into account all available information in the dossier.

7.9.1. Toxicokinetics

There is no data available on the registered substance regarding this endpoint. The data from toxicokinetics with read-across substance were considered during the evaluation process.

7.9.2. Acute toxicity and Corrosion/Irritation

There is no data available on the registered substance. Data in the dossier(s) available on read-across substance were considered during the evaluation process. The acute toxicity of MDI mixed isomers was assessed based on available data from read-across substances 4,4'-MDI, polymeric MDI and 2,4'-MDI.

7.9.3. Sensitisation

Data available in the dossier(s) on read-across substances were considered during the evaluation process. The substance is a skin and respiratory sensitiser based on available data on constituents which have harmonised classification as Skin Sens. 1 and Resp. Sens. 1.

7.9.4. Repeated dose toxicity

There is no specific test data provided on MDI mixed isomers for this endpoint. Data available in the dossier(s) on read-across substances were considered during the evaluation process. The substance may cause damage to respiratory system through prolonged or repeated exposure.

7.9.5. Mutagenicity

Genetic toxicity potential of MDI mixed isomeres was assessed based on avalable data from consistuent substances 4,4'-MDI and 2,4'-MDI. There is no available data on genotoxicity with the registered substance.

The mutagenic potential of MDI monomers and polymer dissolved in DMSO in concentrations of 0-5000 µg/plate was studied. All samples in all strains gave negative results in the absence of post-mitochondrial fraction S9. In the presence of S9 fraction results varied: 4,4'-MDI in TA1535 and TA1537 strains gave negative results, in TA100 and TA98 – positive. 2,4'-MDI gave negative results in TA1535 and TA1537 and TA100 strains, positive results in TA98 and additional TA1538 strain. (Herbold, 1998)

Stability of 4,4'-MDI and 2,4'-toluene diisocyanate (2,4'-TDI) in DMSO was investigated (1998) and (1999). Neither 2,4'-TDI nor 4,4'-MDI was stable in DMSO. Traces of water that are always found in dried commercial DMSO degraded the diisocyanates and led to a number of reaction products, including small amount of TDA or MDA. Reported positive results for MDI obtained from Ames tests with DMSO as a solvent may be attributed to MDA formation during fast degradation of MDI. To confirm this Herbold and Seel studied diisocyanates stability in another, less polar, solvent EGDE. In Ames test solutions of 4,4'-MDI in EGDE, showed consistent negative response in all strains tested, with and without metabolic activation. Isomers of monomeric MDI as well as polymeric MDI, dissolved in EGDE, behaved in a similar manner to 4,4'-MDI. Increasing the water content in a solution that contained isomers of monomeric MDI had no pronounced influence on its stability either.

Analysis of the read-across approach between 4,4'-MDI and the registered substance to predict the results of *in vivo* tests:

The constituents of the registered substance and 4,4'-MDI have common functional group (NCO-group) and belong to the common chemical class - diisocyanates. Regarding the composition, based on the available data, the main difference between the registered substance and 4,4'-MDI appears to be the relative amount of the two main diisocyanate isomeric constituents 4,4'-MDI and 2,4'-MDI. It should be noted that comet assay was performed with a pure 4,4'-MDI. In order to assess the impact of the isomeric constituents on the toxicity and the plausibility of the read-across approach between 4,4'-MDI and the registered substance, the following information was taken into account.

Firstly, the molecular formula of the three MDI isomers is the same, they have the same molecular weights and NCO-values.The registered substance and 4,4'-MDI have common precursors in the manufacturing process.

Secondly, reactions of 2,4'-TDI in aqueous solution with N-acetyl-L cysteine were investigated (2002). A peculiarity of this diisocyanate is the difference in reactivity of the two isocyanate groups. Depending on the reaction conditions the isocyanate group in the 4-position is more reactive than the isocyanate in the 2-position by a factor of 5 to 10. This is partly due to the steric hindrance of the o-NCO group; another factor is the electronic effect of the isocyanate in the 4-position which changes from electron withdrawing to electron releasing after transformation to the thiocarbamoyl moiety. The same theory is applied to the MDI isomers. Provided justification document states that the local toxicity of the isomers depends on the relative reactivities of different NCO-groups that have been measured during the experiments that were conducted under real use conditions, i.e. during polyurethane manufacturing and the application of products. The differences in the reactivity are caused by sterical hindrance and no mesomerism according to "Hückel-Law" can occur (i.e. none or only very minor electronic effects originating from the other aromatic moieties and their substituents). This experimental evidence is indicating that the most reactive NCO-group is the NCO-group in 4-position since 4,4'-MDI reacts 1.8 times faster than 2,4'-MDI.

Thirdly, recently performed *in vitro* study (ECHA, 2018) was provided in order to strengthen the read-across on specific genotoxicity endpoint and to show that differences in reactivity of NCO-groups at the 2- and 4- positions of MDI are functionally negligible. The study provides information on the reactivity of different MDI isomers (2,4'- and 4,4'-MDI) with glutathione (GSH), the major anti-oxidant of the lower airways, which contains the preferred target (cysteine free thiol) for MDI reactivity.

The MDI isomers (2,4' and 4,4') react with GSH at equally rapid rates under physiologic conditions, forming bis(GSH)-MDI conjugates within minutes. The similarity in rate of bis(GSH)-MDI formation with different MDI isomers, despite differences in the relative reactivity of N=C=O in the 2 vs. 4 position, suggests GSH's SH-group reacts substantially faster than the OH-group of polyols, and may be limited by the rate of solubility of MDI in aqueous phase of the simulated lung fluid. Following longer reaction times (>10 minutes) 2,4'-MDI forms greater amounts of mono(GSH)-MDIcy compared to 4,4'-MDI. Mono(GSH)-MDIcy may be stabilized by cyclization, and less likely to transcarbamylate self molecules, hence 2,4'-MDI isomer may be less likely to induce allergy or toxicity.

Cyclized mono(GSH)-MDI conjugates are possible if GSH's distinct amino terminus (γ-glu) reacts with MDI, as well as its free thiol (side chain of cysteine). These conjugates form to varying degrees with 2,4'- and 4,4'-MDI, have longer retention times than bis(GSH)-MDI, and may elute at multiple retention times. The physiologic relevance of cyclized mono(GSH)-MDI vs. bis(GSH)-MDI is unknown; however, if cyclization or other N-linked adducts provide stability it should reduce transcarbamylating potential, and lower antigenicity and toxicity.

Since the reaction of MDI with water in airway fluid is also possible (and complete hydrolysis would result in its corresponding aromatic diamine) the potential hydrolysis of different MDI isomers under physiologic condition (in the presence of GSH, 37°C, pH 7.4) was evaluated as well. MDA was below the limit of detection (0.03µM or < 0.001% of the

starting material) at all the time points tested (1 minute to 2 hours) following 2,4'- and 4,4'-MDI reactions with GSH in aqueous solution.

In conclusion there is no experimental data on the genotoxic potential of the registered substance. Based on the provided data it was possible to conclude that the main constituent 4,4'-MDI is not genotoxic under the testing conditions. The additional data on consistuents (ECHA, 2018) has been used by the Registrant(s) to further justify that the differences in the reactivity of constituents of MDI mixed isomers *in vitro* are negligible. However, the chemical reactivity differences/similarities do not necessarily mean the same differences/similarities in reactivity towards a biological molecular target, such as DNA, in a cell nucleus under *in vivo* conditions. Less reactive molecules may be even favoured to reach such target whereas more reactive molecules react already prior to reaching this target. As no *in vivo* experimental data on the genotoxic potential of the substance and its other consistuents has been provided there is potentially a standard data gap leading to uncertanity and a minor residual concern for potential genotoxicity.

7.9.6. Carcinogenicity

There is no data available on the registered substance. Data in the dossier(s) available on read-across substance were considered during the evaluation process. The MDI isomers (4,4'- and 2,4'-) that make the composition of the registered substance, have the same harmonised classification and are covered by a group entry in Annex VI of CLP Regulation, Index No. 615-005-00-9. The registered substance is also self-classified based on the harmonised classification of MDI (Carc. Cat. 2.).

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

There is no test data available on the registered substance. The Registrant(s) had provided three studies equivalent or similar to OECD 414 (with the main constituent 4,4'-MDI and a read-across substance pMDI) and for the effects on fertility data on the main constituent 4,4'-MDI, pMDI, 2,4-diisocyanato-1-methylbenzene (TDI; CAS 26471-62-5) and 1,6-diisocyanatohexane (HDI; CAS 822-06-0).

Data on macroscopy, gross pathology and histopathology in the reproductive organs of both sexes were examined by Reuzel et al. (1994a) in the 24 months chronic inhalation toxicity and carcinogenicity study of respirable pMDI aerosol in Wistar rats exposed at concentrations of 0, 0.2, 1.0 and 6 mg/m³ for 6h/day, 5 days/week. Compound-related changes were exclusively found in the respiratory tract (NOAEC 0.2 mg/m³) but no treatment related findings on reproductive or any other systemic organ effects were reported. Frequently occurring gross lesions were observed in male rats of the main group including enlarged atrophic testes. These changes were associated with nephrosis, which was the main cause of death in males. The significant increase in testes weight in males at the end of the two-year exposure period was not accompanied by histopathological changes. No concentration-effect relationships were present. In female rats of the main groups, tumorous masses and secretory activity in mammary glands, ovarian cyst(s), and uterine polyps were common findings. Pituitary tumours, mammary tumours, and uterine tumours/polyps were the main causes of death in females. According to the Registrant(s) these lesions in males and females represent normal background pathology of ageing Cpb:WU, Wistar random rats. However, no histological data were presented to corroborate this statement.

In a chronic repeated dose toxicity test (Reuzel et al., 1994b) reproductive organs and tissues were macroscopically and gross pathologically assessed at the autopsy. A detailed histopathological assessment was performed of 10 rats/sex of the control group and 20

rats/sex of the high-concentration group at the end of the exposure (week 14) and of 10 rats/sex of the control and high-concentration group at the end of the post treatment period (in week 18). Histopathological assessment included e.g. adrenals, epididymides, mammary glands, seminal vesicles, testes and uterus. The gross examination at autopsy and histopathological assessment revealed no treatment related systemic effects.

The results of Reuzel studies mentioned above showed effects on testes weights in the main study which did not correlate with histopathological findings. These effects were not described in the one year interim sacrifice exposure groups as well as in the sub chronic exposure study Reuzel et al (1994). Additionally, a literature data indicated that testicular atrophy is known observations in ageing rats observed with a high incidence of up to 80% (Tucker, 1997). All things considered, the observations on testes weights (increase) and the testes size (decrease) may be interpreted as non-treatment related effects. However, it must be noted that sperm motility or function was not investigated as functional aspects of reproduction in the available studies.

Effects on ovaries, mammary glands and uterus occurred with a higher incidence in the chronic inhalation toxicity and carcinogenicity study study (1990) with pMDI, but without clear dose response correlation or a significant deviation to the control groups. These effects were not observed neither in the interim kill groups nor on a macroscopical level in sub-chronic study with pMDI (Reuzel 1994) and in the chronic toxicity study with the main constituent 4,4'-MDI (1995). The Registrant(s) is of the opinion that these observations on ovaries, mammary glands and uterus cannot be interpreted as treatment related effects of any biological relevance. The most plausible explanation, as provided by the study is an increased background pathology of ageing of Cpb:WU Wistar rats. Registrant(s) has additionally referred to chronic toxicity studies which demonstrate that even with a chronic/lifetime exposure duration, effects from pMDI/4,4'-MDI aerosol are confined to the lungs. Effects on systemic organs including reproductive organs were not observed at exposure concentrations revealing respiratory tract toxicity. However, it should be stressed that the ovaries' weights were not reported. Additionally, in the article referred by the Registrant(s), Sanbuissho et al. (2009) concluded based on the results of the tests (validation study) that ovarian toxicity could be detected by a careful histopathological examination and such pathological findings of ovarian toxicity decreases in follicles, increases in atretic follicles, increases in currently formed corpora lutea may reflect the female fertility parameters (irregular esterous cycle, pre-implantation loss). Furthermore, mentioned parameters were not considered in the chronic toxicity studies provided in the dossier(s).

In chronic inhalation study (1995) with respirable aerosols of 4,4'-MDI, 80 female rats per dose group were whole-body exposed to atmospheres of 0.23, 0.70 or 2.05 mg/m³ for 17 hours/day, 5 days/week for up to 24 months. Pathological examination was done on 20 rats/dose of a 12 months exposure group and 20 rats/dose of a 24 months exposure group. The reproductive organs assessed included e.g. adrenals, ovaries, uterus, vagina and mammary gland. Compound-related changes were found in the respiratory tract (LOAEC 0.23 mg/m³), no treatment related findings on reproductive or any other systemic organ effects were reported.

The results of the two-generation reproductive toxicity study (1989) performed with TDI indicated no impact on fertility. The combined reproductive/developmental/neurotoxicity study (OECD 422) conducted by Astroff et al (2000) with HDI did not show statistically significant effects on the mating, fertility, or gestation indices. There were no effects observed on the days to insemination, gestation length, or total number of implantation sites. There were no statistically significant effects on litter size, total number of pups born, sex distribution, mean weight of viable pups, mean number of viable pups or number of stillborn pups. No statistically significant effects were observed on the live birth, viability, lactation, or birth indices. However, it should be noted that data related to TDI and HDI was considered just for information since these substances are not covered by the Registrant(s) category.

Buschmann (1996) investigated developmental toxicity as a part of the chronic inhalation study (1995) where gravid Wistar rats, Crl:(WI)BR, were exposed by whole-body inhalation to clean air (control) and to 1, 3, and 9 mg/m^3 4,4'-MDI, respectively, for 6 hr per day from days 6 to 15 post conception (p.c). Treatment did not influence maternal and/or fetal parameters investigated such as maternal weight gain, number of corpora lutea, implantation sites, pre- and postimplantation loss, fetal and placental weights, gross and visceral anomalies, degree of ossification, although a slight but significant increase in litters with fetuses displaying asymmetric sternebra(e) was observed after treatment with the highest dose of 9 mg/m^3. The relevance of an increase of this minor anomaly in doses which cause toxic effects in dams (reduced food consumption, increased lung weights) is limited and the number observed is within the limits of biological variability, a substance-induced effect in the high-dose group cannot be excluded with certainty. Consequently, a no embryotoxic effect level of 3 mg/m^3 was determined.

A pre-natal developmental toxicity study (1992) was conducted according OECD 414. Mated female Wistar rats (8 per group) were exposed 'whole body' to pMDI aerosol by inhalation at the concentrations of 0, 2, 8 and 12 mg/m³ for 6 h/day from day 6 up to and including day 15 of pregnancy. On day 21 of pregnancy the female rats were killed and a Caesarean section was performed. No clinical signs or mortality related to treatment were observed during the study. No statistically significant differences in number of copora lutea, implantation sites, early and late resorptions. Litter weights is comparable in all groups, no significant differences in sex ratio. No findings in grossly visible abnormalities that were considered to be treatment-related.

Mated Wistar rats, 25/group, were exposed to pMDI aerosol of respirable size for 6 h/day, on gestational days (gd) 6 through 15, at 0, 1, 4, and 12 mg/m^3 (Gamer et al., 2000). Maternal clinical signs, body weights, and feed and water consumption were measured throughout gestation. Maternal toxicity was observed at 12 mg/m^3, including mortality (2 of 24 pregnant), damage to the respiratory tract, reduced body weights and weight gain, reduced liver and increased lung weights, and reduced gravid uterine weight (the last not statistically significantly different from the control value). Developmental toxicity was also observed at 12 mg/m^3, including reduced placental and fetal body weights and an increased incidence of fetal skeletal variations and skeletal retardations. There was no evidence of maternal or developmental toxicity at 1 or 4 mg/m^3. Thus, the no observed adverse effect concentration for maternal and developmental toxicity was 4 mg/m^3. There were no treatment-related teratogenic effects at any concentrations evaluated.

To sum up, there is no multigeneration reproductive toxicity study available with the MDI mixed isomers as well as with the constituents of the substance. Thus, not all relevant parameters for fertility have been investigated for the registered substance. Furthermore, the eMSCA considers the read-across applied by the Registrant(s) not sufficiently justified for this endpoint. Therefore, there is potentially a standard data gap for reproductive toxicity. However, the eMSCA has not identified a specific concern which would require requesting further information under this substance evaluation.

7.9.8. Hazard assessment of physico-chemical properties

The data was taken into account during the evaluation process.

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

Table 10

CRITICAL DNELS/DMELS

Endpoint of concern	Type of effect	Critical study(ies)	Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)	DNEL/ DMEL	Justification/ Remarks
Carcinogenicity: inhalation	The pulmonary effects: interstitial fibrosis, hyperplasia and bronchiolo-alveolar adenomas.	Reuzel et al.(1994)	NOAEC: 0.2 mg/m³ (toxicity) NOAEC: 1 mg/m³ (carcinogenicity)	Local effects - Long-term DNEL: 0.05mg/m³ Acute DNEL (irritation of respiratory tract) 0.1mg/m³	For 4,4'-MDI and pMDI the German MAK Commission established a purely health based OEL (MAK-Value) of 0.05 mg/m³ for inhalable aerosol referring to an 8-hour exposure period, that is the basis for the official national OEL in Germany (listed in TRGS 900). This OEL is used as a surrogate DNEL for long term exposure. A ceiling limit value of 0.1 mg/m³ was settled. This ceiling limit is used as a surrogate DNEL for short-term exposure. Since irritation to the respiratory tract is the most sensitive health effect these DNELs apply for local effect, in absence of any systemic toxicity.
	Impairment of the lung function, ↑lung weights, an inflammatory reaction, interstitial and peribronchiolar fibrosis, alveolar bronchiolisations and a proliferation of the alveolar epithelium, bronchiolo-alveolar adenoma.	2-year chronic toxicity/carcinogenicity inhalation study (1995)	NOAEC: 0.7 mg/m³ air (carcinogenicity)		
Roproductive toxicity	Compound-related changes in the respiratory tract. No treatment related findings on reproductive organs.	Reuzel et al. (1994)	LOAEC for fertility not specified		
	Respiratory tract	2-year chronic toxicity/carcinogenicity inhalation study (1995)	LOAEC for fertility not specified		
	Incidence of fetal skeletal variations and skeletal retardations at maternal toxic dose	Gamer et al. (1994)	NOAEC maternal: 4 mg/m³ air		
	A slight but significant increase in litters with fetuses	Buschmann et al. (1996)	NOAEL developmental: 3 mg/m³ air		

	displaying asymmetric sternebra(e) Fetal abnormalities not specified	Waalkens-Berendsen et al. (1992)	NOAEL: >12 mg/m³ air		

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

The MDI isomers (4,4'- and 2,4'-MDI) that make the majority of the composition of the MDI mixed isomers have the same harmonised classification and are covered by a group entry in Annex VI of CLP Regulation, Index No. 615-005-00-9. The same self classification is applied for the registered substance.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

Not evaluated.

7.10.2. Endocrine disruption - Human health

Not evaluated.

7.10.3. Conclusion on endocrine disrupting properties (combined/separate)

Not evaluated.

7.11. PBT and vPvB assessment

In PBT assessment the degradation products of MDI isomers have been taken into account. The main hydrolysis products of MDI isomers are inert and insoluble oligo- and polyureas with high molecular weights which yields more than 90% of the parent compound. It is unlikely that the oligomeric urea compounds would meet the P criterion. Polyureas are plausibly persistent in the environment, but do not bioaccumulate in living organisms and are not toxic. The other degradation product is MDA. In order to apply the worst case scenario, MDA and its properties were considered in the assessment.

Persistence

It is demonstrated that hydrolysis of the parent compound MDI mixed isomers is the main transformation process taking place after release to the environment. Hydrolysis occurs readily and the half-life in heterogeneous medium for oligomeric MDI is estimated at ca. 20 hours. So one may conclude that the parent compound MDI mixed isomers is not P.

The biodegradation of the transformation product MDA was investigated in accordance with the OECD 302C (non-GLP). MDA was found to degrade by 43% over 28 days. Other screening studies for biodegradation with MDA confirm this outcome - MDA is not readily biodegradable and is inherently biodegradable only in industrial WWTPs not under normal environmental conditions. Therefore MDA fulfils the "potentially persistent" screening criteria as outlined in the REACH Guidance R.11

The transformation products resulting from hydrolysis are the corresponding urea compounds and the stable end products are inert and insoluble polyureas with high molecular weights. The formed polymeric urea probably meets the P criterion.

Bioaccumulation

In a study with the radiolabelled main constituent 4,4'-MDI, BCF-values up to 200 l/kg are found. It should be noted that this value reflects the bioconcentration of water soluble hydrolysis products which includes 4,4'-MDA and low molecular weight ureas. This observation supports the statement that MDI mixed isomers and the transformation products MDA and the oligomeric urea compounds do not meet the B-criterion. Also in a mesocosm study carried out with pMDI, no MDI nor MDA could be detected in fish which confirms that MDI mixed isomers and its transformation products are unlikely to be bioaccumulative. It should also be noted that the polyurea compounds are high molecular weight compounds and therefore it is very unlikely that these compounds would show bioaccumulation potential.

Therefore there is no real indication for potential bioaccumulation of MDI mixed isomers nor transformation products, and MDI mixed isomers can be identified not bioaccumulative (B).

Toxicity

The substance has a self-classification based on Annex VI CLP entry 615-005-00-9 which covers both constituents 4,4'-MDI and 2,4'-MDI. Therefore the substance can be considered meeting the criteria for classification as STOT RE 2 and fulfils the toxicity criterion.

Considering the properties of MDA, as the main transformation product of concern, the substance is classified as Carc. Cat. 1B and STOT RE 2 which according to Annex XIII triggers its identification as toxic.

Based on the results of the available toxicity tests with aquatic organisms MDI mixed isomers is not identified as T. Still, MDA has indicated high level of toxicity to daphnids in long-term studies and is classified as toxic to aquatic life with long lasting effects. Polyurea compounds are expected not to be toxic to environmental organisms.

Considering the classifications of MDI and MDA, MDI mixed isomers is identified toxic (T).

Overall conclusion

Based on the available information MDI mixed isomers is not considered to be PBT substance. The substance itself does not meet the P and B criteria, but meets the T-criterion being self-classified as STOT RE 2 based on the constituents 4,4'-MDI and 2,4'-MDI.

The relevant transformation products are corresponding oligomeric and polymeric urea compounds. It is unlikely that oligoureas fulfil the P criterion and therefore it is appropriate to state that oligomeric ureas do not meet the PBT-criteria. Because of its high molecular weight it can be stated that polymeric ureas, although potentially persistent, are not bioaccumulative nor toxic and consequently do not meet the PBT-criteria.

The hydrolysis degradation product MDA is potentially persistent. However, MDA has no potential to bioaccumulate.

The eMSCA concludes that MDI mixed isomers is not PBT nor vPvB substance.

7.12. Exposure assessment

7.12.1. Human health

The registered substance is widely used by workers and consumers. The most relevant routes of exposure were considered – inhalation, dermal.

All exposure scenarios were assessed with regards to possible exposure of humans arising from the substance itself as well as the more hazardous possible metabolite/degradation products – 2,4'- and 4,4'-MDA.

7.12.1.1. Worker

Exposure assessment considered the isomers (2,4'- and 4,4'-MDI) contained in the substance.

Further information was requested in the course of the substance evaluation to specify the process categories for the intended uses where the use of MDI mixed isomers simultaneously with aprotic polar solvents occurs and to recommend measures to ensure that 2,4'- and 4,4'-MDA is either not formed or exposure to 2,4'- and 4,4'-MDA is controlled due to the simultaneous use. Additional exposure scenarios introduced demonstrated that exposure to 2,4'- and 4,4'-MDA is controlled. Furthermore, simultaneous use of aprotic polar solvents by professionals has been advised against during the substance evaluation.

The eMSCA concludes that the occupational exposure can be considered controlled.

7.12.1.2. Consumer

Exposure assessment considered the isomers (2,4'- and 4,4'-MDI) contained in the substance.

Further information was requested in the course of the substance evaluation concerning worst case scenarios for consumer uses in relation to generation of and consequent possible exposure to 2,4'- and 4,4'-MDA. It was demonstrated that exposure to 2,4'- and 4,4'-MDA is negligible.

The eMSCA concludes that the consumer exposure can be considered controlled.

7.12.2. Environment

Exposure assessment considered the fate of the substance in the environment and the isomers (2,4'- and 4,4'-MDI) contained in the substance.

Releases to the environment are considered controlled with regards to the substance as well as its more hazardous degradation products – 2,4'- and 4,4'-MDA.

The eMSCA concludes that the environmental exposure can be considered controlled.

7.12.3. Combined exposure assessment

Combined exposure assessment has not been performed.

7.13. Risk characterisation

Taking into account the available information and applicable risk management measures and operational conditions as well as the regulatory measures the risks arising from the substance and its more hazardous degradation products – 2,4'- and 4,4'-MDA seem to be adequately controlled. The eMSCA concludes that the provided human health and environmental as well as combined risk characterisation ratio values are all below 1, and thus do not express an unacceptable risk. However, due to potential standard data gaps there could be unidentified risks arising from the use of the substance which may have not been considered under this substance evaluation.

7.14. References

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7.15. Abbreviations

2,4'-MDA - 2,4'-methylenedianiline

2,4'-MDI - o-(p-isocyanatobenzyl)phenyl isocyanate

2,4'-TDI - 2,4'-toluene diisocyanate

4,4'-MDA - 4,4'-methylenedianiline

4,4'-MDI - 4,4'-methylenediphenyl diisocyanate

BCF - Bioconcentration factor

CAS - Chemical Abstracts Service

CMR - Carcinogenic, mutagenic or toxic to reproduction

CoRAP - Community rolling action plan

CSR - Chemical Safety Report

DMSO - Dimethyl sulhpoxide

DMEL - Derived minimal effect level

DNA - Deoxyribonucleic acid

DNEL - Derived no-effect level

EC50 - The effective concentration of substance that causes 50% of the maximum response

ECHA - European Chemicals Agency

ED - Endocrine disrupting

EGDE - Ethylene glycol dimethyl ether

eMSCA - Evaluating Member State

GLP - Good laboratory practice

GSH - Glutathione

LC50 - Median lethal concentration

LOAEC - Lowest observed adverse effect concentration

MAK - Maximum Workplace Concentration

MDA - methylenedianiline

MDI - Methylenediphenyl diisocyanate

MDI mixed isomers - Reaction mass of 4,4'-methylenediphenyl diisocyanate and o-(p-isocyanatobenzyl)phenyl isocyanate / methylene diphenyl diisocyanate

N/A - Not applicable

NOAEC - No observed adverse effect concentration

NOAEL - No observed adverse effect level

NOEC - No observed effect concentration

NOELR - No observable effect loading rate

OECD - Organisation for Economic Cooperation and Development

OEL - Occupational exposure limit

PBT - Persistent, bioaccumulative and toxic

pMDI - polymeric MDI

PNEC - Predicted no-effect concentration

SEv - Substance Evaluation

SVHC - Substances of very high concern

$T_{1/2}$ - (hydrolysis) half life

TDA - Toluenediamine

TRGS - Technical Rules for Hazardous Substances

UVCB - Substance of unknown or variable composition, complex reaction products or biological materials

vPvB - Very persistent and very bioaccumulative

WWTP - Waste Water Treatment Plant