SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

4,4'-methylenediphenyl diisocyanate

EC No 202-966-0

CAS No 101-68-8

Evaluating Member State(s): Estonia

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Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2013

Before concluding the substance evaluation a Decision to request further information was issued on: 13 April 2016.

Further information on registered substances here:

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

DISCLAIMER

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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

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Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

4,4'-methylenediphenyl diisocyanate (4,4'-MDI) was originally selected for substance evaluation in order to clarify the following concerns:

- respiratory and skin sensitiser,
- potential carcinogen, mutagen and toxic for reproduction,
- suspected PBT substance,
- wide dispersive use, including consumer use, and
- high aggregated tonnage.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

- European Union Risk Assessment Report: Methylenediphenyl diisocyanate (MDI),
- Regulation (EC) 1272/2008 annex VI entry (see 7.6.1),
- Regulation (EC) 1906/2006 annex XVII entry no 56.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State Competent Authority (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

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

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

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

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/exposure	X
Actions by the Registrant(s) to ensure safety, as reflected in the registration dossiers(e.g. change in supported uses, applied risk management measures, etc.)	

The outcome of the test requested in the substance evaluation decision[2] on genotoxic properties of the substance clarified that substance did not show genotoxic effects under the test conditions and therefore the concern for genotoxic mode of action was not confirmed. The other hazard concerns for selection of substance for evaluation were clarified based on the available data in the registration dossier(s).

The outcome of the requested data on exposure concerns clarified that exposure to the hydrolysis product 4,4'-methylenedianiline (4,4'-MDA) with more stringent classification is under appropriate control e.g. new uses advised against were introduced. Based on the available exposure data the identified uses of 4,4'-MDI show negligible risk.

Furthermore, ECHA Committees 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 4,4'-MDI.

Based on the above, the eMSCA considers that currently no follow-up regulatory risk management measures at EU level are needed.

5.2. Other actions

Not applicable.

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

Not applicable.

[2] https://echa.europa.eu/documents/10162/0332eec1-7d27-4d56-ab8b-300ff39a0d77

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

4,4'-MDI was originally selected for substance evaluation in order to clarify the following concerns[3]:

- respiratory and skin sensitiser,
- potential carcinogen, mutagen and toxic for reproduction,
- suspected PBT substance,
- wide dispersive use, including consumer use, and
- high aggregated tonnage.

Table 4

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*
PBT Assessment	- *Not PBT/vPvB* - *Degradation products are not PBT/vPvB*
Respiratory and skin sensitiser	- *Respiratory and skin sensitiser, Cat. 1*
Carcinogenicity	- *Carcinogen, Cat. 2*
Mutagenicity	- *Not genototoxic at the site of contact under the test conditions*
Toxicity for reproduction	- *There is no multigeneration reproductive toxicity study available with the registered substance. Thus, not all relevant parameters for fertility have been investigated for 4,4'-MDI. However, the available information from other studies with structurally similar substances do not raise concerns for reproductive toxicity (fertility and development). In addition, exposure to 4,4'-MDI is limited due to the fact that the substance has harmonised classification inter alia Resp. Sens. 1, Skin Sens. 1 and Carc. Cat. 2. the eMSCA considers that no further information needs to be requested under this substance evaluation.*
Exposure Assessment	- *Risks are under control with the applicable measures.*

[3] https://echa.europa.eu/documents/10162/0e5a1a86-ff9a-4349-9180-7f2dbf8a135e

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, 4,4'-MDI 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 2013. 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. The eMSCA concluded that the substance is not PBT, since it is not persistent itself and its persistent degradation product is not bioaccumulative.

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 4,4'-MDA. The Registrant(s) submitted an updated 4,4'-MDI dossier on 29 August 2017, including robust study summaries and an updated CSR.

Taking into account the additional information provided during the substance evaluation, the eMSCA was able to conclude the substance evaluation by 29 August 2018 on all the concerns and found no potential risk that would currently require follow-up actions at the EU level.

7.3. Identity of the substance

Table 5

SUBSTANCE IDENTITY	
Public name:	4,4'-methylenediphenyl diisocyanate
EC number:	202-966-0
CAS number:	101-68-8
Index number in Annex VI of the CLP Regulation:	615-005-00-9
Molecular formula:	C15H10N2O2
Molecular weight range:	250 g/mol
Synonyms:	

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

Structural formula:

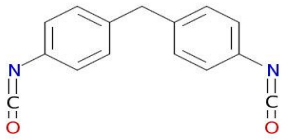

Table 6

DEGRADATION PRODUCT IDENTITY	
Public name:	4,4'-methylenedianiline
EC number:	202-974-4
CAS number:	101-77-9
Index number in Annex VI of the CLP Regulation:	612-051-00-1
Molecular formula:	C13H14N2
Molecular weight range:	198 g/mol
Synonyms:	

7.4. Physico-chemical properties

Table 7

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	*Crystalline solid.* *Colour: white.*
Melting/freezing point	*39 to 43 °C*
Boiling point	*> 300 °C*
Relative density	*1.32 at 20 °C*
Vapour pressure	*Calculated best-fit value of 0.00062Pa at 20 °C*
Water solubility	*An estimated water solubility of 6.8mg/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	*Not oxidising*
Granulometry	*Data waiving*
Stability in organic solvents and identity of relevant degradation products	*Highly unstable in dimethylsulphoxide (DMSO) solvent, water content of the DMSO increasing breakdown. The corresponding diamine is identified as one of the degradation product. More stable in ethyleneglycoldimethylether (EGDME)*

Dissociation constant	*Data waiving*

7.5. Manufacture and uses

7.5.1. Quantities

Table 8

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 9

USES	Use(s)
Uses as intermediate	Not applicable
Formulation	Formulation (including Resin Manufacture), Repackaging and Distribution
Uses at industrial sites	Manufacturing of MDI 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)

Table 10

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
615-005-00-9	4,4'-methylenediphenyl diisocyanate diphenylmethane-4,4'-diisocyanate	202-966-0	101-68-8	Acute Tox. 4 Skin Irrit. 2 Eye Irrit. 2 Resp. Sens. 1 Skin Sens. 1 Carc. 2 STOT SE 3 STOT RE 2	H332 H315 H319 H334 H317 H351 H335 H373	STOT SE 3; H335: C ≥ 5 % Resp. Sens. 1; H334: C ≥ 0,1 % Skin Irrit. 2; H315: C ≥ 5 % Eye Irrit. 2; H319: C ≥ 5 %	C 2

7.6.2. Self-classification

In addition to the harmonized classification, the following classifications or classification for other endpoint are notified to the Classification and Labelling Inventory, classification according to CLP criteria:

- Skin Irrit. 2 (H314) Causes severe skin burns and eye damage.
- Acute Tox. 2 (H330) Fatal if inhaled.
- Acute Tox. 3 (H331) Toxic if inhaled.
- Muta. 2 (H341) Suspected of causing genetic defects.
- STOT SE 3 (H370) Causes damage to organs.
- STOT SE 2 (H371) May cause damage to organs.
- STOT RE 1 (H372) Causes damage to organs through prolonged or repeated exposure.
- EUH204: Contains isocyanates. May produce an allergic reaction.

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 4,4'-MDI in the environment.

Phototransformation of 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 4,4'-MDI. Due to the hydrolytic behaviour of MDI the biodegradation tests would measure only the biodegradation of hydrolysis products – inert polyurea and MDA.

The main hydrolysis products of MDI 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 methylenedianiline (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 4,4'-MDI 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 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 96h. 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 (Klimish 2). 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 T1/2 = 20 hours).

The lowest value determined for the short term toxicity of degradation product MDA to *Daphnia magna* according to OECD 202 is EC50 (48h) = 0.35 mg/L (ECHA, 2015). 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 (Klimish 2). 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, 4,4'-MDI 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 (72h) > 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 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 (72h) 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. 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 4,4'-MDI 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. In a 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 11

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

The human health hazard evaluation focused on clarifying the initial grounds of concern on respiratory and skin sensitisation, potential for carcinogenicity, mutagenicity and toxicity for reproduction.

7.9.1. Toxicokinetics

The data from toxicokinetics was taken into account during the evaluation process.

7.9.2. Acute toxicity and Corrosion/Irritation

Data available in the dossier(s) was taken into account during the evaluation process.

7.9.3. Sensitisation

Data available in the dossier(s) was taken into account during the evaluation process. The substance is skin and respiratory sensitiser.

7.9.4. Repeated dose toxicity

Data available in the dossier(s) was taken into account during the evaluation process.

7.9.5. Mutagenicity

After evaluation of all relevant information initially submitted on 4,4'-MDI it was concluded that further information is required in order to clarify the concern related to genotoxic properties of the registered substance and to clarify whether the substance constitutes risk to human health due to a non-threshold genotoxic mode of action. The concern was that the registered substance may exhibit genotoxic effects at the site of contact, as parent compound or due to the formation of toxicologically relevant metabolites (e.g. 4,4'-MDA which is classified pursuant to Regulation (EC) No 1272/2008 *inter alia* as mutagenic (Muta. 2), carcinogenic (Carc. 1B) and is included in Annex XIV of the REACH Regulation as a substance of very high concern subject to authorisation (Entry 2 of Annex XIV)). Additionally the concern was related to carcinogenicity of 4,4'-MDI and possible genotoxic mode of action for tumour induction at the site of contact. This concern was based on the data described below.

It appears that most of the available test results of *in vitro* genotoxicity assays for 4,4'-MDI rather reflect the properties of reaction products formed under specific assay conditions than the ones of the parent compound. Only in one available *in vitro* bacterial reverse mutation assay (Ames test) (solutions of 4,4'-MDI in ethyleneglycoldimethylether (EGDME) as solvent) consistent negative response has been shown in all of the strains tested with and without metabolic activation (Herbold et al., 1998). The results of the positive *in vitro* gene mutation study in mammalian cells where inappropriate solvents was used dimethylsulphoxide (DMSO) were considered by the Registrant(s) as not reliable due to the assumption that MDI is chemically converted into MDA (Gahlmann et al., 1993), a substance known to produce positive responses *in vitro* genotoxicity assays.

Most of the available tests assessing the genotoxic potential of 4,4'-MDI *in vivo* provided no information on genotoxic activity at the site of contact. The results of an *in vivo* micronucleus test indicated that 4,4'-MDI administered by inhalation did not induce cytogenetic damage (Pauluhn et al., 2001). However it was considered that bone marrow in that study was not adequately exposed. The results of another *in vivo* micronucleus study in mice by inhalation (Lindberg et al., 2011) demonstrated that 4,4'-MDI aerosols at

concentration of 10.7-23.3 mg/m^3 did not significantly increase the frequency of micronucleated polychromatic erythrocytes in mouse bone-marrow or in peripheral blood. However, the authors mentioned that the daily exposure duration was limited to 1h because of the irritating properties of 4,4'-MDI, and the negative result may thus be related to such short exposure time. Authors acknowledged the concern for potential local genotoxic activity by stating that "because diisocyanates are very reactive and react also at the site of first contact, it may have been possible to detect genotoxic effects locally in the respiratory tract".

The Registrant(s) claimed that no free MDA is formed after inhalation exposure to 4,4'-MDI. A number of studies (2003a, 2003b) are available evaluating the fate of inhaled MDI. These studies illustrate consistent metabolic pathway in which MDA is not detected. In addition, the Registrant(s) has noted that biomonitoring studies demonstrate that the intermediary steps of MDI metabolism under plasma physiological conditions proceed entirely without formation of any free amines, including MDA. In *in vitro* studies (Mormann et al., 2006) formation of conjugates of N-acetyl-L-cysteine with 4,4'-MDI in the buffer solution in pH range 5-7 has been shown without formation of 4,4'-MDA. However, provided studies cannot exactly mimic the processes that occur *in vivo*.

In a review of the literature (2005) relating to MDI and TDI and reports of human genetic effects concluded that the results from the various human inhalation and animal studies show a number of similar patterns, but the data, and their interpretation, are not clear. The isocyanates are reactive chemicals and there are a number of studies showing that they can react directly with proteins at the site of administration while producing no, or minimal, DNA binding. The human studies that indicated DNA damage have been poorly designed and/or reported. As a result, not much confidence can be placed in the reported weak positive DNA fragmentation results as an indicator of the direct DNA damaging effects of isocyanates.

In the course of the substance evaluation additional information was requested on genotoxicity. The Registrant(s) provided two Comet assays (a key study 2017 and amended supporting study 2016) following the substance evaluation decision to further evaluate genotoxic effects of the registered substance and its metabolites at the site of contact.

The additionally provided 2016 supporting study was conducted similarly to OECD 489 with 4,4'-MDI via inhalation. Cytodifferentiation and markers for cytotoxicity (e.g. protein, lactate dehydrogenase; LDH) and apoptosis (e.g. annexin V, caspase 3/7) were included into the test design. The dose levels were selected based on earlier inhalation toxicity studies in rats and the dose level for paraffin was selected to match one of the 4,4'-MDI dose levels (but a different time point was examined for that dose). Overall, the study revealed the following results: inhalation exposure to 4,4'-MDI led to a dose dependent mild positive response in the Comet assay observed at day 0 and 1 stating with an exposure of 20 mg/m^3 3h. Increase in tail length (ca. 2.3 fold increase compared to ca. 11 – 22 fold increase in the positive control (MNU administrated orally)) correlated with markers of cytotoxicity, apoptosis and inflammation. A no observed adverse effect concentration (NOAEC) of 10 mg/m^3 (6h) was identified for the Comet response (an exposure by which clear acute respiratory toxicity was still observed). At day three after exposure there was no Comet response even at a very high concentration of 100 mg/m^3 6h. Effects on markers of alveolar toxicity identified with 20 mg/m^3 4,4'-MDI at day 0 correlated with results obtained for the inert organic particle solid paraffin at 25 mg/m^3 at day 1. E.g. no increase in alveolar macrophages, but increase in caspase 3/7 and annexin V was observed together with a mild increase in tail intensity. The increased apoptosis observed for at least one of two evaluated apoptosis parameters after inhalation of 4,4'-MDI, but not after exposure to the genotoxic control compound MNU, allow to put the positive Comet assays result into perspective. Based on knowledge on particle toxicity as well as the results of cytodifferentiation there might be a link to macrophage activation and reactive oxygen species generation, leading to an inflammatory response including oxidative burst, finally resulting in oxidative DNA damage. Direct cytotoxicity in principle may be a complementary mechanism for a positive response at higher 4,4'-MDI concentrations. Likewise genotoxic

effects may be regarded to be a secondary effect. However, this study is considered to be inconsistent with the OECD 489 and did not follow GLP compliance requirements.

The key study (2017) was designed generally in accordance with the OECD 489 (29 Jul 2016) and the objective of the study was to assess the potential of aerosolized 4,4'-MDI to cause DNA damage to the lung and liver of male Wistar rats following a single, 6-hour nose-only inhalation exposure to the concentrations of 2, 5, and 11 mg/m^3 (achieved 2.5, 4.9, and 12 mg/m^3). The dosing regime was chosen taking into account previously conducted studies by e.g. Pauluhn (2001), Kilgour et al. (2002), acute toxicity study (2017) that revealed respiratory irritation, necrosis/apoptosis, and inflammation at the site of contact. Bronchoalveolar lavage (BAL) was the source of cells to evaluate the potential for genotoxic effects in the lung, as these populations represent the site of first contact in the lung. Additional endpoints in the BAL fluid (BALF) or cell pellet were used in conjunction with the Comet assay to evaluate non-specific or direct toxicity of 4,4'-MDI after acute exposure, as recommended by the test guideline. The tested substance did not cause a significant increase in DNA damage in the lung (as evaluated in cells obtained from bronchoalveolar lavage, BAL cells), liver, and stomach under the test conditions. Therefore, 4,4'-MDI was concluded to be negative for the *in vivo* Comet assay under the test conditions. In addition, the substance-related differences noted in BALF endpoints (cytology, alkaline phosphatase, lactate dehydrogenase, total protein, β-glucuronidase activity, and annexin V expression) indicated local cellular toxicity, which was consistent with the lung as the critical mode of action of 4,4'-MDI toxicity. Based on the magnitude of the differences noted in the BALF endpoints, 12 mg/m^3 was considered to be the maximum tolerated concentration (MTC) to avoid confounding secondary DNA damage resulting from local cytotoxic effects.

The eMSCA concludes that under the key study test conditions the substance did not show gentotoxic potential, therefore the concern for genotoxic mode of action was not confirmed.

7.9.6. Carcinogenicity

The concern was related to carcinogenicity of 4,4'-MDI and possible genotoxic mode of action for tumour induction at the site of contact. 4,4'-MDI has harmonised classification: carcinogenic category 2, H351 (suspected of causing cancer). A reliable 2-year chronic toxicity/carcinogenicity inhalation study with pMDI (1990) is available where formation of a pulmonary adenocarcinoma in one male as well as pulmonary adenomas, described as rare in this strain, in males (6/60) and females (2/59) exposed to 6.03 mg/m^3 of pMDI was found. The time sequence of the spectrum of pulmonary changes indicated that recurrent alveolar wall damage by pMDI and/or pMDI-containing alveolar macrophages lead to alveolar bronchiolization and ultimately to bronchioloalveolar tumors. The NOAEL of pMDI was considered to be 0.2 mg/m^3 and the chronic exposure to pMDI at the level of 6.0 mg/m^3 was related to the occurrence of pulmonary tumors. A non-genotoxic mode of action for tumours formation was claimed by the Registrant(s) due to observation of chronic inflammation/irritation in the lungs following lifetime inhalation exposure.

Another 2-year chronic toxicity/carcinogenicity inhalation study (1995) has been conducted with monomeric 4,4'-MDI. Female Wistar rats (80 per exposure group) were exposed (whole body) to 4,4'-MDI in aerosol at 0.23, 0.70, or 2.05 mg/m^3 for 17 h per day, 5 days per week, for up to 24 months. In one high-dose animal, a bronchioloalveolar adenoma was observed. Because of the concentration-related lung effects, 0.23 mg/m^3 is considered as LOAEL. There is no NOAEL in this study. Mortality in this experiment was unusually high in all groups (94-97 %), including the control group, half of the animals died during first 18 months of exposure. Tumors were found in great numbers. NOAEC carcinogenicity for female rats was decided to be 0.7 mg/m^3. There was no MDI-related increase in the organ-specific tumor rate. The number of tumor-bearing rats was identical, and the total number of tumors did not significantly differ between the control and the high dose group 2.05 mg/m^3. Identical number of tumor bearing animals in highest dose vs control group (both 77/80). Total number of tumors at low dose: 195; control: 183. Number of malign tumors

in the high dose group is slightly higher than in the control (n=39 vs n=36). Number of benign tumors was clearly lower in high dose group. The number of animals with metastasis tumors was twice as high in controls than in high dose. A similar number of animals with multiple tumors were seen in both of the groups (61/80; 60/80). A dose related neoplastic effect was only seen in the lungs. In one animal of the high dose group: bronchiole-alveolar adenoma built of dyspastic alveolar cells (type II pneumocytes). No significant difference incidence between controls and high dose group (adenocarcoma, fibroadenoma; adenoma and fibroma) was observed.

The evidence of increased lung tumour formation in rats following lifetime inhalation of MDI is described in expert review article (2001). A non-genotoxic mechanism of MDI action in the lung is indicated. However, epidemiological data does not indicate an increased risk of cancer for workers exposed to MDI.

Feron et al. (2001) performed a comparison of the pulmonary effects described in female rats after chronic inhalation exposure to either polymeric or monomeric MDI (Reuzel et al., 1994 and the chronic inhalation study, 1995). To assist the comparison between both studies, the MDI doses were normalised to total inhalation exposures calculated as 559, 1972, 2881, 6001, 17575 and 17728 mg MDI h/m³. The major pulmonary effects observed included interstitial fibrosis, hyperplasia and bronchiolo-alveolar adenomas, the latter occurring at low incidence in the high exposure groups of both studies (i.e. total inhalation exposures of 17728 and 17575 mg MDI h/m³). Both studies also report the presence of particle-laden macrophages, predominantly in the alveoli close to the alveolar ducts which in some cases, particularly in high dose groups, were associated with areas of fibrosis. Whilst a range of pulmonary lesions was still observed at the 1927 mg MDI h/m³ dose (chronic inhalation study, 1995), the only treatment-related effect seen at the lowest dose of 559 mg MDI h/m³ (Reuzel et al., 1994) was the occurrence of particle-laden alveolar macrophages. As they had normal appearance and were not accompanied by tissue damage or an inflammatory reaction, this was considered a physiological response to the deposition of particles in the lungs. Therefore, the 559 mg MDI h/m³ exposure level was proposed as the NOAEL. In support of this statement, it was suggested that the mild histopathological changes seen in the low exposure animals (1927 mg MDI h/m³) in the chronic inhalation study reported (1995), would not have occurred if the exposure had been for 6 hours/day instead of 18 hours/day. In addition, the analysis concluded that both studies showed similar qualitative responses to exposures to polymeric or monomeric MDI. Therefore, an exposure of 559 mg MDI h/m³ or 0.19 mg MDI/m³ over a 6 hour period was judged to be the NOAEL in both studies. It was concluded that the results of the two studies could be combined to serve as a basis for human risk assessment of MDI.

The studies reviewed in the manuscript (2014) provided in the dossier were conducted with either polymeric or monomeric MDI. Once deposited in the bronchioloalveolar region of the lung, MDI particles interact chemically with protein and other biological macromolecules reducing their concentrations in the lining surface of the lung. To maintain normal homeostasis increased synthesis of secretory proteins by Type II pneumocytes is induced. As the increased synthesis becomes maximized but demand for protective proteins is maintained there is a secondary, compensatory response characterized by an increase in cell replication resulting in bronchioloalveolar hyperplasia in the terminal bronchioles and ultimately, after prolonged exposure to the development of adenomas. The observation that MDI particulates do not accumulate in the lung at doses producing lung tumours, together with the lack of chronic inflammation and cytotoxicity, supports the mechanism is via a non-genotoxic, compensatory response of the lung to maintain homeostasis.

Taking into account the results of the Comet assay (2017), the controlled exposure to 4,4'-MDI and the fact that the substance has harmonised classification Carc. Cat. 2., the eMSCA concludes that further studies clarifying this endpoint are not considered necessary.

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

The Registrant(s) had provided three studies equivalent or similar to OECD 414 (with the registered and a category substance (pMDI)) and for the effects on fertility data on 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 in male rats of the main group were discoloured, cystic, and granular kidneys; enlarged parathyroids; and 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 only treatment related effects were confined to the respiratory tract (increased relative lung weight ratios in the mid- and high concentration groups, histopathological and microscopic changes in all pMDI exposed groups).

The results of Reuzel studies mentioned above were discussed during the substance evaluation period with the Registrant(s) and it was agreed that the effects on testes weights in the main study were not correlated with a 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 provided by the Registrant(s) 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 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 monitor is an increased background pathology of ageing of Cpb:WU Wistar rats. Furthermore, the

Registrant(s) believes that the data regarding the reproductive toxicity endpoint can be covered by the data obtained from chronic toxicity studies and is sufficient to come into conclusion on this issue. According to the Registrant(s) these studies 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 famale 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). Results showed a dose-dependent decrease in food consumption in all substance-treated groups during exposure, returning to normal values after cessation of treatment. The lung weights in the high-dose group were significantly increased compared to the sham-treated control animals. Treatment did not influence any other maternal and/or fetal parameters investigated (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. Although 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. Focal alopecia in 4 animals, general weakness in 1 animal and red conjunctivae in 2 animals were observed. There was transient slight decrease (not significant) of body weight gain as well as food intake was statistically

significantly decreased when compared with the control group at the mid- and high-concentration group from day 6 to 9. Focal alopecia in 1 control animal and 1 exposed animal, ovary cysts in 2 animals with one of them associated with non-pregnancy were observed of the 8 and 12 mg/m³ groups. Statistically significant treatment-related effects on absolute and relative lung weights were seen in the top dose. 1 animal of the mid-concentration group was not pregnant. 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. 1 foetus in control group appeared dysmature (b.w. < 75 % of the mean fetal b.w. of the fetuses of the control group) and 1 foetus appeared to have subcutaneous haemorrhage in the right hind foot and ring-tail. 1 animal showed ringtail in low concentration and 1 animal showed flexed hind paws in mid- and high-concentration groups respectively.

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.

There is no multigeneration reproductive toxicity study available with the registered substance. Thus, not all relevant parameters for fertility have been investigated for 4,4'-MDI. However, the available information from other studies with structurally similar substances do not raise concerns for reproductive toxicity (fertility and development). In addition, exposure to 4,4'-MDI is limited due to the fact that the substance has harmonised classification *inter alia* Resp. Sens. 1, Skin Sens. 1 and Carc. Cat. 2. the eMSCA considers that no further information needs to be requested 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 12

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,	Reuzel et al.(1994)	NOAEC: 0.2 mg/m³ (toxicity) NOAEC: 1 mg/m³	Local effects - Long-term DNEL:	For 4,4'-MDI and pMDI the German MAK Commission

	hyperplasia and bronchiolo-alveolar adenomas.		(carcinogenicity)	0.05mg/m³ Acute DNEL (irritation of respiratory tract) 0.1mg/m³	established a purely health based OEL (MAK-Value) of 0.05 mg/m^3 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/m^3 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. (2000)	NOAEC maternal: 4 mg/m³ air		
	A slight but significant increase in litters with fetuses displaying asymmetric sternebra(e)	Buschmann et al. (1996)	NOAEL developmental: 3 mg/m³ air		
	Fetal abnormalities not specified	A pre-natal developmental toxicity study (1992)	NOAEL: >12 mg/m³ air		

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

The existing Annex VI entry for the substance is considered appropriate.

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

7.11. PBT and VPVB assessment

In PBT assessment the degradation products of MDI have been taken into account. The main hydrolysis products of MDI 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 are considered in the assessment.

Persistence

It is demonstrated that hydrolysis of the parent compound 4,4'-MDI 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 4,4'-MDI 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 radiolabelled 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 4,4'-MDI, 4,4'-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 4,4'-MDI 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 nor its transformation products and 4,4'-MDI can be identified not bioaccumulative (B).

Toxicity

The substance has a harmonised classification based on Annex VI CLP entry 615-005-00-9. The substance meets the criteria for classification as STOT RE 2 and fulfils the toxicity criterion.

Considering the properties of 4,4'-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 4,4'-MDI 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, 4,4'-MDI is identified toxic (T).

Overall conclusion

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

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 4,4'-MDI 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 product – 4,4'-MDA.

7.12.1.1. Worker

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

The eMSCA concludes that there is no concern for occupational exposure.

7.12.1.2. Consumer

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 4,4'-MDA. It was demonstrated that exposure to 4,4'-MDA is negligible.

The eMSCA concludes that there is no concern for consumer exposure.

7.12.2. Environment

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

The eMSCA concludes that there is no concern for environmental exposure.

7.12.3. Combined exposure assessment

Combined exposure assessment has not been performed.

7.13. Risk characterisation

Taking into account the applicable risk management measures and operational conditions as well as the regulatory measures the risks arising from the substance and its more hazardous degradation product – 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.

7.14. References

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7.15. Abbreviations

Not applicable.