SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

For

3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate

EC No 202-112-7

CAS No 91-97-4

Evaluating Member State: France

Dated: 29 November 2018

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: 24 November 2015.

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

3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate (hereafter named "TODI") was originally selected for substance evaluation in order to clarify concerns about:

- Consumer uses
- Sensitisation
- Carcinogenicity and mutagenicity
- PBT properties

During the evaluation also other concerns were identified. The additional concerns were:

- Human exposure
- Environmental risk assessment

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

The completed and ongoing processes are presented below.

OTHER PROCESSES / EU LEGISLATION			
Process	**MSCA**	**Status**	**Outcome**
PBT assessment	France	Completed	Not PBT
Risk Management Option Analysis (RMOA) for diisocyanate group Concern: sensitisation	Germany	Completed	Conclusion document (dated 29/08/2014) published on 23/09/2014[2]. Conclusion: need for follow up regulatory action at EU level. The proposed regulatory action is a restriction. As indicated in the RMOA conclusion document: *"(…) the most effective risk management option would be to integrate a certification scheme defining minimum handling conditions into a REACH restriction. (…)* *The envisaged restriction would prohibit the use of substances which contain more than 0.1wt% of free diisocyanate (of whatever kind), unless a company can prove convincingly that they have an internal system in place that ensures the procedures to handle diisocyanates are strictly followed. This should also include conditions that cover health risks to bystanders (e.g. building occupants), especially from spray foam applications. Compliance to such a system should be shown by participation in a certification scheme that requires maintaining a minimum of certain use conditions.* *This would have the advantage that all diisocyanates (aromatic, aliphatic, prepolymers with free diisocyanate)*

[2] RMOA diisocyanates: https://echa.europa.eu/documents/10162/ab854650-9f0b-419f-9dce-590b80e073f4, accessible at https://echa.europa.eu/pact/-/substance-rev/1989/del/200/col/synonymDynamicField_3413/type/desc/pre/3/view.

			can be covered with one regulatory measure and a minimum level of common handling standards is defined for all of Europe. If, in the end, this option would prove to be not viable, it would still be possible to initiate a SVHC/Authorisation procedure instead. *Health risks for consumers are not influenced by the proposed restriction. These risks and the related risk management options should be analysed separately considering the results of activities of other Member States and of the ongoing substance evaluation for MDI by Estonia*".
Restriction Concern: sensitisation, workers	Germany	Ongoing (currently being examined by the REACH Committee)	Submitted for diisocyanates (including TODI) on 07/10/2016[3]. As indicated in the opinion of RAC, "*The main goal of this restriction proposal is to prevent new cases of respiratory sensitisation from exposure to diisocyanates among all workers and professionals who may be exposed to diisocyanates in the workplace*."
Harmonised classification	Germany	Ongoing (accordance check)	Submitted for TODI on 14/08/2018[4]. The proposed future entry in Annex VI of CLP Regulation by the dossier submitter are: - Resp. Sens. 1, H334 - Skin Sens. 1A, H317.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State Competent Authority (FR-MSCA) to formulate the following conclusions, as summarised in the table below.

[3] https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e180876053

[4]Accessible at https://echa.europa.eu/fr/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e181e79ae4.

Table 1. Conclusion of substance evaluation

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	**Tick box**
Need for follow-up regulatory action at EU level	X
Harmonised Classification and Labelling	X
Identification as SVHC (authorisation)	
Restrictions	X*
Other EU-wide measures - Compliance check - Enforcement	X
No need for regulatory follow-up action at EU level	

** restriction proposal submitted by MSCA Germany*

The concern on skin and respiratory sensitisation has been confirmed during the evaluation. The Registrant now self-classify TODI as Skin Sens. 1A H317 and Resp. Sens. 1 H334. MSCA Germany submitted a proposal for a harmonised classification with the proposed future entry in Annex VI of CLP Regulation: Resp. Sens. 1, H334 and Skin Sens. 1A, H317.

It has not been possible to clarify the concerns initially identified for mutagenicity and carcinogenicity during the Substance Evaluation procedure. After a first year of evaluation, FR-MSCA requested more information on mutagenicity (in vivo mutagenicity study on TODI) and carcinogenicity (available data on TODA) in its draft decision referred to MSC on 27 July 2015. The MSC concluded that exposure had to be clarified first, to ensure proportionality and for animal welfare reasons, and the requests on mutagenicity and carcinogenicity were not included in the final Decision of 24 November 2015. On the basis of the new data received on exposure on 16 February 2017, FR-MSCA concluded that human exposure cannot be excluded. FR-MSCA considers that the concerns raised on mutagenicity and carcinogenicity, if confirmed, could lead to a risk for users of TODI in case they were exposed to it. However, the available information suggests that exposure is likely low or even negligible, provided that uses of the substance and articles made from it are consistent with the registered uses, and that strictly controlled conditions (which are claimed by the Registrant) are indeed implemented and respected.

FR-MSCA notes that TODI is subjected to a restriction proposal on diisocyanates which has been submitted in the course of the follow-up (2nd phase of Substance Evaluation). The restriction is currently being examined by the REACH Committee and aims to manage risks for workers related to sensitisation. If adopted, this restriction will likely impact the uses and conditions of use of diisocyanates, but it is difficult at this stage to predict how the market will adapt to the new regulatory obligations. Efforts toward reducing workers exposure to the substances or substitution may occur as a consequence.

In view of these considerations and prioritisation criteria for substance evaluation, it does not seem proportionate to request new toxicological studies on vertebrates at this stage. FR-MSCA notes however that, with regard to compliance strictly, there may be data gaps on toxicological endpoints (mutagenicity, repeated toxicity and reprotoxicity).

Data are available on mutagenicity and carcinogenicity for other substances of the diisocyanates group (including new data that was not available yet at the time of the first evaluation) and FR-MSCA proposes carcinogenicity and mutagenicity to be assessed in a category approach for diisocyanates. In particular, the new data obtained for structurally similar MDI (EC 202-966-0, CAS 101-68-8) which is currently under investigation by

Estonian MSCA[5] may help clarify the mechanisms of action for carcinogenicity. A classification for mutagenicity and/or carcinogenicity would lead to additional obligations under OSH (occupational safety and health) legislation.

For the environmental concerns, FR-MSCA concludes that TODI is not PBT and that the concerns related to the environmental risk assessment are clarified as no emission is expected in the environment.

4. FOLLOW-UP AT EU LEVEL

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

4.1.1. Harmonised Classification and Labelling

There is currently no entry in Annex VI of CLP for 3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate (TODI). In the registration dossier, the Registrant has self-classified the substance as Skin Sens. 1A H317, Acute Tox. 4 H332, Resp. Sens. 1 H334, Aquatic Acute 1 H400 and Aquatic Chronic 1 H410.

For sensitisation, a proposal for a harmonised classification has been submitted by MSCA Germany submitted on 14/08/2018. The dossier is awaiting accordance check by ECHA. The proposed future entry in Annex VI of CLP Regulation by the dossier submitter are Resp. Sens. 1, H334 and Skin Sens. 1A, H317.

For carcinogenicity and mutagenicity, a classification would lead to additional obligations under OSH (occupational safety and health) legislation. The following considerations are taken into account:

- Other diisocyanates with a similar structure already have a harmonised classification or a self-classification as Carc. 2 H351 (MDI and isomers[6], TDI and isomers[7], TRIDI[8]);
- TODI is hydrolysed into 4,4'-bi-o-toluidine (TODA[9]) which has a harmonised classification as Carc. 1B H350. The hydrolysis product of MDI (MDA[10]), and the hydrolysis product of TDI (TDA[11]), have both harmonised classifications as Carc 1B H350 and Muta 2 H341.
- The mechanism of action for carcinogenicity (i.e. genotoxic or non-genotoxic carcinogen) is currently evaluated for MDI by Estonian MSCA in the context of the substance evaluation.

No data are available for TODI on carcinogenicity. However, based on the available data on other diisocyanates and on their hydrolysis products, FR-MSCA considers that a harmonised classification could be considered for diisocyanates in a grouping approach. The outcomes of the Substance Evaluation of MDI by Estonian MSCA may contribute to clarify the uncertainty on the mechanism for carcinogenicity and the extrapolation of the data from one diisocyanates to another once the mechanism of action is clarified.

[5] CoRAP page for 4,4'-MDI: https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e1807e57f1.

[6] EC 247-714-0, 202-966-0, 219-799-4, 227-534-9.

[7] EC 209-544-5, 202-039-0, 247-722-4.

[8] EC 218-485-4.

[9] EC 204-358-0

[10] EC 202-974-4.

[11] EC 202-453-1.

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

Not currently considered as a suitable risk management option for diisocyanates (see RMOA).

4.1.3. Restriction

A restriction has been proposed to prevent new cases of respiratory sensitisation from exposure to diisocyanates at workplace (see Part A section 2).

4.1.4. Other EU-wide regulatory risk management measures

- *Compliance check*

FR-MSCA noted that the registration dossier may not be fully compliant with the requirements of the REACH regulation for the tonnage band 100-1000 tpa (in particular, there may be data gaps for repeated toxicity (section 7.9.6), mutagenicity (section 7.9.7) and toxicity to reproduction (section 7.9.9)). According to Article 6(2) of REACH, the reduced registration provisions with regard to on-site isolated and transported intermediates do not apply to monomers.

The appropriate regulatory tool to address data gaps and adaptations to the standard information requirements is the compliance check (CCH) under Article 41(b) taking into account the provisions of Article 13(1) and Annex XI(3).

- *Enforcement*

The Registrant claims that the substance is solely used under strictly controlled conditions at downstream user(s) site(s). For this reason he did not investigate all toxicity endpoints which would be normally required under Annex IX, and considers that risks for human health are adequately controlled. As TODI is a monomer and as Articles 17 and 18 do not apply to monomers (according to Article 6(2)), FR-MSCA assumes that "strictly controlled condition" should be be understood as fully closed systems with the same level of containement than would be required under Article 18(4).

However, the new data presented by the Registrant in its update of 16 February 2017 fail to demonstrate total enclosure and FR-MSCA concluded that human exposure cannot be excluded. If the concerns on mutagenicity and carcinogenicity were confirmed, there could be a risk for users of TODI in case they were exposed to it. The available information suggests that exposure is likely low or even negligible, provided that strictly controlled conditions are indeed implemented and respected.

In addition, following the inclusion of TODI in the CoRAP and start of the Substance Evaluation, the Registrant clarified that (on the contrary to the initial information given in the registration dossier) no consumer uses were expected for TODI. The Registrant subsequently updated its registration dossier to advise against consumers uses. The Registrant also indicates in its current registration dossier that articles made from the substance are used by workers. However, FR-MSCA considers that a concern remains regarding exposure of consumers to TODI via articles: indeed, the information in the registration dossier indicates that the articles made from TODI are part of the category AC13g[12]: Other plastic articles, which is rather unspecific; in addition, many types of articles are described in manufacturers' websites (including automobile parts and medical

[12] AC: article category according to Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.12: Use description (Version 3.0, December 2015).

equipment) showing that there are inconsistencies between the registered uses and the uses observed in the market. These uses are not evaluated in the registration dossiers, despite a request being made by FR-MSCA during the Substance evaluation procedure to the Registrant. FR-MSCA considers that National Enforcement Authorities need to ensure that consumers do not come in contact with articles containing TODI.

FR-MSCA recommends an enforcement action by the National Enforcement Authorities in order to ensure that:

1) strictly controlled condiditions are indeed implemented and respected in the downstream user(s) site(s) already identified, and that this conditions of use are adequately communicated via the safety data sheets, so that any new potential downstream users have the adequate information to manage the risks.
2) uses of the substance and articles made from it are consistent with the registered uses (i.e . AC13g (Other plastic articles) handled only by workers) and in particular that uses advised against are indicated in section 2.1 of the safety data sheets and implemented.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

Not applicable.

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

Indication of a tentative plan is not a formal commitment by the evaluating Member State. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions.

Table 2. Follow-up actions

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
CLP Annex VI dossier for carcinogenicity and/or mutagenicity	2019	France MSCA

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate (TODI) was originally selected for substance evaluation in order to clarify concerns about:

- Consumer uses
- Sensitisation
- Carcinogenicity and mutagenicity
- PBT properties

During the evaluation also other concerns were identified by FR-MSCA (evaluating MSCA). The additional concerns were:

- Human exposure
- Environmental risk assessment

Table 3. Evaluated endpoints

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Sensitisation	FR-MSCA concluded that **the concern for skin sensitisation is confirmed**. The Registrant has self-classified the substance as: - Skin Sens 1A, H317 - Resp Sens 1, H334 An intention for a harmonised classification dossier was notified by the German MSCA in the Registry of Intention on 4 August 2017. At the time of drafting of this document, the dossier had been submitted and was awaiting the accordance check. The proposed future entry in Annex VI of CLP Regulation by the dossier submitter are Resp. Sens. 1, H334 and Skin Sens. 1A, H317.

Carcinogenicity and mutagenicity	3 positive *in vitro* mutagenicity studies (bacterial reverse mutation assay, mammalian cell gene mutation assay and mammalian chromosome aberration assay), and 2 negative *in vivo* mutagenicity studies (bone-marrow micronucleus assay and unscheduled DNA synthesis (UDS) assay) are available in the registration dossier, but FR-MSCA considers that the UDS assay is not suitable to conclude on mutagenicity. In addition, one notifier has self-classified the substance as Muta 2 in the list of classification and labelling notifications present in the ECHA C&L Inventory. FR-MSCA concluded that **the concern for mutagenicity remains**. No data are available on carcinogenicity for TODI. However, based on the structural similarities of TODI with other diisocyanates (MDI and isomers, TDI and isomers, TRIDI), which have either a harmonised or a self-classification as Carc. 2 H351, and based on the hydrolysis product of TODI, TODA (4,4'-bi-o-toluidine, EC 204-358-0, CAS 119-93-7) which has a harmonised classification as Carc. 1B H350, FR-MSCA concluded that **the concern for carcinogenicity remains**. After a first year of evaluation, the MSC concluded that exposure had to be clarified first, so as to ensure the proportionality principle and for animal welfare reasons. Consequently, no new data on mutagenicity and carcinogenicity were requested on TODI in the final Decision of 24 November 2015. The Registrant(s) were nevertheless reminded of the provisions of article 41 of the CLP regulation stating that the Notifiers and Registrants shall make every effort to come to an agreed entry to be included in the inventory for Mutagenicity. Moreover, the Registrant was invited to consider the option to self-classify the substance as Carc. 1B based on the degradation of TODI into TODA, in addition to the existing self-classifications. At the time of drafting of this document, the Notifiers and the Registrants have not come to an agreed C&L entry to be included in the inventory for mutagenicity and the Registrant has not self-classified the substance as Carc. 1B. In the context of the evaluation of 4,4'-MDI by Estonian MSCA for mutagenicity as a ground for concern, in order at the end to elucidate the mechanism of action for carcinogenicity (i.e. genotoxic or non-genotoxic carcinogen), new *in vivo* data were obtained for MDI (Comet assay). The data is currently under evaluation. FR-MSCA considers that it may be worthwhile to take into account the result of this evaluation when available. **Proposed outcome**: FR-MSCA proposes **carcinogenicity and mutagenicity to be assessed in a grouping approach for diisocyanates when more data will become available on MDI**. Furthermore, FR-MSCA observes that the registration dossier of TODI may not be compliant with Annex IX with regards to Article 13(1) and Annex XI(3) for mutagenicity and this could be addressed under CCH.
PBT properties	Based on its degradation product TODA, TODI is considered not B. The relevant hydrolysis product of TODI is TODA (4,4'-bi-o-toluidine; CAS 119-93-7). TODA is classified Carc. 1B in Annex VI of the CLP. Therefore, the T criterion is considered to be met based on human health classification. No conclusion can be made for the P criterion. The P criterion was not considered further, since the substance does not meet the B criterion. Therefore the substance is not considered as PBT. The concern is considered as clarified.
Consumer uses	The Registrant now advises against consumer uses. Articles are expected to be used only by workers. However there is a concern that some articles may come in prolonged contact with consumers and this is not assessed in the dossier.

	Proposed outcome: enforcement.
Human exposure	Additional information was provided on 16 February 2017 following the requests made in the Substance Evaluation Decision from 24 November 2015. The new information fails to demonstrate full enclosure at workplace and non-exposure of workers. Therefore, the concern remains. **Proposed outcome: enforcement.**
Environmental risk assessment	Additional information was provided on 16 February 2017 following the requests included in the Substance Evaluation Decision of 24 November 2015. No emission is expected in the environment. The concern is considered as clarified.

In the course of the evaluation, FR-MSCA observed that the registration dossier may not be fully compliant with the requirements of the REACH regulation for the tonnage band 100-1000 tpa (in particular, repeated toxicity, mutagenicity and toxicity to reproduction). According to Article 6(2) of REACH, the reduced registration provisions with regard to on-site isolated and transported intermediates do not apply to monomers.

The appropriate regulatory tool to address data gaps and adaptations to the standard information requirements is the compliance check (CCH) under Article 41(b) taking into account the provisions of Article 13(1) and Annex XI(3).

7.2. Procedure

Pursuant to Article 44(2) of the REACH Regulation, 3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate (TODI) was included in the Community Rolling Action Plan (CoRAP)[13] for evaluation in 2013. The Competent Authority of France was appointed to carry out the evaluation. The substance evaluation started on 20 March 2013.

The evaluation was targeted to mutagenicity, carcinogenicity, sensitisation, PBT properties, human exposure, environmental exposure and risk characterisation. The main source of information for the evaluation was the registration data.

Based on the evaluation of the available data, FR-MSCA concluded that there was a need to request further information to clarify the concerns relating to mutagenicity, carcinogenicity, ecotoxicity, human and environmental exposure, and therefore pursuant to Article 46(1) of the REACH Regulation prepared a draft decision to request further information. The draft decision was submitted to ECHA on 11 June 2015. The decision was substantially modified and agreed by the Member State Committee; the requests related to hazards were removed and a new section IV (notes for consideration by the Registrant) was included. The final decision was issued to the Registrant(s) on the 24 November 2015.

On 23 August 2017, the Registrant updated its registration dossier. Several pieces of information were missing to meet the requests of the final decision, and after several exchanges between the Registrant and FR-MSCA, the Registrant updated its registration dossier on 16 February 2017 to comply with the final decision. The substance evaluation conclusion and evaluation report was prepared taking into account the updated registration data and chemical safety report (CSR).

On 15 June 2018, the final draft of the conclusion document was sent to ECHA.

[13] https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e1807e53a6

On 10 July 2018, ECHA provided comments on the draft conclusion document. FR-MSCA took into account the comments, completed the PBT assessment and sent the final version to ECHA on 4 December 2018.

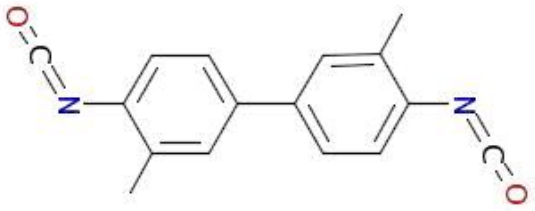
7.3. Identity of the substance

Table 4. Substance identity

SUBSTANCE IDENTITY	
Public name:	3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate (TODI)
EC number:	202-112-7
CAS number:	91-97-4
Index number in Annex VI of the CLP Regulation:	Not listed
Molecular formula:	C16H12N2O2
Molecular weight range:	264.28 g/mol
Synonyms:	1-isocyanato-4-(4-isocyanato-3-methyl-phenyl)-2-methyl-benzene 1-isocyanato-4-(4-isocyanato-3-methylphenyl)-2-methylbenzene TODI o-Tolidine diisocyanate bitolylene diisocyanate

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

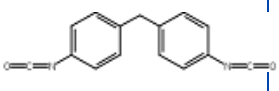
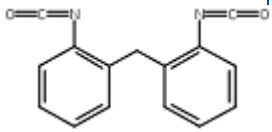
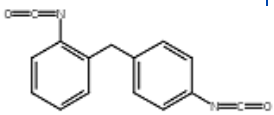
Structural formula:



FR-MSCA proposes to address the concerns on mutagenicity and carcinogenicity in a grouping approach with other diisocyanates. Indeed the diisocyanates all share the common structure –N=C=O (isocyanate).

Substance identity of the read-across substances used in the registration dossier:

Table 5. Substance identity of the read-across substances used in the registration dossier

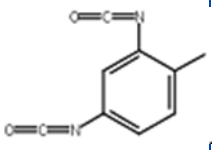
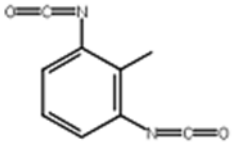
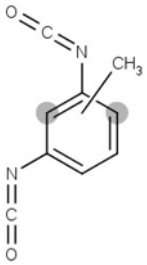
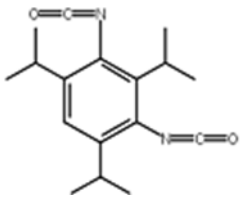
SUBSTANCE IDENTITY				
Public name:	methylenediphenyl diisocyanate	4,4'-methylenediphenyl diisocyanate	2,2'-methylenediphenyl diisocyanate	o-(p-isocyanatobenzyl)phenyl isocyanate
EC number:	247-714-0	202-966-0	219-799-4	227-534-9
CAS number:	26447-40-5	101-68-8	2536-05-2	5873-54-1
Index number in Annex VI of the CLP Regulation:	615-005-00-9	615-005-00-9	615-005-00-9	615-005-00-9
Molecular formula:	C15H10N2O2			
Molecular weight range:	250.25 g/mol			
Synonyms:	Methylenediphenyl diisocyanate (MDI) including the following specific isomers (see group members)	4,4'-MDI; diphenylmethane-4,4'-diisocyanate; 1,1'-methylenebis(4-isocyanatobenzene); numerous other synonyms listed[14]	2,2'-MDI; diphenylmethane-2,2'-diisocyanate; 1,1'-methylenebis(2-isocyanatobenzene); 1-isocyanato-2-[(2-isocyanatophenyl)methyl]benzene	2,4'-MDI; 2,4'-methylenediphenyl diisocyanate; diphenylmethane-2,4'-diisocyanate ; 2,4'-diisocyanatodiphenyl methane ; benzene, 1-isocyanato-2-[(4-isocyanatophenyl)methyl]-; other synonyms listed[15]
Structural formula				

[14] https://echa.europa.eu/substance-information/-/substanceinfo/100.002.697

[15] https://echa.europa.eu/substance-information/-/substanceinfo/100.025.031

Additional diisocyanates with a harmonised or self-classification as Carc. 2 H351 may be useful to consider for a category approach:

Table 6. Substance identity of additional diisocyanates with a harmonised or self-classification as Carc. 2 H351

SUBSTANCE IDENTITY				
Public name:	4-methyl-m-phenylene diisocyanate	2-methyl-m-phenylene diisocyanate	m-tolylidene diisocyanate	2,4,6-triisopropyl-m-phenylene diisocyanate
EC number:	209-544-5	202-039-0	247-722-4	218-485-4
CAS number:	584-84-9	91-08-7	26471-62-5	2162-73-4
Index number in Annex VI of the CLP Regulation:	615-006-00-4	615-006-00-4	615-006-00-4	Not listed
Molecular formula:	C9H6N2O2			C17H22N2O2
Molecular weight range:	174.16 g/mol			286.37 g/mol
Synonyms:	2,4-TDI	2,6-TDI	80/20 TDI or 65/35 TDI	TRIDI
Structural formula				

7.4. Physico-chemical properties

Table 7. Overview of the physicochemical properties

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	TODI is a solid white-yellowish and odourless substance in pelleted form.
Vapour pressure	0.00295 Pa at 25°C estimated by the program MPBPVPWIN, which is part of the program compilation EPI Suite using the Modified Grain method. This value is confirmed by measured vapor pressure of MDI (structurally close molecule). As experimental measurements of substances with appreciable very low vapour pressure and instability in presence of humidity provide technical difficulties, an experimental study on the vapour pressure of

	TODI was not performed but estimated with QSAR. This value was confirmed with value of MDI. The vapour pressure of TODI's hydrolysis degradation product 3,3'-Dimethylbenzidine (TODA) cannot be estimated due to lack of reliable data.
Water solubility	In accordance with column 2 of REACH Annex VII, the test on water solubility (required in REACH Regulation, Annex VII; Section 7.7) does not need to be conducted if the substance is hydrolytically unstable at pH 4,7 and 9 (half-life less than 12 hours). According to the study on determination of the hydrolysis of TODI as a function of pH (see section 7.7.1.1.1), the half-life of TODI was determined to be far below 12 hours (max.: 1.2 h at pH 7) and therefore found to be hydrolytically unstable.
Partition coefficient n-octanol/water (Log Kow)	Given TODI very high reactivity with water (half-life of TODI in water < 1min) and other protonic solvant (octanol), partition coefficient is not relevant and this property doesn't need to be assessed for isocyanate molecules.
Flammability	The test item TODI did not ignite in the preliminary test (experimental study (2008) [ref. 23]. Thus, it was not considered highly flammable. No further testing is required. Additionally, based on the hydrolysis study (see section 7.7.1.1.1) and on experience in handling and use, neither flammability in contact with water nor pyrophoric abilities are expected. Thus, these studies are waived.
Auto Flammability	Using a linear heating rate of 0.5 °C/min, no self-ignition temperature of TODI was observed up to 72 °C (melting point was determined to be 71.5 °C).
Flash point	TODI is a solid (pelleted form). Thus, the determination of the flash-point according to EU Method A.9 is not applicable as this method is only applicable to liquid substances whose vapour can be ignited.
Explosive properties	In accordance with column 2 of REACH Annex VII, the determination of explosiveness does not need to be conducted as there are no chemical groups associated with explosive properties present in TODI (refer to Guidance on information requirements and chemical safety assessment, Chapter R.7a).
Oxidising properties	A test on oxidising properties (Annex VII, section 7.13) does not need to be conducted as there are no chemical groups associated with oxidising properties present in TODI (refer to Guidance on information requirements and chemical safety assessment, Chapter R.7a).
Granulometry	After determination of the tap density (0.75 g/mL), the particle size distribution of TODI was found to be [1000 µm; 2000 µm] applying machine sieving, specified by the range [x1, x2] of two sieves where Rx1 >= 90% and Rx2 <= 10%. Seven sieves of sizes (µm) 63, 125, 250, 500, 1000, 2000 and 4000 were used. No particles with a diameter below 63 µm were found (and with 125 µm only 0.2%).
Stability in organic solvents and identity of relevant degradation products	In accordance with column 2 of REACH Annex IX, the test on stability in organic solvents and identity of relevant degradation products does not need to be conducted as the stability of TODI in organic solvents is not considered as a relevant (chemical) property. In addition, it should be noted that isocyanates molecules will react with many solvents. As such, TODI is not stable in protic solvents such as methanol and some aprotic solvents such as acetone and DMSO.
Dissociation constant	In accordance with column 2 of REACH Annex IX, the test on dissociation constant does not need to be conducted if the substance

	is hydrolytically unstable at pH 4, 7 and 9 (half-life less than 12 hours). According to the study on determination of the hydrolysis of TODI as a function of pH (see section 7.7.1.1.1), the half-life of TODI was determined to be far below 12 hours (max.: 1.2 h at pH 7) and therefore found to be hydrolytically unstable.
Melting point/freezeing point	The melting point of TODI was determined to be 71.7 °C at 101.29 kPa using a linear heating rate of 1 °C/min.
Boiling point	The test material (TODI) was determined to decompose at approximately 644 K (371°C) at 101.42 kPa before boiling. Thus, no value for boiling temperature could be determined.
Density	Following EU-method A.3, the relative density (D4/20) of TODI was determined to be 1.331 g/cm3 at 20 °C (95 % confidence interval).
Surface tension	In accordance with column 2 of REACH Annex VII, the test on surface tension does not need to be conducted if the water solubility is lower than 1 mg/L at 20°C (see water solubility). According to the study on hydrolysis as a function of pH (see section 7.7.1.1.1) TODI was found to be hydrolytically unstable. The degradation products are found to be insoluble in organic and aqueous solvents in short-term toxicity study on fish and aquatic invertebrate) and assumed to form inert, insoluble polyureas in water (see section 7.7.1.1.1). Thus, determination of surface tension for TODI is scientifically not feasible.

7.5. Manufacture and uses

7.5.1. Quantities

Table 8. Aggregated tonnage (per year)

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

There is one registrant.

7.5.2. Overview of uses

The uses of the substance reported below are the ones described in the disseminated registration dossier[16]. During the course of the evaluation, FR-MSCA had access to information about downstream uses which are claimed as confidential business information and are not displayed below.

[16] https://echa.europa.eu/registration-dossier/-/registered-dossier/10067/3/1/7

Table 9. Uses

USES	Use(s)
Uses as intermediate	Refer to Uses at industrial sites
Formulation	*No exposure scenario*
Uses at industrial sites	**Industrial use of intermediates** - ERC 6a: Use of intermediate - PROC 1: Use in closed process, no likelihood of exposure - PROC 2: Use in closed, continuous process with occasional controlled exposure - PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities - PROC 15: Use as laboratory reagent - SU 12: Manufacture of plastics products, including compounding and conversion - Substance supplied to that use as such **Use of monomer in polymerisation processes** - ERC 6c: Use of monomer in polymerisation processes at industrial site (inclusion or not into/onto article) - PROC 1: Use in closed process, no likelihood of exposure - PROC 2: Use in closed, continuous process with occasional controlled exposure - PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities - PROC 15: Use as laboratory reagent - SU 12: Manufacture of plastics products, including compounding and conversion - Substance supplied to that use as such **Use at industrial site leading to inclusion into/onto article** - ERC 5: Use at industrial site leading to inclusion into/onto article - PROC 1: Use in closed process, no likelihood of exposure - PROC 2: Use in closed, continuous process with occasional controlled exposure - PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities - PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation - PROC 21: Low energy manipulation of substances bound in materials and/or articles - SU 12: Manufacture of plastics products, including compounding and conversion - Substance supplied to that use in a mixture - Subsequent service life is relevant for this use
Uses by professional workers	No exposure scenario
Consumer Uses	Consumer uses are advised against
Article service life	**Widespread use of articles with low release (outdoor)** - Articles used by workers - AC 13g: Other plastic articles

	- ERC 10a: Widespread use of articles with low release (outdoor) - PROC 21: Low energy manipulation of substances bound in materials and/or articles - PROC28: Manual maintenance (cleaning and repair) of machinery - Substance not intended to be released from article **Widespread use of articles with low release (indoor)** - Articles used by workers - AC 13g: Other plastic articles - ERC 11a: Widespread use of articles with low release (indoor) - PROC 21: Low energy manipulation of substances bound in materials and/or articles - PROC28: Manual maintenance (cleaning and repair) of machinery - Substance not intended to be released from article

Table 10. Uses advised against

USES	Use(s)
Consumer Uses	**Consumer uses are advised against** - ERC 8a: Widespread use of non-reactive processing aid (no inclusion into or onto article, indoor) - ERC 8b: Widespread use of reactive processing aid (no inclusion into or onto article, indoor) - ER C8c: Widespread use leading to inclusion into/onto article (indoor) - ERC 8d: Widespread use of non-reactive processing aid (no inclusion into or onto article, outdoor) - ERC 8e: Widespread use of reactive processing aid (no inclusion into or onto article, outdoor) - ERC 8f: Widespread use leading to inclusion into/onto article (outdoor) - ERC 9a: Widespread use of functional fluid (indoor) - ERC 9b: Widespread use of functional fluid (outdoor) PC 0: Other: No consumer use

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate (TODI) is not listed on Annex VI of CLP.

An intention for a harmonised classification for skin and respiratory sensitisation was notified by German MSCA in the Registry of Intention on 4 August 2017. At the time of drafting of this document, the dossier had been submitted and was awaiting the accordance check. The proposed future entry in Annex VI of CLP Regulation by the dossier submitter are Resp. Sens. 1, H334 and Skin Sens. 1A, H317.

7.6.2. Self-classification

In the registration(s)[17]:

Table 11. Self-classification

Classification		Spec. Conc. Limits, M-factors
Hazard Class and Category Code(s)	Hazard statement code(s)	
Acute Tox. 4	H332: Harmful if inhaled.	
Resp. Sens. 1	H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled.	
Skin Sens. 1A	H317: May cause an allergic skin reaction.	
Aquatic Acute 1	H400: Very toxic to aquatic life.	M = 1
Aquatic Chronic 1	H410: Very toxic to aquatic life with long lasting effects.	M = 1

The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory[18]:

- Acute Tox. 4, H302: Harmful if swallowed. (1 notification)
- Acute Tox. 4, H312: Harmful in contact with skin. (1 notification)
- Skin Irrit. 2, H315: Causes skin irritation. (1 notification)
- Eye Irrit. 2, H319: Causes serious eye irritation. (1 notification)
- Muta. 2, H341: Suspected of causing genetic defects. (1 notification)

Number of Aggregated Notifications: 6.

7.7. Environmental fate properties

7.7.1. Degradation

7.7.1.1. Abiotic degradation

7.7.1.1.1. Hydrolysis

Data on hydrolysis are summarised in the following table:

Table 12. Available data on hydrolysis

Method	Results	Remarks	Reference
EU Method C.7 (Degradation: Abiotic Degradation: Hydrolysis as a Function of pH) (EEC No. L383 A, dated December 1992)	Half-life (DT50): t1/2 (pH 4): <= 2 min at 25 °C t1/2 (pH 4): <= 2 min at 50 null	2 (reliable with restrictions) supporting study experimental result	Experimental study (2009) [ref. 25]

[17] Based on last updated dossier: 21 June 2017.

[18] Accessed 27 October 2017.

Method	Results	Remarks	Reference
OECD Guideline 111 (Hydrolysis as a Function of pH)	t1/2 (pH 9): <= 2 min at 25 null t1/2 (pH 9): <= 2 min at 50 null t1/2 (pH 7): 16 h at 25 °C; Rate constant: 0 ; Type: (pseudo-)first order (= DT50) t1/2 (pH 7): 1.2 h at 50 °C; Rate constant: 0.01 ; Type: (pseudo-)first order (= DT50) Recovery (in %): pH 4: ca. 0 at 25 °C after 1130 min pH 4: ca. 0 at 50 °C after 940 min pH 9: ca. 0 at 25 °C after 990 min pH 9: ca. 0 at 50 °C after 810 min pH 7: ca. 0 at 25 °C after 1147 min pH 7: ca. 0 at 50 °C after 230 min Transformation products: yes	**Test material: 3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate (TODI) CAS 91-97-4** Form: solid	

As an isocyanate, TODI should be considered theoretically as hydrolytically unstable.

Experimental study (2009) [ref. 25] assessed the hydrolysis potential of TODI according to standard guidelines OECD 111 and EU Method C.7 with significant deviations. Only a preliminary test with TODI is performed at 2 temperatures (25°C and 50°C). Based on this test, TODI should be considered as hydrolytically unstable. As a consequence, Tier 2 (hydrolysis kinetic) and Tier 3 (identification of hydrolysis products) of guidelines should have been performed. However, no degradation product is explicitly identified, and it is only mentioned that in a pre-study before the preliminary test, two hydrolysis products (m/z 240 and 215) appeared after 60min of contact between TODI and water. The Registrant postulated that the relevant hydrolysis product is TODA (4,4'-bi-o-toluidine; CAS 119-93-7). Based on the available information, FR-MSCA can support this conclusion.

The hydrolysis reaction was evaluated based on the formation of the degradation product TODA. The half life of TODI at pH 4 and 9, at 25 and 50 °C was lower than or equal to 2 minutes; at pH7 the half life of TODI was 16 hours and 1.2 hours at 25 and 50 °C respectively (analysed by the degradation product TODA).

No robust half life can be considered for the environmental risk assessment. As no degradation product is explicitly identified, only TODA has been considered as a hydrolysis product of TODI.

FR-MSCA notes that TODI has a structural similarity with MDI (methylenediphenyl diisocyanate; CAS 26447-40-5). According to the EU Risk Assessment Report (RAR) of MDI (2005)[19], the type of dispersion in water is a key parameter for diisocyanate hydrolysis (see Yakabe et al. (1992) cited in MDI RAR (2005) for more detail). In conditions inducing poor dispersion of diisocyanate in water, the reaction of diisocyanate with water induces the formation of diamine that could readily react with unreacted diisocyanate for producing insoluble solid polyureas. In conditions of high dispersion, formation of insoluble solid

[19] European Chemicals Bureau (2005). EU Risk Assessment Report: Methylenediphenyl diisocyanate (MDI). EU Risk Assessment Report, 3rd Priority List, Vol. 59, 2005. Report no.: Volume 59. Report date: 2005-01-01.

polyureas is expected to be low. By analogy, depending on the type of dispersion, FR-MSCA expects that TODA cannot be the only relevant hydrolysis product of TODI.

7.7.1.1.2. Phototransformation/photolysis

No relevant information is available for photolysis / phototransformation in air, water and soil.

7.7.1.2. Biodegradation

7.7.1.2.1. Biodegradation in water

7.7.1.2.1.1. *Screening tests*

The studies on biodegradation in water (screening tests) are summarized in the following table:

Table 13. Screening tests for biodegradation in water

Method	Results	Remarks	Reference
Test type: ready biodegradability activated sludge, domestic, non-adapted OECD Guideline 301 D (Ready Biodegradability: Closed Bottle Test) EU Method C.4-E (Determination of the "Ready" Biodegradability - Closed Bottle Test)	under test conditions no biodegradation observed % Degradation of test substance: -4.8 after 28 d (O2 consumption)	1 (reliable without restriction) key study experimental result **Test material: 3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate (TODI) CAS 91-97-4** Form: solid	Experimental study (2009) [ref. 31]
Test type: ready biodegradability activated sludge, domestic, non-adapted Japan: Guidelines for Biodegradation Testing of Chemicals by microorganisms etc. OECD Guideline 301 C (Ready Biodegradability: Modified MITI Test (I))	under test conditions no biodegradation observed % Degradation of test substance: 3 after 28 d (O2 consumption) 6 after 28 d (HPLC method)	2 (reliable with restrictions) supporting study read-across from supporting substance (structural analogue or surrogate) **Test material : 4,4'-bi-o-toluidine (TODA) CAS 119-93-7** Form: solid	Ministry of Economy, Trade and Industry (METI) (1981) [ref. 27]
Read-across based on study with MDI according to OECD Guideline 302 C (Inherent Biodegradability), see IUCLID section 5.2.1.	% Degradation of test substance: (0 %Degr. indicated. Based on the short half-life in water, the substance is essentially unavailable for biodegradation.)	2 (reliable with restrictions) supporting study read-across from supporting substance (structural analogue or surrogate) **Test material: Methylenediphenyl diisocyanate (MDI) CAS 26447-40-5**	European Chemicals Bureau (2005) [ref. 16]

7.7.1.2.1.2. *Summary and discussion of biodegradation in water and sediment*

Experimental study (2009; key study; Reliability Index (RI)=1) [ref. 31] investigated the ready biodegradability of test item TODI in a Closed Bottle Test over a period of 28 days according to standard guidelines OECD 301D and EU Method C.4. The biodegradation was followed by the oxygen uptake of the microorganisms during exposure. As a reference item Sodium benzoate was tested simultaneously under the same conditions as the test item, and functioned as a procedure control. Under the test conditions the percentage biodegradation of TODI reached a mean of -4.8 % after 28 days based on ThODNO3. Therefore this study shows that TODI and its degradation products are not readily biodegradable.

METI (1981; RI=2) [ref. 27] performed a ready biodegradability test on TODA following the standard guideline OECD 301C. Under the test conditions, the percentage of biodegradation of TODA reached 3% based on ThOD (Theoretical oxygen demand) and reached 6% by HPLC after 28 days. Therefore the test item can be considered to be not ready nor primarily biodegradable.

Moreover TODA has structural similarity with MDA (4,4'-methylenedianiline; CAS 101-77-9). According to the MDA RAR (EU, 2001)[20] [ref. 15], MDA is not readily biodegradable, stable to hydrolysis, with a half-life estimated at 1900 days and 10000 days in the water and sediment compartment respectively. Concerning biodegradation of MDA in soil compartment, experiments with radiolabelled MDA revealed that the substance forms covalent bonds with the organic fraction in aerobic and anaerobic conditions. Such mechanisms disrupt the biodegradation of MDA as revealed by experiments with radiolabelled MDA. In the RAR of MDA (EU, 2001), it is assumed that the half life of MDA in soil is 1000 days.

Two additional studies performed according to OECD 308 and OECD 309 added in the registration dossier of MDA. These tests were performed using radiolabelled MDA. The position of the label was in Methylene-14C. These both studies could be considered as reliable with a RI = 2 (reliable with restriction). In the OECD 309 study (Experimental study, 2013 [ref. 36]), after the test duration of 92 days, a half-life of 13.8 days and 21 days at 12°C were recorded for both test system. However, the degree of production of $^{14}CO_2$ was 25.5% and 18.1%. The disappearance of the parent test material was associated with the appearance of several major metabolites throughout the study. These metabolites were not identified and no DT50 was proposed. In the OECD 308 study (Experimental study, 2013 [ref. 35]), performed with 14C-labeled, test substance shift from water layer to the non-extractable fraction of the sediments. At the end of the study, 69.3 and 90.2% of the applied radioactivity was detected in the non extractable fraction of the aerobic samples taken from both system. The total amount of applied radioactivity transformed into $^{4}CO_2$ after 100 days of incubation was between 2.8% and 5.7% in aerobic conditions. In anaerobic conditions, the production of CO2 was below 1% for both systems.

Therefore, these studies show a rapid dissipation of the substance in water leading to dissipation half lives below the threshold value for the P criteria suggesting that the P criteria is not fulfilled. Nevertheless, it was shown formation of several metabolites above 10% for which no DT50 was determined due to technical reasons, and also high formation of non extractable residues. Mineralization of the test substance was low in both tests.

Based on the available information, the P status of MDA and hence for TODA could not be concluded.

[20] European Chemicals Bureau (2001). EU Risk Assessment Report: 4,4'-methylenedianiline (MDA). EU Risk Assessment Report, 1st Priority List, Vol. 9, 2001. Report no.: Volume 9. Report date: 2001-11.

7.7.1.2.2. Biodegradation in soil

No degradation experiment was performed with TODI in soil.

7.7.1.2.3. Summary of biotic degradation

The Registrant considers that TODI and its degradation products are not readily biodegradable, and based on the available data, FR-MSCA can support this conclusion.

Based on the available information, the P status of MDA and hence for TODA could not be concluded.

7.7.2. Environmental distribution

7.7.2.1. Adsorption/Desorption

The studies on adsorption/desorption are summarized in the following table:

Table 14. Studies on adsorption/desorption

Method	Results	Remarks	Reference
Study type: calculation Calculation according to KOCWIN (v2.00): estimation using estimated or experimentally derived log Kow	Adsorption coefficient: Koc: 178000 - 427600 L/kg at 25°C log Koc: 5.25 — ca. 5.63 dimensionless at 25°C (QSAR predicted value. The substance is within the applicability domain of the model)	2 (reliable with restrictions) supporting study estimated by calculation **Test material: 3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate (TODI) CAS 91-97-4**	Brunn, A. (2009a) [ref. 8] Brunn, A. (2010a) [ref. 10]
Study type: calculation Calculation according to KOCWIN (v2.00): estimation using estimated or experimentally derived log Kow	Adsorption coefficient: Koc: ca. 150 — ca. 3190 L/kg at 25°C log Koc: ca. 2.18 — ca. 3.5 dimensionless at 25°C (QSAR predicted value. The substance is within the applicability domain of the model)	2 (reliable with restrictions) supporting study read-across based on grouping of substances (category approach) **Test material: 4,4'-bi-o-toluidine (TODA) CAS 119-93-7**	Brunn, A. (2010a) [ref. 10]
Study type: estimation by calculation REACH guidance on QSARS R.6 , May 2008	Adsorption coefficient: Koc: 1 at 25 °C (pH 1) Koc: 1 at 25 °C (pH 2) Koc: 3.03 at 25 °C (pH 3) Koc: 61.9 at 25 °C (pH 4) Koc: 258 at 25 °C (pH 5) Koc: 347 at 25 °C (pH 6) Koc: 359 at 25 °C (pH 7) Koc: 361 at 25 °C (pH 8) Koc: 361 at 25 °C (pH 9) Koc: 361 at 25 °C (pH 10)	2 (reliable with restrictions) supporting study read-across from supporting substance (structural analogue or surrogate) **Test material: 4,4'-bi-o-toluidine (TODA) CAS 119-93-7**	Anonymous (2013)

Results from QSAR computations indicate that the estimated log Koc of TODI is 5.6311, thus indicating that adsorption of the test substance to solid soil phase is expected. However, as hydrolysis of TODI is very fast, it can be assumed that TODI has a transient presence in aquatic compartment. The Registrant postulates that the relevant hydrolysis product of TODI is TODA (4,4'-bi-o-toluidine; CAS 119-93-7). As a consequence, information on adsorption/desorption properties of TODA are needed for environmental risk assessment of TODI. In the information provided by the Registrant, the adsorption potential of TODA is estimated by calculation with KOCWIN of EPI suite. The Koc of TODA at 25 °C was estimated to be 3190 L/kg (MCI method) and 150 L/kg (Kow method). According to KOCWIN help document, the MCI method is more accurate than the log Kow methodology. Consequently, the estimated Koc for TODA is 3190 L/kg, *i. e.* log Koc = 3.5. The adsorption of TODA should be considered as moderate to strong, and FR-MSCA can support this conclusion.

7.7.3. Bioaccumulation

7.7.3.1. Aquatic bioaccumulation

The studies on aquatic bioaccumulation are summarised in the following table:

Table 15. Studies on aquatic bioaccumulation

Method	Results	Remarks	Reference
calculation Estimations of BCF using KOCWIN of EPI Suite compilation were performed for TODI Estimations of BCF using KOCWIN of EPI Suite compilation were performed for TODA (the postulated product of hydrolysis of TODI equivalent or similar to OECD Guideline 305 (Bioconcentration: Flow-through Fish Test)	BCF: 4569 (L/kg wet-wt) (estimation using KOCWIN of EPI Suite compilation) (BCF for TODI) BCF: 16.25 (L/kg wet-wt) (estimation using KOCWIN of EPI Suite) (BCF for TODA) Elimination: estimations using KOCWIN of EPI Suite: (QSAR predicted value. The substance is within the applicability domain of the model)	1 (reliable without restriction) key study estimated by calculation **Test material: 3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate (TODI) CAS 91-97-4** **and** **4,4'-bi-o-toluidine (TODA) CAS 119-93-7** Form: solid	Brunn, A. (2009b) [ref. 9] Brunn, A. (2010b) [ref. 11]
Cyprinus carpio aqueous (freshwater) flow-through Total uptake duration: > 0 — < 8 wk Details on estimation of bioconcentration: Each of fish and test water was sampled and analyzed at five points (2, 3, 4, 6 and 8 weeks). Fish body was pretreated and the concentration of TODA in the	BCF: > 4.8 — < 34 dimensionless (whole body w.w.) (steady state) BCF: > 10 — < 83 dimensionless (whole body w.w.) (steady state)	2 (reliable with restriction) read-across from supporting substance (structural analogue or surrogate) **Test material: 4,4'-bi-o-toluidine (TODA) CAS 119-93-7** Form: crystalline	Ministry of Economy, Trade and Industry (METI) (1984) [ref. 27]

Method	Results	Remarks	Reference
fish was analyzed by HPLC. Test water was pretreated and the concentration of TODA in the water was analyzed by HPLC. BCF was calculated from the ratio of the concentration of TODA in the fish to the concentration of TODA in the water. Japan: Guidelines for Bioaccumulation Testing of Chemicals in fish			

7.7.3.2. Summary and discussion of bioaccumulation

The aquatic bioaccumulation potential of TODI is assessed based on information provided by the Registrant using a Weight of Evidence approach (WoE). No information about the terrestrial bioaccumulation was provided. As hydrolysis of TODI is very fast, it can be assumed that TODI has a transient presence in aquatic compartment. As a consequence, bioaccumulation in aquatic compartment should be based on its hydrolysis product TODA, according to the Registrant, and based on the available information, FR-MSCA can support this conclusion. (METI, 1984; RI=2) [ref. 27] performed a bioaccumulation test, according to Japanese guideline for bioaccumulation testing of chemicals in fish (Cyprinus carpio) in flow through exposure. No bioaccumulation of TODA was observed. The BCF values were determined to be below 100. For the concentration of 0.2 mg /L a BCF of 4.8 to 34 was determined. For the concentration of 0.02 mg /L a BCF of 10 to 83 was determined. The reliability of 2 could be assigned to this study even if the control mortality is not given. Brunn,2009, 2010; RI=1 [ref. 8 to 11] estimated bioaccumulation potential of TODA by estimated BCF by calculation with EPI suite compilation. Estimations using KOCWIN of EPI Suite compilation (log Kow used: 2.34 resulted in BCF value of 16.25 L/kg ww for TODA. Both results revealed that BCF of TODA is < 100 L/kg, which indicate a low potential of bioaccumulation on aquatic organism.

The substance is screens as potentially bioaccumulative in air-breathing organisms. However, a weight of evidence based on toxicokinetic data available in the EU-RAR of MDA, it can be conclude that the substance is quickly eliminated from the organisms. Therefore, based on a read-across between MDA, structurally similar to TODA, it could be conclude that TODA and hence TODI is not bioaccumulative in air-breathing organisms.

Therefore, FR-MSCA considers that TODA does not fulfil the B criteria based on a weight of evidence.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

Data on toxicity to aquatic organisms submitted by the Registrant are only focused on TODI. According to the OECD guidance No. 23, TODI should be considered as a difficult substance, because of its high reactivity with water, leading to its complete and fast hydrolysis (i. e. DT50, 25°C < 1 day). As a consequence, TODI can have only a transient existence in water and potential aquatic toxicity should be due to its degradation products. Moreover, because of its tendency to polymerize, test solutions should be prepared by adding the substance very slowly to a vessel which is part-filled with water and being stirred rapidly. Once the substance has been added, the vessel should be topped up with water to the required volume and stirred continuously for a sufficient duration to ensure

complete hydrolysis. This procedure should enable a solution of the hydrolysis products to be produced without the formation of polymers. According to the available information in the registration dossier for each aquatic toxicity tests described below, not enough details about preparation of test solution is provided by the Registrant in each available acute toxicity tests; therefore the adequacy of the used protocol for limiting potential polymerization of TODI and its hydrolysis products cannot be assessed. Moreover, it is mentioned that insoluble degradation product in water and solvent is observed in test preparation. However, it should also be noted that the solubility of TODI (and its degradation/hydrolysis product) in water was increased by an auxiliary solvent. L(E)C50 have been derived using time weighted average concentrations which could be considered as an adequate estimation to refer to a substance concentration which was reduced due to hydrolysis.

Moreover, supporting ecotoxicity data on TODA (4,4'-bi-o-toluidine; CAS 119-93-7), the relevant hydrolysis product of TODI was added to complete the dossier.

All these available data on TODI and TODA are considered as reliable and lead to the conclusion that the T criteria is not fulfilled for the environment.

7.8.1.1. Fish

7.8.1.1.1. Short-term toxicity to fish

The results are summarised in the following table:

Table 16. Short-term effects on fish

Method	Results	Remarks	Reference
Oncorhynchus mykiss freshwater semi-static OECD Guideline 203 (Fish, Acute Toxicity Test) EU Method C.1 (Acute Toxicity for Fish)	LC50 (96 h): 0.25 mg/L test mat. (meas. (TWA)) based on: mortality (95 % CL) LC50 (96 h): 1 mg/L test mat. (nominal) based on: mortality (95% CL)	2 (reliable with restriction) experimental result **Test material: 3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate (TODI) CAS 91-97-4** Form: solid	Experimental study (1998) [ref. 33]
Oryzias latipes freshwater short-term toxicity to fish according to OECD Guideline 203 (Fish, Acute Toxicity Test)	LC50 (96h): 13 mg/L test mat. (nominal) based on: mortality	2 (reliable with restriction) supporting study experimental study **Test material: 4,4'-bi-o-toluidine (TODA) CAS 119-93-7**	Japanese Ministry of Environment (MOE) 2001

7.8.1.2. Aquatic invertebrates

7.8.1.2.1. Short-term toxicity to aquatic invertebrates

The results are summarized in the following table:

Table 1417. Short-term effects on aquatic invertebrates

Method	Results	Remarks	Reference
Daphnia magna freshwater static OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test) EU Method C.2 (Acute Toxicity for Daphnia)	EC50 (48 h): > 1.2 mg/L test mat. (meas. (TWA)) based on: mobility EC50 (48 h): > 4 mg/L test mat. (nominal) based on: mobility	2 (reliable with restriction) supporting study experimental result **Test material: 3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate (TODI) CAS 91-97-4** Form: solid	Experimental study (1998) [ref. 34]
Daphnia magna Freshwater static according to OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test)	EC50 (24h): 11 mg/L test mat. (nominal) based on: not specified EC50 (48h): 4.5 mg/L test mat. (nominal) based on: not specified NOEC (24h): 3.2 mg/L test mat. (nominal) based on: not specified NOEC (48h): 2.2 mg/L test mat. (nominal) based on: not specified	2 (reliable with restriction) supporting study experimental study **Test material: 4,4'-bi-o-toluidine (TODA) CAS 119-93-7**	Japanese Ministry of Environment (MOE) 2001

7.8.1.3. Algae and aquatic plants

The results are summarized in the following table:

Table 1518. Effects on algae and aquatic plants

Method	Results	Remarks	Reference
Scenedesmus subspicatus (new name: Desmodesmus subspicatus) (algae) static OECD Guideline 201 (Alga, Growth Inhibition Test) EU Method C.3 (Algal Inhibition test)	EC50 (72 h): > 4 mg/L test mat. (nominal) based on: growth rate EC50 (72 h): > 1.5 mg/L test mat. (meas. (TWA)) based on: growth rate NOEC (72 h): >= 4 mg/L test mat. (nominal) based on: growth rate NOEC (72 h): >= 1.5 mg/L test mat. (meas. (TWA)) based on: growth rate	2 (reliable with restriction) supporting study experimental result **Test material: 3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate (TODI) CAS 91-97-4** Form: solid	Experimental study (1998) [ref. 26]
Pseudokirchneriella subcapitata (previous names: *Raphidocelis subcapitata*, *Selenastrum capricornutum*) (algae) Freshwater toxicity to aquatic algae and cyanobacteria	EC50 (72h): 4.6 mg/L test mat. (nominal) based on: growth rate EC50 (48h): 4.1 mg/L test mat. (nominal) based on: growth rate	2 (reliable with restriction) supporting study experimental study	Japanese Ministry of Environment (MOE) 2001

Method	Results	Remarks	Reference
	EC50 (72h): 2 mg/L test mat. (nominal) based on: biomass NOEC (72h): 1 mg/L test mat. (nominal) based on: growth rate NOEC (48h): 1 mg/L test mat. (nominal) based on: growth rate NOEC (72h): 0.32 mg/L test mat. (nominal) based on: biomass	**Test material: 4,4'-bi-o-toluidine (TODA) CAS 119-93-7**	

7.8.1.4. Other aquatic organisms

The results on aquatic micro-organisms are summarized in the following table:

Table 1619. Effects on micro-organisms

Method	Results	Remarks	Reference
activated sludge, domestic freshwater static OECD Guideline 209 (Activated Sludge, Respiration Inhibition Test) EU Method C.11 (Biodegradation: Activated Sludge Respiration Inhibition Test) EPA OPPTS 850.6800 (Modified Activated Sludge, Respiration Inhibition Test for Sapringly Soluble Chemicals)	EC50 (3 h): > 1000 mg/L test mat. (nominal) based on: respiration rate	2 (reliable with restriction) supporting study experimental result **Test material: 3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate (TODI) CAS 91-97-4** Form: solid	Experimental study (2008) [ref. 32]

7.8.2. Terrestrial compartment

Information on terrestrial toxicity of TODI is waived by the Registrant, based on exposure considerations. Concerning the industrial uses of the TODI, according to the Registrant, TODI is processed in closed systems, in strictly controlled conditions, and consequently, the fraction released to waste water and to soil were estimated to be equal to 0 for the following uses:

- industrial use of monomer in polymerisation processes;
- industrial use of intermediates;
- use at industrial site leading to inclusion into/onto article.

Some descriptions of the closed systems and the strictly controlled conditions for each use have been provided by the downstream users and a qualitative risk assessment was proposed considering no emission to the environmental compartments.

In addition, to cover the service-life of manufactured articles measured data have been provided by the downstream users, which showed very low release. A quantitative

assessment considering no emission to the environment was also proposed for service-life of articles.

7.8.3. PNEC derivation and other hazard conclusions

Table 20. PNEC derivation and other hazard conclusions

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks/Justification**
Freshwater	PNEC aqua (freshwater): 0.25 µg/L	Assessment factor: 1000 Extrapolation method: assessment factor PNEC value is derived from the lowest acute toxicity endpoint available for the most sensitive species: LC50 (96h) = 0.25 mg/L for *Oncorhynchus mykiss* Nevertheless, it should be noted that the release of TODI to aquatic compartments is not to be expected as TODI is used under strictly controlled conditions only. No PNEC was proposed by the Registrant.

7.8.4. Conclusions for classification and labelling

TODI is rapidly hydrolysed. Nevertheless, based on the available information on biotic degradation, FR-MSCA concludes that TODA (hence TODI) could be considered not ready biodegradable.

The lowest acute toxicity endpoint is available for the most sensitive species: LC50 (96h) = 0.25 mg/L for *Oncorhynchus mykiss.*

Therefore, FR-MSCA considers that TODI should be classified as Aquatic Acute 1 (m-factor = 1) and Aquatic Chronic 2.

7.9. Human Health hazard assessment

7.9.1. Read-across hypothesis

FR-MSCA proposes to address the concerns on mutagenicity and carcinogenicity in a grouping approach with other diisocyanates. Indeed the diisocyanates all share the common structure –N=C=O (isocyanate) which reacts with electrophiles compounds and hydrolyses to amines. This hypothesis could be assessed on the basis of the available data on diisocyanates and in particular the new data obtained on 4,4'-MDI, when available.

7.9.2. Toxicokinetics

No data available on TODI.

In its registration dossier, the Registrant included a statement on toxicokinetics based on physico-chemical properties of TODI and a read-across with MDI [ref. 18]. The Registrant states that diisocyanates react with electrophiles compounds such as water, alcohols, amines, etc. and FR-MSCA agrees with this statement.

No data is available on the absorption of TODI following oral, dermal and inhalation exposure. Following oral exposure, the Registrant assumes that TODI would likely be hydrolysed in the stomach and form insoluble degradation products which would not be able to cross the gastro-intestinal tract membranes. FR-MSCA agrees that TODI is likely to react in the gastrointestinal tract, but cannot reach a conclusion regarding the identity of the reaction products nor their bioavailability due to the lack of data in the registration dossier to support this assumption.

No data is available on the metabolisation of TODI to identify and quantify metabolites. The Registrant assumes that TODI is likely to be excreted mainly in faeces and in form of GSH-conjugates via urine, based on an analogy with inhaled MDI; however no data are available on TODI to support this hypothesis.

7.9.3. Acute toxicity

- **Acute toxicity: oral**

The Registrant concluded that the substance is not toxic (LD_{50} ≥ 2000 mg/kg bw) following administration of a single dose by gavage in arachis oil (experimental study (1998) [ref. 4]). Based on the available information, FR-MSCA can support this conclusion.

- **Acute toxicity: inhalation**

The Registrant concluded that the substance is moderately toxic by inhalation and should be classified as **Acute Tox. 4 H332: harmful if inhaled** (LC50 (4h) for dust >1 but ≤ 5 mg/L, namely: LC50 (4h): 2.74 (1.85-4.07) mg/L air (all animals), LC50 (4h): 2.06 (1.37-3.08) mg/L air (male), LC50 (4h): 4.44 (1.55-12.7) mg/L air (female)) in a rat study (1998) [ref. 7]). Based on the available information, FR-MSCA can support this conclusion. FR-MSCA notes however that the results of this study should be considered with caution as the respirable fractions (mass median aerodynamic diameter (MMAD) < 4 µm) were low and no data on the fraction with a MMAD < 10 µm were available.

- **Acute toxicity: dermal**

The Registrant concluded that the substance is not toxic (LD_{50} ≥ 2000 mg/kg bw) following a single exposure by dermal route (experimental study (1998) [ref. 5]). Based on the available information, FR-MSCA can support this conclusion.

7.9.4. Irritation and corrosion

- **Skin**

Based on animal data on TODI, the Registrant concluded that the substance is not irritating/corrosive to skin (observation of very slight erythema/oedema, reversible in an experimental study (1998) [ref. 1]). Based on the available information, FR-MSCA can support this conclusion.

- **Eye**

Based on animal data on TODI, the Registrant concluded that the substance is not irritating/corrosive to eyes (observation of minimal to moderate conjunctival irritation, which was reversible, transient diffuse corneal opacity, transient iridial inflammation, in an

experimental study (1998) [ref. 2]). Based on the available information, FR-MSCA can support this conclusion.

- **Respiratory tract**

No data available.

7.9.5. Sensitisation

- **Skin**

Based on animal data on TODI (Guinea Pig Maximization Test (1998) [ref. 3], which produced a 90 % (9/10) sensitisation rate), the Registrant concluded that the substance is sensitising to skin and should be classified as **Skin Sens. 1A H317: may cause an allergic skin reaction**. Based on the available information, FR-MSCA can support this conclusion.

This endpoint will be addressed by German MSCA in a harmonised classification proposal. At the time of drafting of this document, the dossier had been submitted and was awaiting the accordance check. The proposed future entry in Annex VI of CLP Regulation by the dossier submitter are Resp. Sens. 1, H334 and Skin Sens. 1A, H317.

- **Respiratory system**

No data on TODI.

The Registrant concluded that TODI should be considered as a respiratory sensitiser and should be classified as **Resp. Sens. 1 H334: may cause allergy or asthma symptoms or breathing difficulties if inhaled**, on the basis of the conclusion on skin sensitisation and of the data on other diisocyanates on skin and respiratory sensitisation, which share the isocyanate functional group as a common structural alert [ref. 29].

The induction of respiratory sensitisation to diisocyanates by dermal route is known and is considered relevant for humans as detailed in the RAC Opinion[21] on the Annex XV dossier proposing restrictions for diisocyanates (adopted 5 December 2017).

Based on the available information, FR-MSCA can support this conclusion.

This endpoint will be addressed by German MSCA in a harmonised classification proposal. At the time of drafting of this document, the dossier had been submitted and was awaiting the accordance check. The proposed future entry in Annex VI of CLP Regulation by the dossier submitter are Resp. Sens. 1, H334 and Skin Sens. 1A, H317.

7.9.6. Repeated dose toxicity

Only a 28-day oral (gavage) study was provided by the Registrant (rats, 5/sex/dose, doses: 10, 150 and 1000 mg/kg bw/d, vehicle: arachis oil) (1998, [ref. 21]).

In the 28-day study, the Registrant established a NOEL (no observed effect level) of 150 mg/kg bw/d (nominal) (male/female). At the highest dose of 1000 mg/kg bw/d, the following effects were observed: salivation, red/brown staining around the mouth, reduction in body weight and dietary intake in males and slightly in females, reduction in plasma glucose in males; at necropsy, residual test material was found in the stomach of several males and females and the gastro-intestinal tract of one male had gaseous

[21] RAC Opinion on an Annex XV dossier proposing restrictions for diisocyanates (adopted 5 December 2017) ECHA/RAC/RES-O-0000001412-86-174/F. https://echa.europa.eu/documents/10162/ddc6108d-a33e-3087-6a6a-8754783c2aa8.

distension; hyperkeratosis and occasional acanthosis was found in the forestomach of males and females.

The Registrant highlighted that "*the systemic toxicity identified was probably attributable to the degradation product(s) of TODI*". FR-MSCA notes that these degradation products were not identified nor quantified, but agrees that TODI could react with the vehicle (arachis oil) to form a long fatty chain with TODA in one extremis (linked throuth an amide bound to the fatty acid), and maybe with other electrophile compounds in the gastrointestinal tract.

FR-MSCA notes several deficiencies in the study design and reporting: "too high doses" spacing, animals not fasted prior to haematology/blood chemistry exam, no identification/quantification of degradation products from the test material.

The Registrant submitted waivings for 28-day studies by inhalation and dermal route and for a 90-day study.

- The Registrant justified the waiving of the inhalation study as inhalation exposure is not expected "*based on the provided thorough and rigorous exposure assessment*" (low vapour pressure, no particles with a diameter below 63 µm). FR-MSCA disagrees that no exposure can be expected (see section 7.12).
- The Registrant justified the waiving of the dermal study as dermal exposure is not expected "*based on the provided thorough and rigorous exposure assessment*". FR-MSCA disagrees that no exposure can be expected (see section 7.12).
- Based on Annex IX, 8.6.2, a 90-day study should have been submitted. Instead the Registrant provided a waiving as an adaptation to the standard requirement. The justification is that "*no exposure is to be expected because TODI is used under strictly conditions only (…) no DNELs have to be derived and a sub-chronic study (90 days) would not improve the risk assessment".* However, the Registrant has not proven that there is no exposure (as highlighted in section 7.12 below).

A compliance check (CCH) would be the adequate regulatory tool to assess these adaptations to the standard requirements (Article 13(1), Annex XI(3)).

7.9.7. Mutagenicity

- ***In vitro* data**

The mutagenicity of TODI has been investigated in three *in vitro* studies.

In a **bacterial reverse mutation assay (i.e. Ames test)** conducted in accordance with a method equivalent or similar to OECD test Guideline 471 (Bacterial Reverse Mutation Assay) (anonymous / JETOC (1996), [ref. 6]), duplicate plates of five *S. typhimurium* strains (TA 100, TA 1335, TA 98, TA 1537, TA 1538) and *E. coli* WP2uvrA strain were exposed to the test material at 10, 20, 50, 100, 200, 500, 1000, 2000 µg/plate with and without metabolic activation. The vehicle was DMSO. The test material was TODI with a purity > 99.9%. Positive results were obtained in the presence of metabolic activation for TA 98 and TA 1538 at concentrations of 10 to 1000 µg/plate (an evaluation of 2000 µg/plate was not possible due to growth inhibition).

In a **mammalian cell gene mutation assay** conducted in accordance with OECD test Guideline 476 (*In vitro* Mammalian Cell Gene Mutation Test) (experimental study (1999) [ref. 13]), mouse lymphoma L5178Y cells were exposed to the tested material in 3 independent experiments, at the following concentrations:

- experiment 1: 2, 4, 8, 12, 16 µg/mL with and without metabolic activation (3h exposure);

- experiment 2: 4, 8, 16, 20, 24 µg/mL without metabolic activation (24h exposure) and 4, 8, 12, 14, 16 µg/mL with metabolic activation (3h exposure);
- experiment 3: 4, 6, 8, 10, 12 µg/mL without metabolic activation and 6, 8, 10, 12, 14 µg/mL with metabolic activation (3h exposure)

The vehicle used was acetone. The test material was TODI with a purity > 99.9%. TODI induced small but statistically significant increases in mutant frequency in each of 3 independent experiments (without metabolic activation in experiment 1 (dose-related), with metabolic activation in experiment 2 (dose-related), and with (dose-related) and without metabolic activation in experiment 3).

In an ***in vitro*** **mammalian chromosome aberration test** conducted in accordance with a method equivalent or similar to OECD test Guideline 473 (*In vitro* Mammalian Chromosome Aberration Test) (anonymous / JETOC (1996), [ref. 6]), CHL cells were exposed to the test material at the following concentrations: 0.1, 0.2, 0.3, 0.4, 0.5 mg/mL (24h, 48h, without metabolic activation) and 0.2, 0.3, 0.4, 0.5, 0.6 mg/mL (6h, with and without metabolic activation). The vehicle was DMSO. The purity of the tested substance was unspecified but the Registrant confirmed that the typical purity of TODI is 99.8% (range 99.5-100%). Slightly positive results were obtained with metabolic activation.

- ***In vivo*** **data**

The genotoxicity of TODI has been investigated in two *in vivo* studies.

In a **bone-marrow micronucleus assay** (chromosome aberration) conducted in accordance with OECD test Guideline 474 (Mammalian Erythrocyte Micronucleus Test) (experimental study (1998) [ref. 12]), Albino Crl:CD-1TM (ICR) BR mice (males/females) were exposed to the test substance in a single dose at the nominal concentrations of 125 mg/kg bw (sacrifice 24h after exposure), 250 mg/kg bw (sacrifice 24h after exposure) and 500 mg/kg bw (sacrifice 24h and 48h after exposure) following a range-finding assay. FR-MSCA notes that the route of administration of the test material is not totally clear: in the range-finding study, both oral and intraperitoneal (IP) routes were tested; no premature deaths or clinical signs were observed via the oral route and it is reported that the IP route was consequently selected for the main study; this information is also reported in the executive summary. However, in the description of the method, oral route is mentioned. The vehicle was arachis oil. The test material was TODI with a purity > 99.9%. The PCE/NCE ratio was reduced at 500 mg/kg bw (24h) ($p<0.01$) and 125 mg/kg bw (24h) ($p<0.05$), and toxicity was observed (mortality at high dose; clinical signs at all doses), showing that the substance was absorbed and that target tissues were exposed. No significant increase in the frequency of micronuclei in polychromatic erythrocytes of mice was observed under the conditions of the test. The test was considered negative.

In a GLP-compliant **unscheduled DNA synthesis (DNA damage and/or repair) (UDS test)** conducted in accordance with OECD test Guideline 486 (Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells in vivo) (experimental study (1999) [ref. 14]), Crj: CD(SD) rats (males) were exposed by gavage to the test material at the nominal concentrations of 700 and 2000 mg/kg bw (experiment 1: perfusion 16h after dosing; experiment 2: perfusion 2h after dosing), following a range-finding assay. The vehicle was arachis oil. The purity of the test substance was unspecified but the Registrant confirmed that the typical purity of TODI is 99.8% (range 99.5-100%). No signs of toxicity were observed. No increase in the incidence of unscheduled DNA synthesis was observed at any time point. The test was considered negative.

FR-MSCA agrees with the general Registrant's conclusion based on the available data but considers that this UDS test is not suitable to assess the genotoxicity of TODI.

Indeed, no data is available to support that TODI has been absorbed in the gastro intestinal tract and has been able to reach the target tissues. In the range finding assay and in the main experiments, no toxicity was observed. No toxicity was observed neither in the range-finding assay by oral route for the micronucleus study(see above).

In addition, TODI is likely to react with the vehicle (arachis oil) to form a long fatty chain with TODA at one end. Due to the lack of information on oral absorption and distribution, it is not possible to conclude if the liver was reached by the substance and that this test result is reliable.

Finally, the UDS test is no longer recommended to assess genotoxic carcinogens as it is considered of low sensitivity (Kirkland and Speit, 2008 [ref. 22]).

- **Summary and discussion of mutagenicity**

TODI was examined in three *in vitro* genetic toxicity studies (with and without simulated metabolic activation) and two different *in vivo* genetic toxicity studies.

In these assays, the tested substance TODI has a high purity (typical purity 99.8% with a range of 99.5%-100%). This information is very important to ensure that the observed results are not due to mutagenic impurities. Based on the information submitted by the Registrant, FR-MSCA considers that due to selective purification and reactivity of TODI, the impurities are most likely structural isomers of TODI.

The impact of the vehicle on the test results was not studied nor discussed in the registration dossier. The stability of TODI in organic solvents and the identity of relevant degradation products were not studied (refer to section 7.4). TODI is unstable in water and, therefore, DMSO and acetone were used in *in vitro* tests and arachis oil in *in vivo* tests.

Impact of aprotic polar solvents: FR-MSCA notes that diisocyanates were shown to be unstable in aprotic polar solvents such as dimethylsulfoxide (DMSO), resulting in the formation of amines (Herbold *et al*., 1998 [ref. 17]; Seel *et al*., 1999 [ref. 30]). For assessing the *in vitro* genotoxicity of TODI, DMSO and acetone (also an aprotic polar solvent) were used. Based on the available information on structurally similar aromatic diisocyanates, degradation of TODI into TODA (4,4'-bi-o-toluidine, CAS 119-93-7, EC 204-358-0) in aprotic polar solvents cannot be excluded, and **it is not possible to conclude whether the positive results observed in the *in vitro* tests are due to TODI and/or TODA and/or other degradation products.** TODA is not registered under REACH and therefore no registration dossier is available; however TODA has a harmonised classification as Carc. 1B (index 612-041-00-7). Even if there is no harmonised classification for mutagenicity, data found in the literature for TODA are equivocal (NTP report n°390[22] [ref. 28]; You *et al*. (1993) [ref. 35]; HSDB data bank [ref. 19]; IARC monography on benzidine and derivatives (2010) [ref. 20]). Therefore, no clear conclusion on genotoxicity mechanism can be drawn.

Impact of arachis oil: FR-MSCA considers that TODI will likely react with the vehicle (arachis oil) to form a long fatty chain with TODA in one extremis, which may impact the results of the micronucleus study to an unkown extent (considering that intraperitoneal administration was used), and which will **likely impact the results of the UDS study by preventing gastro-intestinal absorption and reaching of the substance to the target tissues**. FR-MSCA notes that in the 28-day study with administration of TODI by oral route in arachis oil, absorption of the test material seems poor as residual material was found in the gastrointestinal tract.

FR-MSCA considers that the UDS test is unsuitable to conclude on the mutagenicity concern, considering that no data is available to support that TODI has been absorbed in the gastro intestinal tract and has been able to reach the target tissues, that TODI is likely to react with the vehicle, and that this method is not considered suitable to assess genotoxic carcinogens as it is considered of low sensitivity (Kirkland and Speit (2008)). Therefore, only one potentially suitable *in vivo* assay (micronucleus, which assesses chromosomal aberration) is available to assess this endpoint.

[22] *Toxicology and carcinogenesis studies of 3,3'-dimethylbenzidine dihydrochloride in F344/N rats, NTP n°390.*

Based on these tests, FR-MSCA does not support the conclusions of the Registrant and considers that there is still a concern related to mutagenicity of TODI. This is further supported by the fact that one notifier has self-classified the substance as Muta 2 in the list of classification and labelling notifications present in the ECHA C&L Inventory. Therefore FR-MSCA concludes that the concern for mutagenicity remains.

In order to elucidate the mutagenicity of TODI, FR-MSCA requested new data in its draft decision referred to MSC on 27 July 2015: *in vivo* Comet assay (test guideline OECD 489) with TODI via inhalation route and investigation of the lung and liver or, at the discretion of the Registrant, i.e. if they identify the need to evaluate effects on germ cells, alternatively a Transgenic Rodent Assay (test guideline OECD 488). The request was dropped (along with all other requests on hazard endpoints) from the final version of the Decision, considering that exposure has to be clarified first, so as to ensure proportionality principle and for animal welfare reasons. In the final decision of 24 November 2015, the Registrant(s) were nevertheless reminded of the provisions of article 41 of the CLP regulation stating that the Notifiers and Registrants shall make every effort to come to an agreed entry to be included in the inventory.

On the basis of the new data received on 16 February 2017 following the requests in the Substance Evaluation Decision of 24 November 2015, FR-MSCA concludes that human exposure cannot be excluded, although probably exposure does not occur at high concentrations. In its follow-up evaluation, FR-MSCA also took into account the outcome of the evaluation of 4,4'-MDI by Estonia. New *in vivo* data (Comet assay) were generated for MDI and FR-MSCA considers that it may be worthwhile to take into account the result of the evaluation of these new data when it will be available.

As of now the Notifiers and Registrants have not come to an agreed C&L entry to be included in the inventory for mutagenicity.

FR-MSCA considers that the concern for mutagenicity should still be addressed. However the issues of proportionality principle and animal welfare remain when it comes to requesting new data to elucidate this concern. Also, new data became available on structurally similar MDI and a restriction is ongoing which also targets TODI. As a consequence, FR-MSCA will not request new data on TODI at the time being in the context of the Substance Evaluation. Nevertheless, FR-MSCA notes that without the UDS test the standard requirements seem not to be fulfilled for mutagenicity. This could be addressed under compliance check (CCH). In vitro tests may also be inadequate and could also be targeted in a CCH. FR-MSCA also proposes to address mutagenicity in a grouping approach with other diisocyanates.

7.9.8. Carcinogenicity

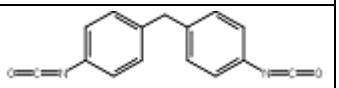
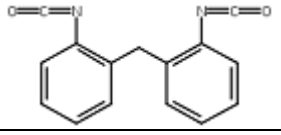
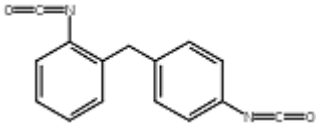
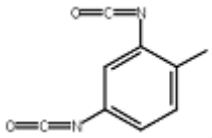
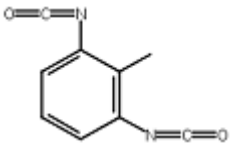
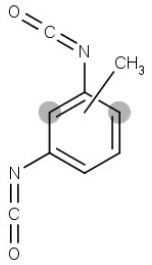
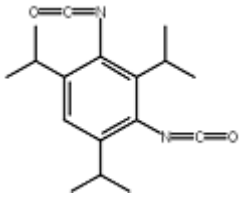
According to the REACH regulation, carcinogenicity study is not listed in the Annex for standard information requirements for a substance with a tonnage < 1000 tons/year. No data is available to assess the carcinogenicity of TODI in the registration dossier (aggregated tonnage 100 – 1000 tons/year). The only repeated study available in the dossier is a 28-days study by oral route, but, using this route, only low amount of TODI seemed to be absorbed; and the study duration is too short.

TODI is unstable in water and is likely hydrolysed to TODA (4,4'-bi-o-toluidine, CAS 119-93-7, EC 204-358-0). TODA has an harmonised classification as Acute Tox. 4 H302, Carc. 1B H350 and Aquatic Chronic 2 H411 (index no. 612-041-00-7). Considering the reactivity of TODI and due to the lack of data on its metabolism, as a worst-case approach FR-MSCA considers that TODI is totally metabolised in TODA in organisms.

In addition, data in the literature on the structurally similar substances MDI and TDI, which have a harmonised classification as Carc. 2 H351, and on their hydrolysis products MDA and TDA, which forms in a similar way as TODA is formed from TODI, and which have a harmonised classification as Carc. 1B H350 and Muta. 2 H341, raise a concern for

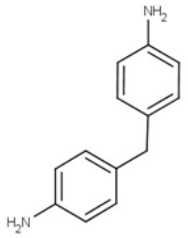
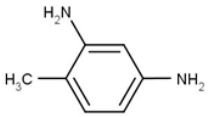
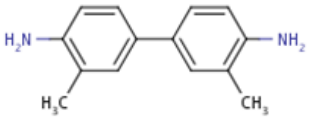
carcinogenicity. The substance TRIDI (2,4,6-triisopropyl-m-phenylene diisocyanate, CAS 2162-73-4, EC 218-485-4) has a self-classification as Carc. 2 H351. The structures and their classification for carcinogenicity and mutagenicity are summarised in Table 17 and Table 18 below.

Table 17. Registered diisocyanates with a harmonised or self-classification as Carc. 2 H351 (excluding reaction products and polymers)[23]

EC Name	Abbreviation	EC No.	CAS No.	Index No.	Structure
methylenediphenyl diisocyanate	MDI (group)	247-714-0	26447-40-5	615-005-00-9	
4,4'-methylenediphenyl diisocyanate	4,4'-MDI	202-966-0	101-68-8	615-005-00-9	
2,2'-methylenediphenyl diisocyanate	2,2'-MDI	219-799-4	2536-05-2	615-005-00-9	
o-(pisocyanatobenzyl)phenyl isocyanate	2,4'-MDI	227-534-9	5873-54-1	615-005-00-9	
4-methyl-m-phenylene diisocyanate	2,4-TDI	209-544-5	584-84-9	615-006-00-4	
2-methyl-m-phenylene diisocyanate	2,6-TDI	202-039-0	91-08-7	615-006-00-4	
m-tolylidene diisocyanate	80/20 TDI or 65/35 TDI	247-722-4	26471-62-5	615-006-00-4	
2,4,6-triisopropyl-m-phenylene diisocyanate	TRIDI	218-485-4	2162-73-4	None (only a self-classification is available)	

[23] C&L inventory consulted 22 February 2018. 183 substances (including reaction products and pre-polymers) are found in the C&L inventory with keyword containing "diisocyanate"; among them: 1 has a classification notification as Carc. 1B (Tolylene 2,5-diisocyanate, EC 622-946-9) but this substance is not found in the registration database; 47 have a classification as Carc. 2 (7 harmonised and 40 self-classifications/notifications).

Table 18. Harmonised classification as Carc. and as Muta. of the hydrolysis products of MDI, TDI and TODI

EC Name	Abbreviation	EC No.	CAS No.	Index No.	Structure	Classification (CM)	Remarks
4,4'-methylenedianiline	MDA	202-974-4	101-77-9	612-051-00-1		Carc 1B H350 Muta 2 H341	Identified as SVHC
4-methyl-m-phenylenediamine	TDA	202-453-1	95-80-7	612-099-00-3		Carc 1B H350 Muta 2 H341	Identified as SVHC
4,4'-bi-o-toluidine	TODA	204-358-0	119-93-7	612-041-00-7		Carc 1B H350	Not registered

Data available in the literature on the carcinogenic and mutagenic effects of these substances in animals are presented below. In humans there is inadequate evidence of carcinogenicity.

Summary of data for MDI/MDA

For MDI, tumors in the lungs were observed in animals in a chronic toxicity/carcinogenicity inhalation study (refer to registration dossier of MDI). No carcinogenicity studies by oral or dermal route are available.

Two hypothesis were proposed to explain the carcinogenicity mechanism:

- Oncogenesis based on irritation and an epigenetic mechanism,
- Or oncogenesis resulting from the formation of MDA, which is mutagenic (classified Muta. 2 H341 under regulation (EC) 1272/2008 as mentioned above).

Moreover, in the EU Risk Assessment Report (RAR) of MDI (2005) [ref. 16], it was concluded that this substance has no genotoxic properties although conflicting results were obtained in *in vitro* test systems. *In vivo*, in one micronucleus test, the response in MDI-treated animals did not differ significantly from the control animals. Nevertheless, high levels of erythrocytes with micronuclei were exhibited, thus raising a doubt on the validity of the test. In another study, methodological deficiencies (including the fact that the micronucleus test was not designed according to standard protocols) preclude the interpretation of the potential positive results. To address this uncertainty an *in vivo* rat micronucleus test by inhalation on MDI was designed. The results of this study indicated that "aerosolized inhaled MDI at concentration as high as 118 mg/m^3 (a concentration high enough to produce specific toxic effects (…)) did not induce cytogenetic damage *in vivo"*. Other studies that have investigated relevant endpoints, such as DNA-adduct formation, did not demonstrate any significant binding after topical or inhalatory exposure to MDI in animals.

MDI is currently being evaluated by Estonian MSCA for ground of concern on mutagenicity in order to elucidate the mechanism of action of carcinogenicity (i.e. genotoxic or non-

genotox carcinogen) and a decision was issued on 13 April 2016[24]. An *in vivo* mammalian alkaline comet assay (OECD 489) on Wistar rat via inhalation route, with examination of lungs and liver, was requested by 20 July 2017; glandular stomach tissue was required to be harvested and stored, and analysed it negative results were obtained in liver and lungs).

Considering the structural similarity between MDI and TODI, it could be assumed that TODI has a similar toxicological behavior. Consequently, it is not possible to dismiss the carcinogenic potential of TODI by inhalation route.

Summary of data for TODA

Considering the reactivity of TODI and the absence of toxicokinetic study on metabolism, FR-MSCA considers as a worst case that TODI will be totally metabolised in TODA in organisms. Thus, the carcinogenicity data on TODA could be applied to TODI. In a 14-month study of NTP by oral route with 3,3'-dimethylbenzidine dihydrochloride (CAS 612-82-8, analogue to TODA), there was a clear evidence of carcinogenic effects on male rats as indicated by benign and malignant neoplasms of the skin, Zymbal's gland, preputial gland, liver, oral cavity, small and large intestine, lungs, and mesothelium. For female F344/N rats, there were benign and malignant neoplasms of the skin, Zymbal's gland, clitoral gland, liver, oral cavity, small and large intestine, mammary gland, and lungs. Tumors observed in this study are scattered throughout the entire body, not on one site only, and appear at all doses.

Concerning the genotoxicity endpoint of TODA, even if there is no harmonized classification for this point, data found in literature are equivocal (NTP report n°390 [ref. 28]; You *et al*. (1993) [ref. 35]; HSDB data bank [ref. 19]; IARC monogarphy on benzidine and derivatives (2010) [ref. 20]). Such as for TODI, no clear conclusion on genotoxicity mechanism can be drawn.

The issue on the mechanism leading to carcinogenicity (epigenetic or genotoxicity) is thus also raised for TODI as for MDI.

FR-MSCA concluded that the concern for carcinogenicity remains.

In order to elucidate if TODI is a carcinogen or not, FR-MSCA requested new data in its draft decision referred to MSC on 27 July 2015: available data on carcinogenicity of TODA; derivation of a toxicological reference value (TRV) (derived no effect level (DNEL) or derived minimal effect level (DMEL) which covers the carcinogenicity concern of TODA), and revision of the risk assessment with the previous TRV. The requests were based on the consideration that since no quantitative data on metabolism from TODI to TODA were available, in a worst case situation, all available TODI was considered as being metabolised into TODA and therefore the toxicity of TODA should also be considered for risk assessment. A non-exhaustive bibliographic search was conducted by FR-MSCA, and in the NTP study (14-months) with 3-3'-dimethylbenzidine, effects were observed at all doses included the lowest (1.8 mg/kg/d for males and 3 mg/kg/d for female) whereas NOEL for TODI in the 28-days study was 150 mg/kg/d.

The requests were dropped (along with all other requests on hazard endpoints) from the final version of the Decision following the discussion in MSC, considering that exposure had to be clarified first, so as to ensure proportionality principle and for animal welfare reasons. In the final decision from 24 November 2015, the Registrant(s) were nevertheless invited to consider the option of self-classification as Carc. 1B based on the degradation of TODI into TODA, in addition to the existing self-classifications.

On the basis of the new data received on 16 February 2017 following the requests in the Substance Evaluation Decision from 24 November 2015, FR-MSCA concludes that human exposure can occur but probably not at high concentrations.

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

FR-MSCA estimates that the concern for carcinogenicity should still be addressed. However the issues of proportionality principle and animal welfare remain when it comes to requesting new data (i.e. a carcinogenicity study) to elucidate this concern. As a consequence, FR-MSCA will not request new data under this Substance Evaluation.

Instead, considering that data are available for other substances which belong to the diisocyanates group, and that the mechanism of carcinogenicity is currently under assessment for MDI by Estonian MSCA, FR-MSCA proposes carcinogenicity to be assessed in a grouping approach for diisocyanates, when the data will be available.

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

Not assessed during the evaluation of the substance (not targeted in Substance Evaluation – no initial concern).

As only a screening study is available [ref. 24], FR-MSCA notes that there may be a data gap which could be addressed under compliance check (CCH).

7.9.10. Hazard assessment of physico-chemical properties

Based on the available data, FR-MSCA considers that TODI is not flammable and has no explosive or oxidising properties according to CLP regulation.

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

Due to the lack of suitable data, no DNEL/DMEL were derived by FR-MSCA for any endpoint.

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

FR-MSCA supports the self classification made by the Registrant:

- Skin Sens. 1A H317
- Acute Tox. 4 H332
- Resp. Sens. 1 H334

In addition, FR-MSCA considers that classification for carcinogenicity/mutagenicity should be considered for the whole diisocyanates group.

7.10. Assessment of endocrine disrupting (ED) properties

Not assessed during the evaluation of the substance (not targeted in Substance Evaluation – no initial concern).

7.11. PBT and vPvB assessment

7.11.1. Assessment of PBT/vPvB Properties

7.11.1.1. PBT/vPvB criteria and justification

7.11.1.1.1. Persistence assessment

Evidence of P or vP properties

TODI and its degradation products should be considered as not readily biodegradable. It should be noted that the Registrant postulates that the relevant hydrolysis product of TODI is TODA (4,4'-bi-o-toluidine; CAS 119-93-7). Experimental data revealed that TODA should be considered as not ready nor primarily biodegradable.

Moreover TODA has structural similarity with MDA (4,4'-methylenedianiline; CAS 101-77-9). According to the MDA RAR (EU, 2001) [ref. 15], MDA is not readily biodegradable, stable to hydrolysis, with a half-life estimated at 1900 days and 10000 days in the water and sediment compartment respectively. Concerning biodegradation of MDA in soil compartment, experiments with radiolabelled MDA revealed that the substance forms covalent bonds with the organic fraction in aerobic and anaerobic conditions. Such mechanisms disrupt the biodegradation of MDA as revealed by experiments with radiolabelled MDA. In the RAR of MDA (EU, 2001), it is assumed that the half life of MDA in soil is 1000 days.

Additional studies following OECD 308 and OECD 309 guideline [ref. 35 and 36], available in the registration dossier of MDA, show dissipation half lives of MDA below the threshold value for the P criteria suggesting that the P criteria is not fulfilled. Nevertheless, it was shown formation of several metabolites above 10% for which no DT50 was determined due to technical reasons, and also high formation of non extractable residues. Mineralization of the test substance was low in both tests.

As a consequence, based on the available information, the P status of MDA and hence for TODA could not be concluded.

FR-MSCA conclusion on P / vP properties: cannot be concluded.

7.11.1.1.2. Bioaccumulation assessment

Criteria based on Annex XIII of REACH

- Not B / vB based on BCF <= 2000 L/kg: As hydrolysis of TODI is very fast, it can be assumed that TODI has a transient presence in aquatic compartment. As a consequence, the evaluation of bioaccumulation of TODI in aquatic compartment should be based on its hydrolysis products. The Registrant postulates that the relevant hydrolysis product of TODI is TODA (4,4'-bi-o-toluidine; CAS 119-93-7). Experimental data on aquatic bioaccumulation of TODA revealed BCF values below 100. For the concentration of 0.2 mg /L a BCF of 4.8 to 34 was determined. For the concentration of 0.02 mg/L a BCF of 10 to 83 was determined. Experimental data are supported by BCF estimated by calculation. Estimations using KOCWIN of EPI Suite compilation were performed for TODA (log Kow used: 2.34), resulting in BCF value of 16.25 L/kg ww for TODA. Both result revealed that BCF of TODA is < 100 L/kg, which indicates a low potential of bioaccumulation on aquatic organism by using BCF as endpoint.

Brunn (2009, 2010; RI=1; [ref. 8 to 11]) estimated bioaccumulation potential of TODA by estimated BCF by calculation with EPI suite compilation. Estimations using KOCWIN of EPI Suite compilation were performed for TODA (log Kow used: 2.34), resulting in BCF value of 16.25 L/kg ww for TODA. Both result revealed that BCF of TODA is < 100 L/kg, which indicate a low potential of bioaccumulation in aquatic organism by using BCF as endpoint.)

The substance is screened as potentially bioaccumulative in air-breathing organisms. However, based on a weight of evidence based on toxicokinetic data available in the EU-RAR of MDA, it can be concluded that the substance is quickly eliminated from the organisms. Therefore, based on a read-across between MDA, structurally similar to TODA, it could be concluded that TODA and thus TODI is not bioaccumulative in air-breathing organisms.

FR-MSCA conclusion on B / vB properties: not B/vB

7.11.1.1.3. Toxicity assessment

Acute toxicity data are available for TODI and its relevant hydrolysis product TODA (4,4'-bi-o-toluidine; CAS 119-93-7). A low toxicity was observed for tested aquatic organisms. These results lead to the conclusion that the T criteria is not fulfilled for the environment for both substances.

However the relevant hydrolysis product TODA. TODA (4.4'-bi-o-toluidine; CAS 119-93-7) is classified Carc. 1B in Annex VI of the CLP.

Therefore, the T criterion is considered to be met based on human health classification.

FR-MSCA conclusion on T properties: not T based on aquatic ecotoxicity data but T criterion is considered to be met based on human health classification.

7.12. Exposure assessment

Tonnage band: 100-1000 tpa.

TODI is a diisocyanate which is used as an intermediate to produce plastic articles. The substance is registered for industrial uses only. There is 1 Registrant.

The following exposure scenarios available in the (disseminated) registration dossier[25] were assessed as part of evaluation of the substance:

- **Use as such as an intermediate and as a monomer in polymerization processes** to produce plastic products
    - ERC 6a: use of intermediate and ERC 6c: use of monomer in polymerisation processes at industrial site (inclusion or not into/onto article)
    - SU 12: manufacture of plastics products, including compounding and conversion
    - PROC 1: use in closed process, no likelihood of exposure; PROC 2: use in closed, continuous process with occasional controlled exposure; PROC 8b: transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities; and PROC 15: use as laboratory reagent.
- **Use in a mixture at industrial site for inclusion into/onto articles** to produce plastic products
    - ERC 5: use at industrial site leading to inclusion into/onto article
    - SU 12: manufacture of plastics products, including compounding and conversion

[25] On 8 March 2018.

  - PROC 1: use in closed process, no likelihood of exposure; PROC 2: use in closed, continuous process with occasional controlled exposure; PROC 8b: transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities: PROC 14: production of preparations or articles by tabletting, compression, extrusion, pelletisation; and PROC 21: low energy manipulation of substances bound in materials and/or articles.

- **Articles made from TODI** (AC 13g: other plastic articles) are used by workers indoor and outdoor in a widespread manner with low release
  - ERC 10a: widespread use of articles with low release (outdoor) and ERC 11a: widespread use of articles with low release (indoor)
  - PROC 21: low energy manipulation of substances bound in materials and/or articles; and PROC 28: manual maintenance (cleaning and repair) of machinery.

The uses of TODI by consumers are advised against by the Registrant. One of the initial grounds for concern which justified the inclusion of TODI in the CoRAP was that consumer uses were expected, based on the available information at that time. As a consequence, in the updated dossiers from 31 July 2013 and further updates, the Registrant advised against consumers uses of TODI (ERC 8a: widespread use of non-reactive processing aid (no inclusion into or onto article, indoor); ERC 8b: widespread use of reactive processing aid (no inclusion into or onto article, indoor); ERC 8c: widespread use leading to inclusion into/onto article (indoor); ERC 8d: widespread use of non-reactive processing aid (no inclusion into or onto article, outdoor); ERC 8e: widespread use of reactive processing aid (no inclusion into or onto article, outdoor); ERC 8f: widespread use leading to inclusion into/onto article (outdoor); ERC 9a: widespread use of functional fluid (indoor) and ERC 9b: widespread use of functional fluid (outdoor)).

The Registrant claimed that the substance is used in closed systems under strictly controlled conditions and declared that the facility would be converted to a fully closed system by the end of 2013. This was confirmed by a declaration from the only downstream user on the 4th July 2015. This justification was used by the Registrant to waive the submission of several hazard studies which should normally have been provided in accordance with the standard information requirements listed in the Annex VII, VIII and IX of REACH. However, FR-MSCA considered that the different waivings were unsufficiently supported and justified by the information available in the registration dossier. In addition, FR-MSCA notes that Articles 17 and 18 do not apply to monomers according to Article 6(2) and therefore a full registration dossier should have been provided.

Additionally, during the evaluation of the substance, FR-MSCA considered that there were not enough details in the registration dossier to conclude that the uses of the substance are safe for humans and the environment at all steps of the life cycle of the substance (from the industrial use of the substance to the service life of the articles). In particular, the descriptions of the systems in place and of the phases with potential exposure were not sufficiently detailed, the details of the risk management measures applied and recommended to the user were not provided, the efficiency of the operational conditions and risk management measures regarding human exposure and environmental exposure were not supported by quantitative data, in particular regarding the claim of no release to the environment when considering that exposure estimates were calculated, and the parameters used to calculate the exposure estimates were not clearly indicated. The type of articles made from TODI was not given in the registration dossier. Also, exposure from use of granulates and articles was not addressed in the registration dossier, and FR-MSCA was not able to conclude whether workers and/or the environment could be exposed to TODI, TODA or other degradation/reaction substances of concern likely to migrate out of the polymer. Therefore, based on the information from the registration dossier, FR-MSCA identified additional concerns on human exposure and environmental risk assessment.

As a consequence, FR-MSCA considered that further information was needed on uses of TODI and exposure to TODI, to the degradation product TODA and/or to potential other degradation/reaction substances of concern likely to migrate out of the polymer. The following information was requested in the final Decision of 24 November 2015:

1. Detailed exposure scenarios for industrial uses (polymerisation, research and development, compounding) by providing:
    - A detailed description of systems and Strictly Controlled Conditions (SCCs) used for the different intended fields of processing [detailed description of phases with potential exposure during the polymerisation step (including sampling); research and development activities, reference documents followed and corresponding up-to-date certificates, and details of the risk management measures applied and recommended to the user];
    - Recent quantitative data on TODI and the transformation product TODA in industrial settings (investigating the dermal and inhalation exposure of workers) and surrounding environment to demonstrate the efficiency of those systems and conditions regarding human and environmental exposure;
    - Exposure scenarios and estimations for workers and the environment for the research and development and compounding steps, and, if not under SCCs, for the polymerisation step;
    - Explanations and justifications of all the parameters used for the calculations of human and environmental exposure based on the guidance documents.
2. Provide the following information:
    - Details on the life cycle (from the chemical use to the service-life of manufactured articles) for each use and/or each type of manufactured articles, including a description of the downstream uses of the granulates and details on the articles;
    - Justify the level of residues of TODI, the transformation product TODA and potential other degradation/reaction substances originating from TODI and likely to migrate out of the polymer. This should be achieved by specifying the range of number of equivalents of TODI used in the polymerisation process and by providing a total extraction study;
    - Propose the corresponding exposure scenario and estimation for each situation of potential emission based on the amounts determined in the total extraction study.

The registration dossier was updated on 23 August 2016 and on 16 February 2017.

Details are in a confidential annex.

7.12.1. Human health

7.12.1.1. Worker

Following the requests included in the decision from 24 November 2015, the Registrant provided on 16 February 2017 a qualitative risk assessment, and the downstream user provided further descriptions and measurements at workplace. This new information fails to demonstrate full enclosure at workplace and non-exposure of workers. Therefore, based on the available information, FR-MSCA considers that exposure of workers cannot be excluded and therefore the concern remains. Consequently FR-MSCA considers that an enforcement action (inspection) by the National Enforcement Authorities for downstream uses would be necessary to ensure that closed systems are properly required in the safety data sheets and implemented.

Regarding the use of articles (articles service life), the Registrant did not provide any quantitative assessment, considering that the monomer would be completely reacted. The downstream user provided measured data which show very low release; however, the representativeness of these data cannot be adequately assessed by FR-MSCA since the life cycle of the articles is not described. Indeed, the information in the registration dossier indicates that the articles made from TODI are part of the category AC 13g: Other plastic articles, which is rather unspecific. However, the following other pieces of information were found by FR-MSCA:

- A supplier of TODI[26] specifies that "*TODI-based elastomers offer excellent heat resistance and hydrolysis resistance properties along with superior mechanical properties. From the manufacturing stand point, TODI-based prepolymer can be stored for certain period, and TODI, because of its longer pot life, is easier to handle than NDI-based products.*" and that TODI is used to make "*Sealing (oil sealing, piston ring, water sealed, etc.), Automobile parts (grille, shock absorbers, bumoer extensions, roof, door, window and body, etc.), Industrial use (belt, roll, caster, etc.), Electric (coating agent, etc.), Medical equipment (artificial, organ, etc.)"*. The USA branch of the same company also states in its website[27] that "*Because of its unique properties of heat resistance and hydrolysis resistance, TODI urethane elastomer can be used in various areas including: Sealing (Oil seals, Piston Rings, Water seals, etc.); Automobile parts (Grille, shock absorbers, bumper extension, roof, door, window and Body parts, etc.); Industrial use (Belts, Rollers, Casters, etc.); Electric (Coating agent, etc.); Medical equipment (Artificial organ, etc.); Personal computer parts (HDD, etc.)*". Consistent information was also found in Mitsubishi's website[28].
- Safety Data Sheets (SDS) were collected from the Internet (probably not exhaustively) but no more information was found about possible uses. None of the consulted SDS contained any exposure scenarios in appendix.
- On Espacenet Patent search (European Patent Office)[29], 18 results were found for the keywords {"TODI" and "diisocyanate"} for 2000 (1), 2001 (1), 2002 (1), 2008 (1), 2009 (2), 2011 (4), 2012 (3), 2013 (1), 2015 (1), 2017 (3) (see Appendix 1); they suggest possible various uses such as cast outer cover of golf ball, cleaning blade, elastomers used to dampen the oscillations of machinery / buffering and shock-absorbing elements (train-ferries, ship building and engineering, traffic tools, vehicles, bridge shock-absorbing blocks, etc.), micropore polyurethane elastomer which can be used as an elastic bearing plate of high speed railways, polyurethane cement, resin for shoes, water-lubricated bearing material, no-puncture tire filling material.
- As summarised on the German IGS-Public Informationssystem für gefährliche Stoffe (IGS-Public 11/2017 - Information system for dangerous substances):
    - TODI is included in the (not legally binding) positive list of German Umweltbundesamt (UBA) for coatings in the Drinking Water Supply (QM(T)=1 mg/kg as NCO)[30] but there is no certitude that TODI is actually used for this purpose.
    - Use as food contact material: TODI is included in Annex I of Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food (Union list of authorised monomers, other

[26] http://www.nisso-chem.de/todi.html accessed 16/03/2018.

[27] http://www.nissoamerica.com/sp/TODI.html accessed 16/03/2018.

[28] http://www.micchem.com/todi.html accessed 16/03/2018.

[29] http://worldwide.espacenet.com/?locale=en_EP accessed 21/03/2018.

[30] https://www.umweltbundesamt.de/sites/default/files/medien/374/dokumente/160316_beschichtungsleitlinie_neu.pdf. Dated 16/03/2016.

starting substances, macromolecules obtained from microbial fermentation, additives and polymer production aids): TODI is not authorised to be used as additive or polymer production aid, is authorised to be used as monomer or other starting substance, the migration results can NOT be corrected by the Fat Consumption Reduction Factor (FRF); specific migration limit: 1 mg/kg in final product expressed as isocyanate moiety; according to DG SANCO[31] there are no applications for this substance. The US Food and Drugs Administration (FDA) reports in the CEDI database (cumulative estimated daily intakes)[32] that estimated dietary concentration in the food is 0.5 ppb, that the cumulative estimated daily intake determined by OFAS for the food contact substance is 0.000025 mg/kg bw/d. This information is considered of no relevance in EU since no applications were made for use as food contact materials in EU (see bullet above). In any case, food contact materials are exempted from considerations of the risk to human health in the CSR (REACH, Article 14(5)(a)).

No information was found on the following databases (accessed 21/03/2018): CAREX Canada[33], Health Canada[34], EU Cordis[35], MEGA-DE[36], KEMI database[37], USA household products database[38], CPCat[39], USA OSHA[40], Haz-Map[41], SPIN database[42], IPChem[43].

Based on this information, especially regarding the use as artificial organs, FR-MSCA is not sure that the provided extraction study is a worst-case or even representative of possible conditions of use of the articles. Therefore workers exposure may not be excluded although they would probably be exposed to TODA and/or other degradation products of TODI, due to the reactivity of TODI. FR-MSCA considers that the concerns for mutagenicity and carcinogenicity should still be addressed. Also, since some uses described on the Registrant's website may imply consumers' exposure, FR-MSCA recommends an enforcement action by National Enforcement Authorities to ensure that the real uses of TODI correspond to the registered uses.

7.12.1.2. Consumer

One of the initial ground for concern which justified the inclusion of TODI in the CoRAP was that consumer uses were expected, based on the available information at that time. In the updated dossiers from 31 July 2013 and further updates, the uses of TODI by consumers were advised against. It covers ERC 8a: widespread use of non-reactive processing aid (no inclusion into or onto article, indoor); ERC 8b: widespread use of reactive processing aid (no inclusion into or onto article, indoor); ERC 8c: widespread use leading to inclusion into/onto article (indoor); ERC 8d: widespread use of non-reactive processing aid (no inclusion into or onto article, outdoor); ERC 8e: widespread use of reactive processing aid (no inclusion into or onto article, outdoor); ERC 8f: widespread use leading to inclusion

[31] https://webgate.ec.europa.eu/foods_system/main/index.cfm?event=substance.view&identifier=169 accessed 21/03/2018.

[32] https://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/CEDI/default.htm accessed 21/03/2018.

[33] http://www.carexcanada.ca/en/profiles_and_estimates/.

[34] http://recherche-search.gc.ca/rGs/s_r?st=s&langs=eng&st1rt=0&num=10&cdn=health

[35] http://cordis.europa.eu/projects/home_en.html.

[36] http://www.dguv.de/ifa/GESTIS/Expositionsdatenbank-MEGA/Expositionsdaten-aus-MEGA-in-Publikationen/Publikationen-nach-Stoffen/index.jsp.

[37] http://webapps.kemi.se/flodesanalyser/FlodesanalyserSok.aspx.

[38] http://hpd.nlm.nih.gov/cgi-bin/household/list?tbl=TblChemicals&alpha=A.

[39] http://actor.epa.gov/cpcat/faces/search.xhtml.

[40] https://www.osha.gov/opengov/healthsamples.html.

[41] https://hazmap.nlm.nih.gov/.

[42] http://spin2000.net/.

[43] https://ipchem.jrc.ec.europa.eu/RDSIdiscovery/ipchem/index.html#discoveryl.

into/onto article (outdoor); ERC 9a: widespread use of functional fluid (indoor) and ERC 9b: widespread use of functional fluid (outdoor).

Following the requests included in the Decision from 24 November 2015, the Registrant provided on 16 February 2017 exposure scenarios corresponding to the article service life which specifies that articles are used by workers. However, FR-MSCA considers that a concern remains regarding exposure of consumers to TODI via articles. Indeed, the information in the registration dossier indicates that the articles made from TODI are part of the category AC13g: Other plastic articles, which is rather unspecific, but the Registrant website specifies that TODI is used to make automobile parts and medical equipment (including artificial organs) (see above), but considering that such uses are not evaluated in the registration dossiers, despite a request being made by FR-MSCA during the Substance evaluation, FR-MSCA considers that enforcement by National Enforcement Authorities is necessary to ensure that uses advised against are reported in the safety data sheets and that that consumers do not come in contact with articles containing TODI.

7.12.2. Environment

Concerning the industrial uses of the TODI, according to the Registrant, the substance is processed in closed systems, in strictly controlled conditions, and consequently, the fractions released to waste water and to soil were estimated to be equal to 0 for the following uses:

- industrial use of monomer in polymerisation processes;
- industrial use of intermediates;
- use at industrial site leading to inclusion into/onto article.

Some descriptions of the closed systems and the strictly controlled conditions for each use have been provided by the downstream users and a qualitative risk assessment was proposed considering no emission to the environmental compartments.

In addition, to cover the service-life of manufactured articles, measured data have been provided by the downstream users, which showed very low release in environmental conditions. A quantitative assessment considering no emission to the environment was also proposed for service-life of articles.

7.13. Risk characterisation

7.13.1. Human health

Uncertainties remain on hazards (mutagenicity and carcinogenicity) and on the level of human exposure. Therefore no quantitative risk characterisation can be done.

On the basis of the new data received on exposure on 16 February 2017, FR-MSCA concluded that human exposure cannot be excluded. FR-MSCA considers that the concerns raised on mutagenicity and carcinogenicity, if confirmed, could lead to a risk for users of TODI in case they were exposed to it. However, the available information suggests that exposure is likely low or even negligible, provided that uses of the substance and articles made from it are consistent with the registered uses, and that strictly controlled conditions (which are claimed by the Registrant) are indeed implemented and respected. Enforcement is recommended to verify both aspects.

In parallel, a classification for carcinogenicity and mutagenicity can be envisaged as it would lead to additional obligations under OSH (occupational safety and health) legislation. For this purpose a grouping approach with other substance of the diisocyanate group is proposed.

7.13.2. Environment

Concerning the industrial applications, risks are considered properly managed for the environment if TODI is processed in closed systems under stricly controlled conditions, as intended by the Registrant and the downstreams users, for the following categories of uses:

- industrial use of monomer in polymerisation processes;
- industrial use of intermediates;
- use at industrial site leading to inclusion into/onto article.

Concerning the service-life of articles, as measured data demonstrated only very low release from articles in environmental conditions, risks can be considered acceptable to the environment.

7.14. References

Refer to the confidential annex for the full references.

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7.15. Abbreviations

AC	Article category
AF	Assessment factor
BCF	Bioconcentration factor
BW	Body weight
CAS	Chemical abstracts service
CCH	Compliance check
CHL	Chinese hamster lung
CLP	Classification, labelling and packaging (Regulation (EC) No 1272/2008)
CoRAP	Community Rolling Action Plan
CSR	Chemical safety report
DMEL	Derived minimal effect level
DNEL	Derived no effect level
eMSCA	Evaluating Member State Competent Authority
ERC	Environmental release category

FR	France
IUCLID	International Uniform Chemical Information Database
LD50	Median lethal dose. The dose causing 50 % lethality
MMAD	Mass median aerodynamic diameter
MS	Member State
MSC	Member State Committee
MSCA	Member State Competent Authority
NCE	Normochromatic erythrocytes
NOAEL	No observed adverse effect level
NOEC	No observed effect concentration
NOEL	No observed effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OC	Operational conditions
PCE	Polychromatic erythrocytes
PBT	Persistent, Bioaccumulative, Toxic
PNDT	Pre-natal developmental toxicity
PNEC	Predictive No Effect Concentration
PROC	Process category
QSAR	Quantitative structure–activity relationship
RAC	Risk Assessment Committee
RAR	Risk Assessment Report
RCR	Risk characterisation ratio
RMM	Risk management measures
RMOA	Risk Management Option Analysis
SCC	Strictly Controlled Condition
SDS	Safety Data Sheet
SEAC	Socio-Economic Assessment Committee
SU	Sector of end-use
SVHC	Substance of very high concern
ThOD	Theoretical oxygen demand
TPA	Tonnes per annum
TRV	Toxicological reference value
TWA	Time weighted average
UDS	Unscheduled DNA synthesis
vPvB	Very Persistent and very Bioaccumulative

7.16. Appendix 1

Publicly available results of the query on Espacenet Patent search (European Patent Office) for the keywords {"TODI" AND "diisocyanate"} on 21/03/2018 at http://worldwide.espacenet.com/?locale=en_EP:

Title	Publication number	Publication date	Inventor(s)	Applicant(s)	Abstract
PROCESS FOR PRODUCING COMPACT OR CELLULAR POLYURETHANE ELASTOMERS BASED ON 3,3'-DIMETHYL DIPHENYL 4,4'-DIISOCYANATE-CONTAINING POLYISOCYANATE MIXTURES AND ISOCYANATE PREPOLYMERS SUITABLE THEREFOR	**HU9903321 (A2); HU9903321 (A3)**	2000-02-28	BOLLMANN HEINZ [DE] BRUNS UTE [DE] GENZ MANFRED [DE] HASELHORST WALTER [DE] HELLMANN GERHARD [DE] JESCHKE TORSTEN [DE] PEUKER HARTMUT [DE] SCHOLZ WOLFGANG [DE] STRAUSS MICHAEL [DE] VOELKEL RUEDIGER [DE]	BASF AG., LUDWIGSHAFEN/RHEIN	Preparation of polyurethane elastomers involves reacting (a) high molecular polyhydroxyl compounds and optionally (b) low molecular chain extenders and/or crosslinking agents containing hydroxyl (OH) groups with (c) organic polyisocyanates in the presence or absence of (d) catalyst, (e) blowing agent and (f) additives. The polyisocyanate comprises 3,3'-dimethyl-diphenyl 4,4'-diisocyanate (TODI) in conjunction with toluylene diisocyanate (TDI), diphenylmethane diisocyanate (MDI), 1,2-diphenylethane diisocyanate (DIBDI), phenylene diisocyanate (PDI), aliphatic diisocyanate(s) with 4-12 carbon atoms and/or cycloaliphatic diisocyanate(s) with 6-18 carbon atoms. Also claimed are certain prepolymers containing isocyanate groups (NCO prepolymers). Preferably the polyisocyanates are a fluid mixture of TODI with TDI, MDI, DIBDI, PDI, HMDI and/or IPDI; a melt of TODI and 4,4'-MDI; or an NCO prepolymer. Suitable NCO prepolymers are prepared by (1) reacting (c) with (a) or (a) and (b); (2) preparing a polyadduct containing urethane groups by reacting part or all of (a) or (b) with the diisocyanate(s) except TODI, especially with MDI, and reacting the polyadduct with TODI; (3) preparing a polyadduct containing urethane groups by reacting (a) or (a) and (b) with (c) except TODI, especially with 3,3'-diphenylmethane diisocyanate, in an equivalent ratio of OH groups in (a) or (a) and (b) to isocyanate groups in (c) of 1:(.1 to 6) and reacting the polyadduct and TODI in an equivalent ratio of OH groups to isocyanate groups of 1:(0.02-6).
PELLETAL o-TOLIDINE DIISOCYANATE	**JP2001011039 (A)**	2001-01-16	SHIOUMI TETSUO TSUCHIDA NAGAHIKO KANEHIYOU KOUJI	NIPPON SODA CO	PROBLEM TO BE SOLVED: To obtain pelletal o-tolidine diisocyanate freed from caking, blocking and ill-modified fine powder contamination so as to improve environmental aspect of its production and use as a result of diminishing fine powder emission. SOLUTION: This pelletal o-tolidine diisocyanate is obtained, for example, by the following process: o-tolidine isocyanate (TODI) in the form of a solution is force-fed by a pump and fed to a revolving drum having many dripping ports or issue ports, and then fed via the dripping or issue ports onto a steel belt in revolution until its feed comes to a given level, and the TODI solution thus fed is cooled and solidified on the steel belt and then pelletized; the pellets thus obtained, in turn are fed into a hopper, where the pellets are weighed and packaged into the final product; wherein both the size (diameter) and thickness of each of the pellets are recommended to be such as not to be crushed in packaging, storing and transporting them, for example, being pref. 2-10 mm and 0.3-3.0 mm, respectively.

Title	Publication number	Publication date	Inventor(s)	Applicant(s)	Abstract
Solid golf ball with cast cover	**US6371870 (B1)**	2002-04-16	CALABRIA JOHN [US] SNELL DEAN A [US] WU SHENSHEN [US]	ACUSHNET CO [US]	A solid golf ball comprising a solid core, an encapsulating coating having a thickness of about 0.001 to 0.01 inches and a cast polyurethane outer cover layer. The cast outer cover layer is comprised of a prepolymer and a curing agent, wherein the prepolymer is made from a polyol selected from the group of polyether, polyester and polylactone and a diisocyanate selected from the group of 4,4'-diphenylmethane diisocyanate (MDI) and 3,3'-dimethyl-4,4'-biphenylene diisocyanate (TODI) and toluene diisocyanate (TDI). The encapsulating coating is a thermosetting latex material that is applied to the solid core through a solution.
CLEANING BLADE MEMBER	**US20080027184 (A1)**	2008-01-31	UENO MIYUKI [JP] ABE SHUJI [JP] NODA SHUHEI [JP]	SYNZTEC CO LTD [JP]	The present invention provides a cleaning blade member which can be excellently produced by molding and which exhibits small variation in physical properties with temperature, and excellent wear resistance. The cleaning blade member formed of a castable polyurethane member produced through hardening and molding a polyurethane composition containing at least a polyol, a polyisocyanate, and a diamino compound, wherein the diamino compound has a melting point of 80 DEG C. or lower, the polyisocyanate is a blend of 4,4'-diphenylmethane diisocyanate (MDI) and 3,3-dimethylphenyl-4,4-diisocyanate (TODI), and the ratio of TODI in the entirety of polyisocyanate is 30 to 100% by weight.
METHOD FOR MANUFACTURING AND APPLICATION OF CAST ELASTOMERS	**RU2007124485 (A); RU2442800 (C2)**	2009-01-10	НЕФЦГЕР Хартмут (DE), БАРНС Джеймс Майкл (DE), ДИТРИХ Мартин (AT), ВЕХОВСКИ Дирк (AT)	БАЙЕР МАТИРИАЛЬСАЙЕНС АГ (DE), Гетцнер Веркштоффе ГмбХ (AT), BAJER MATIRIAL'SAJENS AG, GETTSNER VERKSHTOFFE GMBKH	FIELD: chemistry. ^ SUBSTANCE: the method relates to cast elastomers used as oscillation dampening elements to dampen the oscillations of any kinds of machinery, more specifically in construction of train-ferries, ship building and engineering, etc. The said cast elastomers are produced from the (A) NCO-prepolymer of the high-melting polyisocyanate taken from the group consisting of 1,5-naphthalene diisocyanate (NDI), para-phenylene diisocyanate (PPDI) and 3,3'-dimethyl-4,4'-bi-phenyl diisocyanate (TODI); and (b) a mixture of polyols of (b1) 50-85 mol-% in regard to (b1) and (b2), -hydro-ë-hydroxy-poly-(oxytetramethylene) with the molecular weight ranging from 500 to 5000 g/mol and hydroxy functionality of 2,0; (b2) 15-50 mol-% in regard to b1) and b2), -hydro-ë-hydroxy-poly-(oxypropylene-1,2) and/or -hydro-ë-hydroxy-poly-(oxypropylene-1,2-so-oxyethylene) with the molecular weight ranging from 900 to 4000 g/mol and hydroxy functionality ranging from 1,9 to 2,7, whereas the hydroxyl value of the polyol mixture of (b1) and (b2) ranges from 36 to 90 mg KOH/g; and (B) at least one chain extender taken from a group of aliphatic diols with two hydroxil groups (preferably where they are primary groups) and the average molecular weight ranging from 62 to 202 g/mol, trifunctional polyols, polyols (b1), polyols (b2), water and their mixtures, as well as aromatic diamines; (C) if required, additive agents and supplements, where the molecaular ratio of the NCO-groups to the active groups of all components ranges from 1,04 to 1,25 and the ratio of the storage modulus G' measured at -30C and the same parameter measured at 110C (in accordance with DIN EN ISO 6721-1) ranges from 0,8 to 2.

Title	Publication number	Publication date	Inventor(s)	Applicant(s)	Abstract
					Described is a method of producing the said cast elastomers. ^ EFFECT: production of the polyurethane materials with improved properties related to the temperature dependence of material properties: storage modulus G', loss-angle tangent tan and loss modulus G'' while retaining all other good properties. ^ 2 cl, 12 ex, 3 tbl
ENVIRONMENTALLY FRIENDLY POLYURETHANE CEMENT COMPOSITION	**KR100892247 (B1)**	2009-04-09	CHO HEON YOUNG [KR] CHOI JUNG KYU [KR] SHIM HYUN SEOP [KR]	JIN DO HWA SUNG CO LTD [KR] CARECON CO LTD [KR]	A polyurethane-cement composition is provided to ensure an excellent adhesive property to a substrate and relatively low temperature dependence, thereby preventing the polyurethane-cement composition from being exfoliated from the substrate even through the polyurethane-cement composition is exposed to high temperature. A polyurethane-cement composition comprises the 50-1000wt% of dry mortar on a basis of the 100wt% of resin mixture containing a base resin and a hardener in a ratio of 1 to 1. The base resin is synthesized by aromatic isocyanate and aliphatic isocyanate monomers. The aromatic isocyanates are one or more isocyanates selected from the group consisting of TDI, MDI, polymeric MDI, TODI and p-phenylene isocyanate. The aliphatic isocyanates are one or more isocyanates selected from the group consisting of hexamethylene diisocyanate, hydrogenated MDI and isophoron diisocyanate.
Polyurethane resin for shoes	**CN102079808 (A); CN102079808 (B)**	2011-06-01	WENQING ZHONG RENFANG ZHANG	HAINING CHONGSHUN CHEMICAL CO LTD	The invention discloses polyurethane resin for shoes, comprising a component (A) and a component (B). The polyurethane resin for shoes is characterized in that the component (A) comprises 100 parts of polyester polyol and 8-30 parts of ethylene glycol and/or butanediol, the component (B) comprises 40-60 parts of 3,3'-dimethyl-4,4' diphenyl diisocyanate and 30-45 parts of polyester polyol and/or polyether glycol. A finished product prepared by substituting TODI (3,3-Tolidine-4,4-Diisocyanate) for MDI (4,4'-Diphenylmethane Diisocyanate) through a foaming reaction has the matter properties, suchas excellent compression ratio, better wear resistance, bending resistance, tensile strength, tearing strength, and the like under low density.; Because of the steric hindrance effect and the electronic effect of 3,3'-dimethyl-4,4'diphenyl diisocyanate methyl-o-side, the activity of the polyurethane resin is weaker than the activity of the diphenylmethane diisocyanate, and the prepared prepolymer is stable and mild in the foaming reaction without generating a bubble falling phenomenon. Because the activity of the TODI reaction is weaker than that of the MDI reaction, the storage stability of the isocyanate combination liquid is greatly improved.

Title	Publication number	Publication date	Inventor(s)	Applicant(s)	Abstract
Method for preparing microporous polyurethane elastomer	**CN102093535 (A); CN102093535 (B)**	2011-06-15	YINGTAO YANG RUIHONG HOU YIQIAN CAO YAJUN YANG	SHANGHAI CARTHANE CO LTD	The invention relates to a method for preparing a microporous polyurethane elastomer, in particular to a microporous polyurethane elastomer which is prepared through a foaming reaction that a chain extender containing a mixture of water, a high molecular weight polyalcohol, a catalyst and a foam stabilizer is stirred and blended into a mixed prepolymer prepared by stirring and blending a prepolymer containing a terminal isocyanate group and prepared by reacting a polyalcohol and 1,5-naphthalene-diisocyanate (NDI) and 3,3'-dimethyl-4,4'-diphenyldiisocyanate (TODI). The invention aims to improve the processability and the storage stability of the NDI and effectively reduce the cost of raw materials of the NDI while keeping the excellent performance of the NDI.; The product prepared by the method is mainly used for bearing high-strength damping elements of dynamic fatigue, such as buffering and shock-absorbing elements of traffic tools, such as vehicles and the like, bridge shock-absorbing blocks and the like.
Method for preparing 3,3'-dimethyl-4,4'-biphenyl diisocyanate (TODI)-based thermoplastic polyurethane elastomer	**CN102181037 (A); CN102181037 (B)**	2011-09-14	YALIN SHI LILI SU YONGJI WEI QINGLUN YAO YONG ZHANG	LIMING RES INST CHEMICAL IND	The invention discloses a method for preparing a 3,3'-dimethyl-4,4'-biphenyl diisocyanate (TODI)-based thermoplastic polyurethane elastomer. The method comprises the following steps of: (1) adding dehydrated macromolecular diol into TODI, and reacting for 1 hour at the temperature of between 95 and 120 DEG C to generate a prepolymer component A containing 8.0 to 14.0 percent of isocyanate group (NCO); (2) mixing macromolecular diol, chain extender and other auxiliary agents uniformly, keeping the temperature at 40 to 60 DEG C, and mixing the mixture and the component A at the temperature of between 60 and 90 DEG C, wherein the molar ratio of the NCO to the OH group is 0.95:1-1.10:1; and (3) pouring the bubble removed mixture into a die of 160 to 180 DEG C, stirring in 15 to 20 minutes, and curing the stripped semi-finished product for 20 to 24 hours at the temperature of between 100 and 120 DEG C to obtain a finished product. The viscosity difference of the component A and the component B is low in the method, the component A and the component B are easily combined, and the performance of the product can be regulated by regulating the proportion of the macromolecular diol and the small molecular chain extender in the component B.
Heat-resistant thermoplastic polyurethane elastomer and preparation method thereof	**CN102199269 (A); CN102199269 (B)**	2011-09-28	YALIN SHI LILI SU YONGJI WEI QINGLUN YAO YONG ZHANG YAMENG WANG	LIMING RES INST CHEMICAL IND	The invention discloses a heat-resistant thermoplastic polyurethane elastomer and a preparation method thereof. The preparation method comprises the following steps of: dehydrating 55-80 parts of macromolecular dihydric alcohol, then adding the dehydrated macromolecular dihydric alcohol into TODI (Toluene Diisocyanate), reacting at the temperature of 75-120 DEG C to generate a prepolymer which has good storage stability and contains 3.0% to 9.0% of NCO; uniformly mixing 1.5-13 parts of chain extender, 0.001-0.1 part of catalyst, 0.05-1 part of oxidation inhibitor, 0.2-1 part of ultraviolet light absorbent and 0.2-2 parts of light stabilizer, and then mixing with the prepolymer in the step (a); vacuumizing and deforming

Title	Publication number	Publication date	Inventor(s)	Applicant(s)	Abstract
					the mixture in the step (b), and then pouring into a mould of 140-200 DEG C for demoulding for 10-25min; and curing the demoulded semi-finished products in a drying oven of 100-120 DEG C for 20-24 hours to obtain a finished product. The polyurethane elastomer has good high-temperature resistant property; the ratio of the storage modulus measured at 75 DEG C and 150 DEG C is less than 1.5; and the polyurethane elastomer has good integrated mechanical property and low cost.
METHOD OF MANUFACTURING THERMOPLASTIC POLYURETHANE ELASTOMER	**JP2012062340 (A); JP5609460 (B2)**	2012-03-29	WATANABE TETSUYA	NOK CORP	PROBLEM TO BE SOLVED: To provide a method of manufacturing a thermoplastic polyurethane elastomer using TODI as a diisocyanate compound, in which the extrusion molding is possible.SOLUTION: The method of manufacturing a thermoplastic polyurethane elastomer is characterized as follows. The diol having 65-85 wt.% of 1,4-butanediol and 35-15 wt.% of 1,3-butanediol is used as a chain extender, together with a urethane prepolymer derived from a polyol and 3,3'-dimethyl biphenyl-4,4'-diisocyanate, to cause the chain elongation reaction, and the thermoplastic polyurethane elastomer is manufactured.
Micropore polyurethane elastomer material and preparation method and use thereof	**CN102532466 (A); CN102532466 (B)**	2012-07-04	ZHANYOU CHEN WENYING ZHOU YAMENG WANG YONGJI WEI	LIMING RES INST CHEMICAL IND	The invention discloses a micropore polyurethane elastomer material and a preparation method and use thereof. The micropore polyurethane elastomer material is composed of two components. The A component includes polyether polyatomic alcohol P1, polyether polyatomic alcohol P2, chain extension agents, foam stabilizers, water, tertiary amine catalysts and hollow glass microspheres by weight percentage. The B component comprises methylene diphenyl diisocyanate (MDI), TODI, and polyether polyatomic alcohol P1. P1 is selected from polytetrahydrofuran polyatomic alcohol with number-average molar mass as 1000-6000 and functionality as 2-3. P2 is selected from propylene oxide polythene oxide copolyether polyatomic alcohol with number-average molar mass as 2000-6000, functionality as 3-4 and primary hydroxyl content larger than or equal to 70%.; The isocyanate index number of the A component and the B component is 1.1. The A component and the B component are prepared respectively, quickly and evenly mixed according to proportion, poured in a mould and solidified to obtain the micropore polyurethane elastomer which can be used as an elastic bearing plate of high speed railways.
MICROCELLULAR FOAMS WITH IMPROVED MECHANICAL PROPERTIES	**WO2012098145 (A1)**	2012-07-26	EIPPER ANDREAS [DE] KUNST ANDREAS [DE] MOHMEYER NILS [DE] PRISSOK FRANK [DE] HOLWITT ULRICH	BASF SE [DE] EIPPER ANDREAS [DE] KUNST ANDREAS [DE] MOHMEYER NILS [DE] PRISSOK FRANK [DE]	The invention relates to a cellular polyisocyanate polyaddition product that can be obtained by mixing a) polyisocyanates including at least one polyisocyanate selected from the group consisting of 1,5-naphthylene diisocyanate (NDI), ditolyl diisocyanate (TODI), and diphenylethane diisocyanate (EDI), b) high-molecular-weight compounds with groups that are reactive towards isocyanate groups, c) optionally crosslinking agents, d) solid particles, e) water, f) optionally catalysts, g) optionally foaming agents, and h) optionally other additives into a reaction mixture, and allowing the reaction mixture to fully cure.

Title	Publication number	Publication date	Inventor(s)	Applicant(s)	Abstract
			[DE] BOLLMANN HEINRICH [DE] FREIDANK DANIEL [DE] WETTACH HENNING [DE]	HOLWITT ULRICH [DE] BOLLMANN HEINRICH [DE] FREIDANK DANIEL [DE] WETTACH HENNING [DE]	
WATER-LUBRICATED BEARING MATERIAL	**JP2013007006 (A)**	2013-01-10	WATANABE TETSUYA	NOK CORP	PROBLEM TO BE SOLVED: To provide a water-lubricated bearing material excellent in water resistance and small in hardness degradation caused due to water absorption.SOLUTION: The water-lubricated bearing material is configured such that a polyurethane elastomer consisting of polycarbonatediol and diisocyanate is made to contain 5 to 35 pts.wt. of polyethylene wax based on 100 pts.wt. of polycarbonatediol. It is preferable that 3,3'-dimethylbiphenyl-4,4'-diisocyanate (TODI) is used as the diisocyanate.
Polyurethane elastomer and preparation method thereof	**CN104817683 (A); CN104817683 (B)**	2015-08-05	SU LILI SHI YALIN HAN BING ZHENG ZHI WANG ZHEN	LIMING RES INST CHEMICAL IND	The invention discloses a polyurethane elastomer and a preparation method thereof, wherein the polyurethane elastomer includes two parts. An A part includes, by weight, 100 parts of a macro-molecular glycol, 5-20 parts of 1,5-naphthalene diisocyanate (NDI), and 10-30 parts of p-phenyldiisocyanate (PPDI) or 10-50 parts of 3,3-dimethyl-4,4-biphenyl diisocyanate (TODI); an B part includes, by weight, 100 parts of a macro-molecular glycol, 8-30 parts of a chain extender and 0.02-0.5 parts of a catalyst, wherein the weight ratio of A part to B part is 100/8-30. The prepolymer prepared in the invention is excellent in storage stability, is low in viscosity, is improved in the huge difference of the ratio of the A part to the B part, is free of a specially-equipped elastomer casting machine, is simplified in production and casting and using process, and directly reduces the cost of an elastomer material.
NO-PUNCTURE TIRE FILLING MATERIAL AND PRODUCTION METHOD THEREFOR	**JP2017057241 (A)**	2017-03-23	TOKOKUNI FUYUHIRO KOBAYASHI KENJI	INOUE MTP KK	PROBLEM TO BE SOLVED: To provide a no-puncture tire filling material and production method therefor that has good light weight, ride comfort, rolling resistance and filling material durability.SOLUTION: A no-puncture tire filling material 10 to be accommodated in an annular space 27 constituted by a tire outer cover 20 and a rim 25 was made of an urethane elastomer formed by prepolymer method using a prepolymer made from an isocyanate comprising at least one of 1,5-naphthalene diisocyanate (NDI) and 3'-dimethyl-4,4'-biphenyl diisocyanate (TODI), and a polyol containing 50 to 90 pts.wt. of polytetramethylene glycol.

Title	Publication number	Publication date	Inventor(s)	Applicant(s)	Abstract
Preparation method of polyurethane microporous elastomer	**CN106608960 (A)**	2017-05-03	YANG YAJUN LI MINGYING YAN HEJIA FAN CHUNXIAO	SHANGHAI CARTHANE CO LTD	The invention discloses a preparation method of polyurethane microporous elastomer. The preparation method comprises the steps of 1, making 4, 4'-diphenyl methane diisocyanate react with polyhydric alcohols, so that a polyurethane prepolymer is obtained; 2, adding 3, 3'-dimethyl biphenyl-4, 4'-diyl diisocyanate (TODI) to the polyurethane prepolymer, and conducting stirring, so that a mixed polyurethane prepolymer is obtained; and 3, adding a chain extender to the mixed polyurethane prepolymer, conducting stirring, injecting the mixture into a mold for plastic injection molding, and conducting demolding and curing, so that the polyurethane microporous elastomer is obtained. According to the preparation method of the polyurethane microporous elastomer, the TODI is added as auxiliary isocyanate in the process of preparing the MDI-group polyurethane microporous elastomer; on the basis that excellent mechanical performance of the MDI-group polyurethane microporous elastomer is maintained, dynamic fatigue resistance of the MDI-group polyurethane microporous elastomer is improved; and meanwhile, production cost is effectively controlled.
CLEANING BLADE	**WO2017170988 (A1)**	2017-10-05	OSAJIMA TAKESHI [JP] MUKAI HIDETOMO [JP]	NOK CORP [JP] SYNZTEC CO LTD [JP]	Provided is a cleaning blade 1 which is formed from an elastic body 11, wherein at least an edge part of the elastic body is formed from a cast-type polyurethane member of either: a combination (type A) of a carbonate polyol, naphthalene diisocyanate (NDI), a chain extender, which is formed from a short-chain diol, and, as necessary, a cross-linker, which is formed from a short-chain diol; or a combination (type B) of a polyol, o-toluidine diisocyanate (TODI), a chain extender, which is formed from a diamine compound, and, as necessary, a cross-linker, which is formed from a triol amine compound. The chain extender content of the polyurethane member with respect to the total content is 10 mass% or less, and the cross-linker content of the polyurethane member with respect to the total content is 1 mass% or less. The JIS A-type rubber hardness of the polyurethane member is 80 or greater, and the repulsive elasticity of the polyurethane member is 45% or greater.

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