CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

International Chemical Identification:

3,3'-Dimethylbiphenyl-4,4'-diyl diisocyanate;

[TODI]

EC Number: **202-112-7**

CAS Number: **91-97-4**

Index Number: **n.a.**

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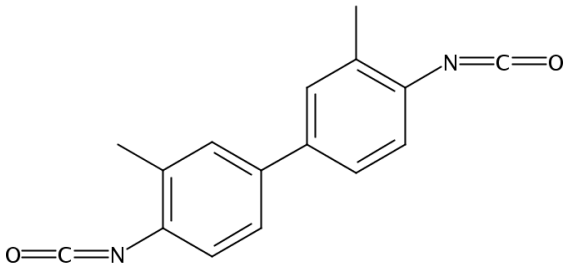
CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	4,4'-Diisocyanato-3,3'-dimethylbiphenyl
Other names (usual name, trade name, abbreviation)	1-Isocyanic acid, 3,3'-dimethyl-4,4'-biphenylylene ester 1,1'-Biphenyl, 4,4'-diisocyanato-3,3'-dimethyl- 4,4'-Diisocyanato-3,3'-dimethyl-1,1'-biphenyl 3,3'-Bitolylene-4,4'-diisocyanate 3,3'-Dimethyl-4,4'-biphenylene diisocyanate 1-isocyanato-4-(4-isocyanato-3-methyl-phenyl)-2-methyl-benzene 1-isocyanato-4-(4-isocyanato-3-methylphenyl)-2-methylbenzene o-Tolidine diisocyanate TODI
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	202-112-7
EC name (if available and appropriate)	3,3'-Dimethylbiphenyl-4,4'-diyl diisocyanate
CAS number (if available)	91-97-4
Other identity code (if available)	-
Molecular formula	$C_{16}H_{12}N_2O_2$
Structural formula	
SMILES notation (if available)	Cc1cc(ccc1N=C=O)c2ccc(N=C=O)c(C)c2
Molecular weight or molecular weight range	264.28 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	-
Description of the manufacturing process and identity of the source (for UVCB substances only)	-
Degree of purity (%) (if relevant for the entry in Annex VI)	-

1.1 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self- classification and labelling (CLP)
3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate EC No. 202-112-7 CAS No. 91-97-4	80-100	-	Acute Tox. 4 (H302/H312/ H332), Skin Irrit. 2 (H315), Eye Irrit. 2 (H319), Skin Sens. 1A/1 (H317), Resp. Sens. 1 (H334),

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self- classification and labelling (CLP)
			Muta 2 (H341), Aquatic Acute 1 (H400), Aquatic Chronic 1 (H410)

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 3: Current, proposed, and resulting harmonised classification and labelling for TODI

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate; [TODI]	202-112-7	91-97-4	Resp. Sens. 1 Skin Sens. 1A Carc. 1B	H334 H317 H350	GHS08 Dgr	H334 H317 H350			
Resulting Annex VI entry if agreed by RAC and COM											

Table 4: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)		
Oxidising gases		
Gases under pressure		
Flammable liquids		
Flammable solids		
Self-reactive substances		
Pyrophoric liquids		
Pyrophoric solids		
Self-heating substances		
Substances which in contact with water emit flammable gases		
Oxidising liquids		
Oxidising solids		
Organic peroxides		
Corrosive to metals		
Acute toxicity via oral route		
Acute toxicity via dermal route		
Acute toxicity via inhalation route		
Skin corrosion/irritation		
Serious eye damage/eye irritation		
Respiratory sensitisation	Harmonised classification proposed	Yes
Skin sensitisation		
Germ cell mutagenicity	Harmonised classification proposed	Yes
Carcinogenicity		
Reproductive toxicity	Hazard class not assessed in this dossier	No
Specific target organ toxicity-single exposure		
Specific target organ toxicity-repeated exposure		
Aspiration hazard		
Hazardous to the aquatic environment		
Hazardous to the ozone layer		

NOTE: This dossier is the result of the combined efforts of ANSES (FR) and BAuA (DE). ANSES prepared the sections on Germ cell mutagenicity and Carcinogenicity and will be responsible at a later stage for replying to any potential comments arising from the Consultation on those hazard

classes. BAuA (DE) prepared the sections on Respiratory and skin sensitisation and will be the responsible party for addressing comments on those sections.

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Not applicable

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

There is no requirement for justification that action is needed at Community level.

According to Article 36 of the CLP regulation, respiratory sensitisation is an endpoint for which Harmonised Classification and Labelling (CLH) is warranted. Although skin sensitisation is not covered by Article 36, there is a close relationship between skin sensitisers and respiratory sensitisers (currently all known low molecular weight chemical respiratory sensitisers are also skin sensitisers). Therefore, it is the view of the Dossier Submitter (DS) that an assessment of skin sensitisation potential is an integral part of the assessment of respiratory sensitisation.

According to Article 36 of the CLP regulation, mutagenicity and carcinogenicity are endpoints for which Harmonised Classification and Labelling (CLH) is warranted. Therefore, no justification is needed.

5 IDENTIFIED USES

A summary of the information available on ECHA's public website (accessed 2017-12-17) is given below[1].

5.1 General

This substance is manufactured and/or imported in the European Economic Area in 10 - 100 tonnes per year. This substance is used in articles and at industrial sites.

5.2 Consumer Uses

ECHA has no public registered data indicating whether or in which chemical products the substance might be used. ECHA has no public registered data on the routes by which this substance is most likely to be released to the environment.

5.3 Article service life

This substance is used in the following activities or processes at workplace: The low energy manipulation of substances bound in materials or articles and manual maintenance (cleaning and repair) of machinery. Other release to the environment of this substance is likely to occur from: outdoor use in long-life materials with low release rate (e.g. metal, wooden and plastic construction and building materials) and indoor use in long-life materials with low release rate (e.g. flooring, furniture, toys, construction materials, curtains, foot-wear, leather products, paper and cardboard products, electronic equipment). This substance can be found in products with material based on: plastic.

5.4 Widespread use by professional workers

ECHA has no public registered data indicating whether or in which chemical products the substance might be used. ECHA has no public registered data on the types of manufacture using this substance. ECHA has no public registered data on the use of this substance in activities or processes at the workplace. ECHA has no public registered data on the routes by which this substance is most likely to be released to the environment.

5.5 Formulation or re-packing

ECHA has no public registered data indicating whether or in which chemical products the substance might be used. ECHA has no public registered data on the use of this substance in activities or processes at the

[1] The text is a mixture of excerpts from ECHA's public website and of text prepared by the DS. Direct use of original text is not specifically marked.

workplace. ECHA has no public registered data on the routes by which this substance is most likely to be released to the environment.

5.6 Uses at industrial sites

ECHA has no public registered data indicating whether or in which chemical products the substance might be used. This substance is used for the manufacture of: plastic products. This substance is used in the following activities or processes at workplace: Closed processes with no likelihood of exposure, closed, continuous processes with occasional controlled exposure, transfer of chemicals at dedicated facilities, laboratory work, production of mixtures or articles by tabletting, compression, extrusion or pelletisation and the low energy manipulation of substances bound in materials or articles. Release to the environment of this substance can occur from industrial use: in the production of articles, as an intermediate step in further manufacturing of another substance (use of intermediates) and for thermoplastic manufacture.

5.7 Manufacture

ECHA has no public registered data on the use of this substance in activities or processes at the workplace. ECHA has no public registered data on the routes by which this substance is most likely to be released to the environment.

6 DATA SOURCES

This report has been created based on the data submitted by the lead registrant in the REACH registration dossier for TODI. In addition, further relevant data on TODI and related diisocyanates were retrieved as part of a general literature search in the context of the restriction proposal for diisocyanates recently submitted to ECHA by DE.

A supplementary literature search was performed in the SCOPUS database on 2017-06-30 for all references in the areas of medicine, pharmacology, toxicology, or environment published in 2015-2017 and containing the keyword „isocyanate". Also the PubMed database was searched for that keyword and time range.

7 PHYSICOCHEMICAL PROPERTIES

Table 5: Summary of physicochemical properties (all data taken from REACH registration dossier)

Property	Value	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Solid	Sensory determination [EPA OPPTS 830.6303 (Physical State)]
Melting/freezing point	Melting point: 71.7 °C (at 101.29 kPa)	Experimental result [OECD Guideline 102 (Melting point / Melting Range): differential scanning calorimetry]
Boiling point	Decomposition at approximately 644 K (371°C) at 101.42 kPa before boiling	Experimental result [EU Method A.2 (Boiling Temperature): differential scanning calorimetry)]
Relative density	1.331 (at 20°C)	Experimental result [OECD Guideline 109 (Density of Liquids and Solids): air comparison pycnometer (for solids)]
Vapour pressure	0.0029 Pa (at 25 °C)	Calculated value [QSAR (MPBPWIN v1.43: Modifiied Grain Method)] This value is confirmed by measured vapor pressure of MDI (structurally close molecule).

<table>
<tr><th>Property</th><th>Value</th><th>Comment (e.g. measured or estimated)</th></tr>
<tr><td>Surface tension</td><td>Determination of surface tension for TODI is scientifically not feasible.
The substance is hydrolytically unstable at pH 4, 7 and 9 (half-life less than 1 min).</td><td>-</td></tr>
<tr><td>Water solubility</td><td colspan="2">Determination of water solubility for TODI is scientifically not feasible.
The substance is hydrolytically unstable at pH 4, 7 and 9 (half-life less than 12 hours).</td></tr>
<tr><td>Water solubility, ctd.</td><td>Water solubility of the hydrolysis degradation product 4,4'-bi-o-toluidine (TODA):
1.3 g/L (at 25°C)</td><td>Handbook data
[CRC Handbook of Chemistry and Physics, 88th edition, 15. June 2007]</td></tr>
<tr><td rowspan="2">Partition coefficient n-octanol/water</td><td>Determination of partition coefficient of TODI is scientifically not feasible.
Given TODI high reactivity with water (half-life of TODI in water < 1min) and other protonic solvent (octanol), partition coefficient is not relevant and this property doesn't need to be assessed for isocyanate molecules.</td><td></td></tr>
<tr><td>Calculated log Kow of the hydrolysis degradation product 4,4'-bi-o-toluidine (TODA): 3.0176</td><td>Calculated value
[QSAR (EPIWIN using KOWWIN v1.68)]</td></tr>
<tr><td>Granulometry</td><td><table><tr><th>Sieve size [µm]</th><th>Distribution</th></tr><tr><td>63</td><td>0.0 %</td></tr><tr><td>125</td><td>0.2 %</td></tr><tr><td>250</td><td>0.6 %</td></tr><tr><td>500</td><td>4.3 %</td></tr><tr><td>1000</td><td>24.2 %</td></tr><tr><td>2000</td><td>70.6 %</td></tr><tr><td>4000</td><td>0.0 %</td></tr></table>
A range of 2000 to 1000 µm covers 90 % of the particle size distribution of TODI. No particles with a diameter below 63 µm were found.</td><td>Experimental result
[CIPAC MT 170 Dry Sieve Analysis of Water Dispersible Granules;
mass distribution: machine sieving]</td></tr>
<tr><td>Stability in organic solvents and identity of relevant degradation products</td><td>N.a. (stability in organic solvents is not a critical property of the substance)</td><td>-</td></tr>
<tr><td rowspan="2">Dissociation constant</td><td>N.a. (hydrolytically unstable)</td><td>-</td></tr>
<tr><td>pKa of the hydrolysis product 4,4'-bi-o-toluidine (TODA): 4.59 (at 25 °C)</td><td>Calculated value
[QSAR (Advanced Chemistry Development (ACD/Labs) Software V11.02 (1994-2013))]</td></tr>
<tr><td>Viscosity</td><td>N.a. (solid)</td><td>-</td></tr>
</table>

8 EVALUATION OF PHYSICAL HAZARDS

Not assessed in this dossier

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

To the best knowledge of the DS, no studies on the ADME properties of TODI in mammals are available. To justify this, the lead registrant refers to the high and rapid reactivity of TODI with water. A hydrolysis test was performed at 50 ± 0.5 °C and 25 ± 2 °C, at pH 4, 7 and 9 which is summarised by the lead registrant as follows:

One sample was analysed at each time point. For each assay, the first 'start' time point for hydrolysis was made as quickly as the sample could be loaded into the HPLC system and analysed (typically 3 to 5 minutes). At the first time point and all subsequent time points at pH 4 and 9 at 50 ± 0.5 °C, the maximal amount of hydrolysis product was measured, hence the $t_{1/2}$ was less than at the first measurement time point. At 25 °C, and pH 9 full hydrolysis was within 30 minutes with 50% at the 'start' time point; at 25 °C, pH 4 full hydrolysis was found at the first time point. It is concluded that TODI hydrolysed rapidly (in less than 30 minutes) at 25 and 50 °C at pH 4 and 9. At pH 7 hydrolysis of 100% was reached within 29 hours (25°C) and 2.5 hours (50°C). For the tests carried out at pH 7 the log-transformed data of peak areas against time were plotted. A line was fitted on the measured data and the rate constant and the half-life were obtained from its slope according to equations 2 and 3. The t1/2 at pH 4 and 9, at 25 and 50 °C was lower than or equal to 2 minutes; at pH 7 the $t_{1/2}$ was 16 hours and 1.2 hours at 25 and 50 °C respectively (Laky, 2009).

While these data confirm the potential of TODI for fast hydrolysis, the DS nevertheless finds that upon contact with skin or the respiratory tract a sufficiently large time window is available for the initial steps of sensitisation to take place.

Furthermore the lead registrant has included an expert statement on the ADME properties of TODI in the REACH registration dossier (SCC, 2010), which however, essentially refers data for MDI without a closer analysis of commonalities or differences between the two substances. In the view of the DS, this statement does not include relevant ADME information with respect to (respiratory or skin) sensitisation.

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity - oral route

Not assessed in this dossier

10.2 Acute toxicity - dermal route

Not assessed in this dossier

10.3 Acute toxicity - inhalation route

Not assessed in this dossier

10.4 Skin corrosion/irritation

Not assessed in this dossier

10.5 Serious eye damage/eye irritation

Not assessed in this dossier

10.6 Respiratory sensitisation

10.6.1 Endpoint definition and evaluation strategy

According to Annex I, section 3.4.1.1 of the CLP regulation "respiratory sensitiser means a substance that will lead to hypersensitivity of the airways following inhalation of the substance" (European Parliament and Council, 2008).

Since there is still no validated and universally accepted test method for identifying respiratory sensitisers, there is currently no standard information requirement under REACH for this endpoint. For the most commercially successful diisocyanates on the market, such as HDI, MDI, or TDI, nevertheless a comprehensive database of human and non-human data is available demonstrating the potential of these substances to cause respiratory sensitisation (RS) in humans. In contrast, for those diisocyanates used in lower volumes such as TODI, the substance addressed by this dossier, data with respect to RS are scarce. For TODI, specifically, no human or animal data related to RS were identified by the DS.

Article 9 of the CLP regulation specifies how the hazard information is evaluated to decide on classification. The strategy followed in this dossier is therefore characterised by a category approach by means of which the knowledge about the RS potential of the three most commonly used diisocyanates HDI, MDI, and TDI is read across to TODI. The use of category-based read-across for classification and labelling is covered by Article 5 1. (2) of the CLP regulation, which in turn refers to the methods listed in section 1 of REACH Annex XI. The category approach is justified in the following section. Finally, all available information is combined in an overall weight-of-evidence assessment in line with CLP Annex I, section 1.1.1.3.

10.6.2 Justification of the category approach

10.6.2.1 Characterisation of the category approach in terms of the ECHA Read-Across Assessment Framework (RAAF, (ECHA, 2017b))

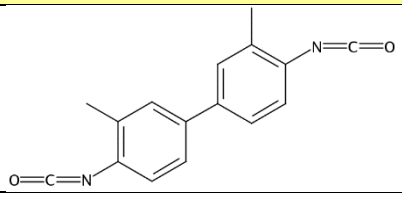
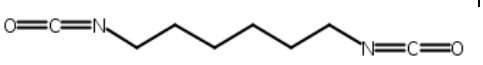
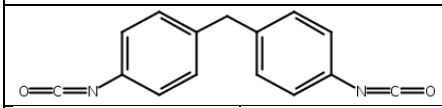
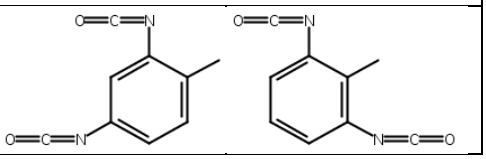
The approach relates to RAAF Scenario 6 (human health), i.e. the read-across hypothesis for the category is based on different compounds which have qualitatively similar properties, with no relevant variations in properties observed among source substances and the same strength predicted for the target substance[2].

The following sub-sections provide the justification for the read-across hypothesis, structured according to the Assessment Elements (AE) relevant for Scenario 6, as listed in Appendix F to the RAAF.

10.6.2.2 AE C.1 Substance characterisation

The identity of the target substance TODI has been characterised above. Table 6 provides information on the identity and harmonised classification of the target substance as well as the category source substances HDI, MDI, and TDI.

Table 6: List of category source substances used for read-across to TODI

EC Name; trivial name used in this report	EC No. CAS no.	CLH for sensitisation (Annex VI to CLP)	Structure
3,3'-Dimethylbiphenyl-4,4'-diyl diisocyanate; TODI	202-112-7 91-97-4	-	
Hexamethylene diisocyanate; HDI	212-485-8 822-06-0	Resp. Sens. 1 Skin Sens. 1	
4,4'-Methylenediphenyl diisocyanate; MDI[$]	202-966-0 101-68-8		
m-Tolylidene diisocyanate (80/20 mixture of 2,4-TDI and 2,6-TDI isomers); TDI[$]	247-722-4 26471-62-5		

[$] The DS is aware that there are other isomers or isomer mixtures of MDI and TDI, but in this report these abbreviations refer only to the isomers listed in this table.

[2] Note that here the terms "no relevant variations" and "same strength" relate to the question "respiratory sensitiser – yes or no?" and not to relative potency.

10.6.2.3 AE C.2 Structural similarity and category hypothesis

As can be seen in Table 6, all members of the group (as well as the target substance) are monomeric diisocyanates, i.e. they share the structural feature of two isocyanate functional groups. The part of the molecular structure linking the two isocyanate groups may be variable.

10.6.2.4 AE C.3 Link of structural similarities and structural differences with the proposed regular pattern

It will be illustrated in the following sections that the respiratory sensitisation property depends solely on the diisocyanate feature common to sources and target, independent of variations in the molecular structure connecting the two isocyanate groups.

10.6.2.5 AE C.4 Consistency of effects in the data matrix

For all three source substances, plenty of human and non-human data are available to consistently demonstrate their potential to cause RS (cf. section below). Consequently, all three congeners share harmonised classification as Resp. Sens. 1. For details, the reader is referred to sections 10.6.4 and 10.6.5 as well as to Annex I.

10.6.2.6 AE C.6 Reliability and adequacy of the source data

This is addressed in the relevant parts of sections 10.6.4 and 10.6.5 as well as in Annex I.

10.6.2.7 AE 6.1 Compounds the test organism is exposed to

In all studies used in this approach, the test organisms have been exposed to the source substances as described in Table 6 above.

10.6.2.8 AE 6.2/6.3 Common underlying mechanism, qualitative/quantitative aspects

In 2012, the Organisation for Economic Co-Operation and Development (OECD) published the Adverse Outcome Pathway (AOP) for skin sensitisation initiated by covalent binding to proteins (OECD, 2012). Enoch and co-workers hypothesised that in a similar way covalent binding of electrophiles to proteins in the lung marks the molecular initiating event (MIE) in a putative AOP for RS. In several publications, the authors characterised the corresponding chemical reaction domains and identified structural alerts which have now been integrated as profilers into the OECD QSAR Toolbox (Enoch et al., 2011; Enoch et al., 2009; Enoch et al., 2014). According to the authors, *"iso(thio)cyanates have been shown to undergo an acylation reaction resulting in the formation of protein adducts"* (Enoch et al., 2011). This is also shown in Figure 1 below.

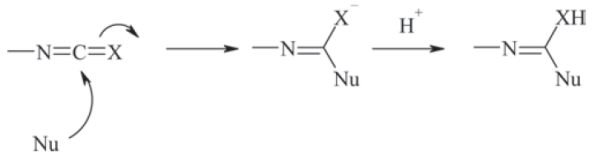


Figure 1: Acylation reaction for isocyanates (X = oxygen). Reproduced from (Enoch et al., 2011)

The isocyanate moiety is indeed a common alert in RS prediction tools. Dik et al. tested five different RS prediction models with a test chemical set also including isocyanates and diisocyanates; all of the models agreed on a positive prediction in all of the cases (Dik et al., 2014). In fact the IR & CSA guidance, chapter R.7a recommends to use the test set from this publication as a source for read-across (ECHA, 2016).

Agius et al. noted that *"low molecular weight agents that can form at least two bonds with native human macromolecules carry a higher occupational asthma hazard. Thus bi- or polyfunctional low molecular weight agents such as diisocyanates and aliphatic or cyclic amines, as well as dicarboxylic acid anhydrides and dialdehydes, rank highly among organic low molecular weight substances"* (Agius, 2000). A potential explanation might be found in that bifunctionality potentially allows for cross-linking of nucleophilic moieties within the same or different proteins which may result in a more marked change of conformation.

The potential reactivity of the diisocyanate source substances given in Table 6 above towards amino acids such as cysteine and lysine has been shown *in chemico* (Lalko et al., 2013).

In summary, the isocyanate functional group marks a well-known structural alert for RS for which there is some evidence that interaction with proteins might occur via an acylation type reaction between the electrophilic NCO functional group(s) and nucleophilic protein moieties such as amino or sulfhydryl groups.

Moreover, with respect to Table 6 above, DE would like to point out that in terms of structure those molecular parts of the source substances separating the two isocyanate groups differ from each other, further highlighting that at least qualitatively the presence of the (two) isocyanate groups is the decisive factor for the RS potential, while the remaining molecular structure is of less importance (it might however have an impact on the physico-chemical and ADME properties and therefore relative potency which are not addressed in this dossier).

10.6.2.9 AE 6.4 Exposure to other compounds than those linked to the prediction

DE is not aware that the presence of other compounds has influenced the outcome of the studies used for the category approach.

10.6.2.10 AE C.6 Bias that influences the prediction

Only the three most commonly used diisocyanates have been used as source substances, because most published literature on diisocyanates relates to these compounds. However, DE notes that a number of further diisocyanates share classification as RS. An overview is given in the recent restriction report for diisocyanates (German CA, 2016) and the associated annex. DE is not aware of any monomeric diisocyanate for which data convincingly show that the substance is not a respiratory (and skin) sensitiser.

10.6.3 Data retrieval, evaluation, and presentation strategy

Based on the above considerations, the strategy for data research and presentation followed in this dossier was chosen by DE as follows:

- Identify all studies in humans and animals for TODI, HDI, MDI, and TDI. Notably, numerous studies demonstrate the ability of diisocyanates to cause symptoms of RS also after dermal exposure (cf. the restriction report for diisocyanates recently submitted by the German MSCA[3]), however, since the definition from the CLP regulation cited in section 10.6.1 clearly asks for inhalation exposure, only studies along this route were evaluated for the current dossier.
- Evaluate and present the relevant human data for the three source substances HDI, MDI, and TDI (no relevant studies were identified for TODI).
- Filter animal data for relevance according to predefined criteria (cf. section 10.6.5).
- Evaluate and present the relevant animal data for the three source substances HDI, MDI, and TDI (no relevant studies were identified for TODI).
- Summarise, compare to the CLP criteria and conclude on a possible potential for RS.

10.6.4 Human data

The CLP regulation notes that evidence for chemical-induced RS (asthma/rhinitis/conjunctivitis/alveolitis) will normally be based on human experience. "*The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated"* (European Parliament and Council, 2008).

Human data relevant for RS assessment may comprise *"consumer experience and comments, preferably followed up by professionals (e.g. bronchial provocation tests, skin prick tests and measurements of specific IgE serum levels); records of workers' experience, accidents, and exposure studies including medical surveillance; case reports in the general scientific and medical literature; consumer tests (monitoring by questionnaire and/or medical surveillance); epidemiological studies."* (ECHA, 2016).

[3] https://echa.europa.eu/registry-of-submitted-restriction-proposal-intentions/-/substance-rev/15016/term, last accessed 2017-10-21

Both immediate (seconds to minutes) and late-onset (up to several hours) hypersensitivity reactions may be present in patients with diisocyanate-induced asthma, with the prevalence of late responses being as high as 70% (Niimi et al., 1996). The delay between onset of (low-level) exposure at work and the manifestation of the asthmatic symptoms, which may be as long as several years after the start of exposure, is of particular concern. In addition, patients often develop persistent bronchial hyperresponsiveness (BHR; often also the more general term "airway hyperresponsiveness/hyperreagibility (AHR)" is used interchangeably) to non-specific stressors including e.g. other chemicals such as methacholine, cold, dust, or physical exercise that can last for years even in the absence of continued exposure, and complete recovery of lung function may never be achieved (Johnson et al., 2004a).

The following endpoints are used regularly for the diagnosis of occupational asthma in human case reports, case studies, and epidemiological studies:

- clinical symptoms: wheezing, dry cough, intermittent shortness of breath, particularly in connection with physical activity,
- lung function testing following unspecific or specific bronchial provocation: Forced Expiratory Volume in one second (FEV_1), Peak Expiratory Flow (PEF), and
- presence of diisocyanate-specific IgE and/or IgG antibodies.

Nevertheless, studies in humans frequently suffer from limitations. The full spectrum of parameters such as the test protocol used, the substance or preparation studied, the extent of exposure, the frequency of effects, the persistence or absence of health effects, the presence of confounding factors, the relevance with respect to group size, statistics, documentation, or the "healthy worker effect" which should all be reported (ECHA, 2016), is rarely, if ever, provided in these reports.

10.6.4.1 Human data for the target substance TODI

No relevant data for TODI were identified during the literature search performed for this dossier.

10.6.4.2 Human data for the source substances HDI, MDI, and TDI

More than 100 case reports and epidemiological studies have been evaluated. An overview of this evaluation is provided in Annex I, Table 1 (case reports) and Tables 2-7 (epidemiological studies). The case reports provide overwhelming proof that humans exposed to the source substances HDI, MDI, and/or TDI may suffer from a broad spectrum of respiratory effects including asthma and pathological changes of the airways. Also a number of fatal cases have been reported, albeit not in recent years. While during the early stages of the development of the disease, respiratory symptoms may eventually be reversed upon removal from exposure, an irreversible remodelling of the airways will eventually take place when exposure is continued. On the other hand these case reports do not allow for an assessment of the frequency of occurrence of respiratory sensitisation to TODI in the human population as they feature only a small number of patients and it is not known which fraction of all exposed persons is affected (and which fraction of the affected is reported). They are therefore not suited for sub-categorisation. In addition, no harmonised approach for sub-categorising respiratory sensitisers is available yet.

An overview of epidemiological studies on diisocyanates and respiratory effects conducted until today with short study descriptions and results is given in Annex 1, Tables 2-7. Despite a large number of available studies, none of these studies is eligible for deriving a reliable Exposure-Response-Relationship (ERR) due to limitations of the studies. This is also inherent in the mechanism of the disease. No study overcomes the problem that sensitive predictive markers for diisocyanate sensitisation are missing and that dermal exposure as well as inhalation peak exposure likely contribute to the induction of sensitisation, but cannot be assessed appropriately to date.

10.6.5 Animal data

The recent update of the IR & CSA guidance, section R.7a notes that *"although predictive models are under validation, there is as yet no internationally recognised animal method for identification of respiratory sensitisation."* (ECHA, 2016).

In concert with human data, some types of animal data may play a supportive role in the qualitative assertion of respiratory sensitisation (ECHA, 2016; ECHA, 2017a; European Parliament and Council, 2008). With respect to the nature of relevant animal data, the CLP regulation states that *"data from appropriate animal studies which may be indicative of the potential of a substance to cause sensitisation by inhalation in humans may include: (a) measurements of Immunoglobulin E (IgE) and other specific immunological parameters in mice; (b) specific pulmonary responses in guinea pigs"*(European Parliament and Council, 2008).

From this wording the DS concludes that (test substance-specific) changes in immunological parameters as well as specific pulmonary responses may be important indicators of RS, whereas the absence of such effects in animals cannot serve as a proof of the absence of RS potential in humans. With respect to the species named in the regulation, over the years various animal species have been used as model species for RS and to the knowledge of the DS there is no scientific argument why immunological changes should only be relevant in mice or pulmonary responses only relevant in guinea pigs.

As a consequence, the animal database available for the three source substances and the target substance TODI has been evaluated and filtered for relevant studies (the complete list of studies is available in Table 8 in Annex I to this dossier). To that end, studies were discarded which used induction routes other than the inhalation route (or mixed designs including e.g. intradermal and inhalation induction). Only true inhalation studies were accepted, while those using intranasal exposure, intratracheal instillation, or oropharyngeal administration were not considered any further.

In the next step, studies were considered unreliable and therefore excluded from assessment if any of the following information was missing or incomplete:

- identity of the test substance
- the physical state of the test substance as applied (aerosol or vapour),
- the inhalation protocol followed (whole-body or head-/nose-only),
- confirmation of the presence of a negative control, and
- the number of animals per dose group.

Animal study designs for respiratory sensitisation have been manifold, involving a variety of species, protocols, and target endpoints, and a standardised protocol with regulatory acceptance is still missing. Therefore a negative result from an animal experiment on RS is not suitable to exclude the need for classification and labelling. Consequently, for the read-across assessment the evaluation concentrated on data providing a positive indication of respiratory sensitisation, therefore for HDI, MDI, and TDI only studies reporting the presence of one or more relevant effects were selected for further processing. Where several experiments were reported in one study report, only those with effects were processed further. Finally, studies using agents other than TODI or the three source substances (as per Table 6) in their monomeric form, i.e. their prepolymers, breakdown products or protein conjugates or other isomers for induction, or for which the exact identity was unclear, were also dismissed.

The effects observed in the remaining studies were captured according to the following four categories (and the experiments included or dismissed accordingly):

- production of test substance-specific IgE and/or IgG antibodies; for this, also experiments without an elicitation/challenge elicitation step were included,
- elicitation of dermal contact hypersensitivity (positive results in skin sensitisation tests upon intradermal or topical challenge); in the view of DE, such experiments would also provide proof of a substance-specific immunological reaction. In the same sense, two reports of a "respiratory LLNA", i.e. an evaluation of the draining mandibular lymph nodes after inhalation induction by means of a stimulation index analogous to that used in the dermal LLNA, were included,
- impact on respiratory function; experiments showing effects on respiratory function were only included if these effects occurred as the result of a test substance-specific challenge, after repeated exposure, or after continuous exposure for several days. The latter two cases were included since the immune response will develop in parallel to repeated/continuous exposure and therefore later exposures or a later stage of long-time continuous exposure will have the character of an elicitation/challenge more than of an induction

exposure. For their relevance in human asthma diagnostics, also animal experiments employing unspecific challenges (e.g. with methacholine) to demonstrate AHR were included, although the CLP criteria ask for "specific pulmonary reactions" (cf. above). A decrease instead of an increase in respiratory rate was attributed to sensory irritation and experiments showing only this effect were excluded from further evaluation (although from a linguistical point of view, this would also constitute a "specific pulmonary reaction"),

- presence of inflammation markers (e.g. seen in histopathological evaluations or found in bronchoalveolar lavage fluid); to delineate RS from mere irritation, studies were only included if a) more than one exposure or a continuous exposure over more than one day occurred and b) at least one effect from any of the other three categories was found in the same study (not necessarily the same experiment).

In the end, a total of 36 experiments from 18 study reports, performed in guinea pigs, mice, and rats qualified for further evaluation. Table 7 provides an overview of the number of studies and their distribution over the different substances and rodent species.

Table 7: Overview of the number of available animal experiments per substance and species

Diisocyanate	Species			Total
	Guinea pigs	Mice	Rats	
TODI	-	-	-	-
HDI	-	3	-	3
MDI	6	-	6	12
TDI	14	7	-	21
Total	20	10	6	36

10.6.5.1 Animal data for the target substance TODI

For TODI, no relevant animal studies/experiments with inhalation exposure were identified during the literature search for this dossier.

10.6.5.2 Animal data for the source substances HDI, MDI, and TDI

Table 8 provides an overview of the results of the experiments with HDI, MDI, and TDI selected for further evaluation regarding the potential of these substances to cause respiratory sensitisation.

Table 8: Studies for evaluating the potential of the source substances HDI, MDI, and TDI to cause RS in rodents following exposure via the inhalation route (sorted by species and year, see section 0 for abbreviations)

Strain	Sex	"Induction" Agent	"Elicitation" Route	"Elicitation" Agent	Physical state	Inhalation type	Animals/group	No. of "induction" exposures	Hours/exposure	Total days	Critical effect	Reference
Guinea pigs												
ESH	F	TDI	-	-	VP	HO	8	2	3	3	AB	(Karol, 1983)
							12	5		5		
			IDE	TDI-GPSA			8				SS	
			INH	TDI-GPSA/ TMI-GPSA			12				RF	
DH	F	TDI	INH	TDI-GPSA	AE	NO	10	5	3	5	AB/RF	(Botham et al., 1988)
DH	F	MDI	-	-	VP	NO	5	5	3	21	AB	(Dearman and Botham, 1990)
			IPE	MDI-GPSA						22		
Hartley	F	TDI	INH	TDI	VP	WB	7	5	3	21	AB/IF/RF	(Huang et al., 1993a)
Hartley	F	TDI	INH	TDI	VP	WB	6	5	3	26	AB/RF	(Aoyama et al., 1994)
Hartley	?	MDI	INH	MDI	AE	NO	≥ 8	1	0.25	21/ 22	RF	(Pauluhn, 1994)
				MDI-GPSA								
		TDI		TDI	VP							
				TDI-GPSA								
DH	F	MDI	INH	MDI	AE	NO	16	5	3	18	AB	(Rattray et al., 1994)

Strain	Sex	"Induction" Agent	"Elicitation" Route	"Elicitation" Agent	Physical state	Inhalation type	Animals/group	No. of "induction" exposures	Hours/exposure	Total days	Critical effect	Reference
?	?	MDI	INH	MDI	AE	NO	16	1	0.25	21/ 28	AB/RF	IUCL: (Bayer, 1995)
DH	F	TDI	-	-	VP	WB	20	1	48 168	3 8	RF	(Gagnaire et al., 1996)
DH	F	TDI	-	-	VP	WB	10	1	134 4	56	RF	(Gagnaire et al., 1997)
DH	F	TDI	INH	TDI/TDI-GPSA	VP	NO	8	1	0.25	21	AB/IF/RF	(Pauluhn and Mohr, 1998)
Hartley	F	TDI	TOP	TDI	AE	NO	8	1	4	15	SS	(Ebino et al., 2001)
Mice												
C57BL/6	F	TDI	INH	TDI	VP	NO	5	30	4	56	AB/IF/RF	(Matheson et al., 2005a)
C57BL/6	F	TDI	INH	TDI	VP	HO	5	1 30	2 4	1 56	AB/IF/RF	(Matheson et al., 2005b)
BALB/c	F	TDI	INH	TDI	VP	WB	6-8	1	4	14	AB/IF	(Ban et al., 2006)
BALB/c	M	HDI TDI	-	-	VP	NO	6	3	0.75 1.5 3 0.75 1.5 3	5	IF	(Arts et al., 2008; de Jong et al., 2009)
Rats												
Wistar	F	MDI	-	-	AE	WB	8 12 20 80	436 65 260 436 520	17	610 98 365 371 728	RF IF	IUCL: (Hoymann et al., 1995)

10.6.5.2.1 Guinea pigs

After exposing female English Smooth-Hair guinea pigs to vapour containing 0.02 ppm TDI twice for 3 h/d within 3 days, Karol demonstrated an increased production of TDI-specific antibodies. After five 3 h/d exposures on 5 consecutive days at concentrations of ≥ 0.12 ppm TDI, again specific antibodies were found (at concentrations ≥ 0.36 ppm); moreover, contact hypersensitivity was observed as a result of intradermal challenge with TDI-guinea pig serum albumin conjugate (TDI-GPSA) at concentrations of ≥ 0.12 ppm. Finally, following a specific bronchial provocation challenge with TDI-GPSA, a significant increase in respiratory rate (RR) was reported at ≥ 0.36 ppm (Karol, 1983).

Botham et al. (1988) reported the production of TDI-specific IgE- and IgG_1 antibodies as well as an increase in RR after bronchial provocation challenge with TDI-GPSA following exposure of female Dunkin-Hartley guinea pigs to 1, 3 or 4 ppm TDI for 3 h/d on five consecutive days (Botham et al., 1988). In 1990, Dearman and Botham used the same exposure protocol in female Hartley guinea pigs with 11 mg/m^3 MDI vapour and found an increased production of specific IgG_1 and – to a lesser degree – IgE antibodies. Intraperitoneal challenge with MDI-GPSA diminished the IgE, but not the IgG response (Dearman and Botham, 1990).

Huang et al. demonstrated increased histamine blood levels as well as mast cell degranulation indices at concentrations ≥ 0.12 ppm TDI after exposing female Hartley guinea pigs to TDI concentrations ranging from 0.03 to 0.37 ppm for 3 h/d over 5 d and challenging them with TDI three weeks later (Huang et al., 1993b). In 1994, the same group used a similar design (with induction concentrations of ≥ 0.02 ppm TDI) and demonstrated formation of TDI-specific IgG antibodies as well as effects on respiratory function (as percentage increase in respiratory rate) at concentrations ≥ 0.2 ppm (Aoyama et al., 1994).

Pauluhn sensitised guinea pigs via inhalation by a single 15 min exposure to 135 mg MDI/m^3 or to 45 mg TDI/m^3. Upon challenge with the same diisocyanate, either unbound or conjugated to GPSA at approximate

concentrations of 12 (MDI) or 4 mg/m^3, 21 d post-induction, increased immediate onset responses in respiratory function (in terms of a dimensionless parameter composed of peak expiratory flow rate, inspiratory and expiratory time/volume and tidal volume) vs. ovalbumin (OVA) controls were observed. The same animals displayed increased acetyl provocation indices vs. OVA when subjected to an acetylcholine provocation test one day later, i.e. 22 d post-induction (Pauluhn, 1994).

Rattray and co-workers reported a slight increase in IgG_1 levels in female Dunkin-Hartley guinea pigs 18 d after five 3 h/d exposures to atmospheres containing ca. 20 mg MDI/m^3 (Rattray et al., 1994).

In another study in guinea pigs, the animals were exposed via inhalation to 132 mg MDI aerosol/m^3 for 20 min. Depending on the test group, challenge by inhalation was performed 21 or 28 days later, using a ramped test design (increasing concentrations of 0/5/15/35 mg MDI/m^3, successively for 20 min per concentration level resulting in a total MDI exposure time of 1 h). According to the authors of the IUCLID summary, *"low anti-MDI antibody titers* [were observed] *in animals sensitized to MDI (15/16). No association between elevated IgG1 anti-MDI antibody titers and respiratory responses or any of the bronchoalveolar lavage parameters could be established. […] Only a borderline sensitisation occurred […]. Mild MDI-specific immediate-onset responses were observed mainly during challenge to slightly irritant concentrations (35 mg/m³). A marked increase of neutrophilic or eosinophilic granulocytes could not be established. An activation of these cells could not be observed. Animals sensitized to high concentrations of aerosolized MDI showed a mild airway hypersensitivity without concomitant influx of inflammatory cells"* (Bayer, 1995).

Gagnaire and co-workers demonstrated the development of AHR/BHR (measured as the dose of acetylcholine in a bronchial provocation test required to cause a two-fold increase in airway resistance vs. baseline) in female Dunkin-Hartley guinea pigs following continuous exposure to 0.08 ppm TDI for 48 h, 0.046 ppm for one week, or 0.029 ppm for eight weeks (Gagnaire et al., 1997; Gagnaire et al., 1996).

Pauluhn and Mohr applied different inhalation exposure designs (1 x 15 min, 5 x 3 h/d, using different concentrations of 3.8 to 51 mg TDI/m^3) to test female Dunkin-Hartley guinea pigs for respiratory sensitisation. They noted AHR/BHR (measured as a "flow-derived dimensionless parameter", or "FDP") after challenge with acetylcholine (ca. on days 20 and 22), TDI (day 21) and TDI-GPSA hapten-protein complex (around day 28). Four weeks into the test, production of TDI-specific IgG_1 antibodies was demonstrated. On sacrifice one day after the conjugate challenge, inflammation markers and histopathological lesions in the airways were observed to a varying degree in all groups (Pauluhn and Mohr, 1998).

Ebino and co-workers demonstrated skin sensitisation upon topical TDI challenge of Hartley guinea pigs sensitised two weeks before by a single four hour inhalation exposure to TDI (Ebino et al., 2001).

10.6.5.2.2 Mice

In studies in C57BL/6 mice using a single, 1-h inhalation challenge following a 6 wk inhalation induction regime (4 h/d, 5 d/wk), Matheson and co-workers (2005) observed *"a marked allergic response evidenced by increases in airway inflammation, eosinophilia, goblet cell metaplasia, epithelial cell alterations, airway hyperresponsiveness (AHR), TH1/TH2 cytokine expression in the lung, elevated levels of serum IgE, and TDI-specific IgG antibodies, as well as the ability to transfer these pathologies to naïve mice with lymphocytes or sera from TDI exposed mice"* (Matheson et al., 2005a; Matheson et al., 2005b).

Ban and co-workers induced sensitisation in female BALB/c mice by 4 h-exposure via whole-body inhalation to 3 ppm TDI on three consecutive days[4]. Challenge was either performed by two single 4 h challenges with 0.3 ppm TDI 7 or 12 days after the end of induction or by a single 4 h inhalation challenge with 2 ppm TDI 14 days after the end of induction, followed by a 1 d tracheal instillation with 50 µg TDI-HAS conjugate/animal one week later. The authors reported increases in a number of inflammation markers including cytokines (with some variability between the two designs) as well as a statistically significant rise of total IgE antibody levels (Ban et al., 2006).

[4] The abstract of this publication claims that induction was performed over „four consecutive days", however, the method section states that induction was performed on „days 0, 1, and 2". Coming from the methods section the latter information is assumed to be more reliable.

Arts and colleagues used a "respiratory local lymph node assay", i.e. a study protocol in which male Balb/c mice were first exposed once per day on three consecutive days to HDI or TDI by inhalation, followed by an evaluation of the proliferation of the draining mandibular lymph nodes three days later. Both diisocyanates caused marked proliferation with the stimulation index exceeding a value of 3 at all inhalation concentrations applied (Arts et al., 2008; de Jong et al., 2009).

10.6.5.2.3 Rats

Hoymann and colleagues performed a combined inhalation chronic toxicity and carcinogenicity test in female Wistar rats using MDI. As a result of between 65 and 520 daily 17 h exposures, the author of the summary in the technical dossier noted "*a dose-dependent impairment of the lung function in the sense of an obstructive-restrictive malfunction with diffusion disorder, increased lung weights, an inflammatory reaction with increased appearance of lymphocytes (but not of granulocytes) in the lung in the high dose group as a sign of specific stimulation of the immune system by MDI*" (Hoymann et al., 1995).

10.6.6 Short summary and overall relevance of the provided information on respiratory sensitisation

10.6.6.1 Human data

For TODI, no human data relevant for the classification as a respiratory sensitiser were identified. However, a large database of human data on the source substances HDI, MDI, and TDI provides undeniable proof that these substances are able to cause RS in humans and are therefore rightfully listed as Resp. Sens. 1 in Annex VI to the CLP regulation.

10.6.6.2 Animal data

Again no relevant data for TODI were identified from the available data base. In contrast, exposure to the three source substances by inhalation was shown to trigger RS in a variety of rodent species as demonstrated by the production of specific antibodies, impairment of respiratory function, and characteristic inflammation markers in BALF. Observed respiratory symptoms (increased respiratory rate, effects on respiratory flow, laboured breathing etc.) resemble those seen in humans with asthma.

Skin sensitisation has also been observed following induction via inhalation.

Overall, the interdependencies and quantitative contributions to sensitisation of factors such as the species and strain used, concentration and total dose received upon induction, or the temporal pattern of dosing are still poorly understood.

10.6.7 Comparison with the CLP criteria

10.6.7.1 Human data

Section 3.4.2.1.2.3 of Annex I to the CLP regulation states that the evidence required to demonstrate RS in humans *"could be: (a) clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include: (i) in vivo immunological test (e.g. skin prick test); (ii) in vitro immunological test (e.g. serological analysis); (iii) studies that indicate other specific hypersensitivity reactions where immunological mechanisms of action have not been proven, e.g. repeated low-level irritation, pharmacologically mediated effects; (iv) a chemical structure related to substances known to cause respiratory hypersensitivity; (b) data from one or more positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction".* Furthermore, section 3.4.2.1.2.5 notes that "*the results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own"* (European Parliament and Council, 2008).

Since for TODI, no study in humans is available, a category approach is used for classification in accordance with CLP Article 5 1. (2) referring to REACH Annex XI, section 1. Numerous case reports and epidemiological studies with the source substances HDI, MDI, and TDI evaluated for this dossier report positive bronchial provocation tests with these substances and are therefore each sufficient on their own to justify classification for RS. In addition, many of the other criteria mentioned above are met by these reports.

On the other hand, no reliable ERR can be established from the database and therefore no reliable relative or absolute potency estimate can be made. In addition, reading across already unreliable potency information from the three different source substances to the target substance would be associated with a high degree of uncertainty. Moreover, no harmonised approach for sub-categorising respiratory sensitisers is available yet.

Still, these data are sufficient to classify TODI as Resp. Sens. 1 in accordance with the CLP regulation.

10.6.7.2 Animal data

Several studies in guinea pigs, mice, and rats with the source substances HDI, MDI, and TDI were identified in which the production of specific antibodies and the impairment of pulmonary function as a consequence of exposure to diisocyanates via inhalation were demonstrated.

According to the criteria already mentioned above (cf. section 10.6.5: *"data from appropriate animal studies which may be indicative of the potential of a substance to cause sensitisation by inhalation in humans may include: (a) measurements of Immunoglobulin E (IgE) and other specific immunological parameters in mice; (b) specific pulmonary responses in guinea pigs"*), these data lend qualitative support to the observations in humans noted in the previous sub-section.

10.6.8 Conclusion on classification and labelling for respiratory sensitisation

In summary, in a weight-of-evidence decision according to CLP Annex I, section 1.1.1, considering:

- general mechanistic knowledge on the biological effects of diisocyanates,
- a category approach using read-across of human and non-human data from the source substances HDI, MDI, and TDI to the target substance TODI, and
- the potential of TODI to cause skin sensitisation (cf. section 10.7 below),

DE concludes that TODI should be classified as Resp. Sens. 1 (hazard statement H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled) while the available data do not allow for sub-categorisation.

10.7 Skin sensitisation

To the knowledge of DE, no studies of the skin sensitising potential of TODI in humans are available. However, skin sensitisation test data in animals summarised in Table 9 below are available which are sufficient for classification and labelling. Therefore, in this case read-across from other diisocyanates is not necessary. Nevertheless it is stressed that all diisocyanates currently classified as respiratory sensitisers in Annex VI to the CLP regulation also are classified as skin sensitisers or, in the case of naphthylene diisocyanate (NDI, CAS 3173-72-6) have data showing their skin sensitisation potential.

Table 9: Summary table of the available animal studies on skin sensitisation for TODI

Method, guideline, deviations	Species, strain, sex, no/group	Test substance, vehicle	Study protocol	Results	Reference
OECD TG 406 (GPMT)/EU B.6 Reliability 2 (reliable with restrictions): Only summary available	Guinea pig, Dunkin-Hartley, female, 10/test group, 5/control	TODI, Arachis oil BP/acetone	Induction *Intradermal (Day 0)* Three pairs of injections: ▪ Freund's Complete Adjuvant (FCA)/ distilled water 1:1, ▪ 0.1% w/v formulation of the test material in arachis oil BP, ▪ 0.1% w/v formulation of the test material in a 1:1 preparation of FCA plus distilled water. *Topical (Day 7)* 50 % w/w TODI in acetone, 48 h, occlusive Challenge (Day 21) Topical, 50% and 25 % w/w TODI in acetone, 24 h, occlusive	80-90% sensitisation rate at both challenge doses of 50 and 25% at all observation time points (24, 48, and 72 h post-challenge) For details, cf. Table 10 Extreme skin sensitiser; Skin Sens. 1A	(Safepharm, 1998)

Table 10: Results obtained in the GPMT test with TODI (Safepharm, 1998)

Reading/hours post-challenge	Group	Conc.	No. with reactions/ total no. in group (%)	Remarks on result
1st/24	Test	25%	8/10	Positive indication of skin sensitisation
	Neg. control	25%	0/5	No indication of skin sensitisation
	Test	50%	9/10	Positive indication of skin sensitisation
	Neg. control	50%	0/5	No indication of skin sensitisation
2nd /48	Test	25%	9/10	Positive indication of skin sensitisation
	Neg. control	25%	0/5	No indication of skin sensitisation
	Test	50%	8/10	Positive indication of skin sensitisation
	Neg. control	50%	0/5	No indication of skin sensitisation
3rd/72	Test	25%	9/10	Positive indication of skin sensitisation
	Neg. control	25%	0/5	No indication of skin sensitisation
	Test	50%	9/10	Positive indication of skin sensitisation
	Neg. control	50%	0/5	No indication of skin sensitisation

In a guinea pig maximisation test (GPMT), TODI produced a 80-90% (8-9/10) sensitisation rate at all challenge concentrations and observation time-points. It was concluded that under the conditions of this assay, TODI was a potent skin sensitiser. For a detailed summary of this study, the reader is referred to Annex I to this dossier (Safepharm, 1998).

10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

While no relevant human data on skin sensitisation caused by TODI were identified, the available GPMT demonstrates the potential of TODI to act as a skin sensitiser with extreme potency in guinea pigs.

10.7.2 Comparison with the CLP criteria

According to the criteria given in Table 3.4.3 of the CLP regulation, skin sensitisers fall into Skin Sens. sub-category 1A based on the results from a GPMT test, if 30% or more of the animals show a positive response

at an intradermal induction concentration of ≤ 0.1%. This criterion is fulfilled for the available GPMT in which at all observation time-points 80-90% of the treated animals showed a positive sensitisation reaction with an intradermal induction concentration of 0.1%. Moreover, according to Table 3.7 of the CLP guidance with a 80-90% sensitisation rate at an intradermal induction concentration of 0.1%, TODI qualifies as an "Extreme Sensitiser" for which the setting of a Specific Concentration Limit (SCL) of 0.001% is recommended in Table 3.9 (ECHA, 2017a).

Table 11: Comparison of experimental results confirming the skin sensitisation potential with TODI in animals with the respective criteria of the CLP regulation and the CLP guidance

Criteria acc. to Table 3.4.3 and Table 3.4.4 of the CLP regulation and Table 3.7 of the CLP guidance		**Reference(s)**	**Sensitisation rate (%)/Intradermal induction dose (%)**	**Resulting Classification**
GPMT				
Skin Sens. 1A, Extreme	≥ 60% responding at ≤ 0.1% intradermal induction dose	(Safepharm, 1998)	80-90/0.1	**Skin Sens. 1A** **Extreme sensitiser** **SCL 0.001% (w/w)**
Skin Sens. 1A, Strong	30% to < 60% responding at ≤ 0.1% intradermal induction dose or ≥ 60% responding at > 0.1 to 1% intradermal induction dose			
Skin Sens. 1B, Moderate	30% to < 60% responding at > 0.1% to 1% intradermal induction dose or ≥ 30% responding at > 1% intradermal induction dose			

10.7.3 Conclusion on classification and labelling for skin sensitisation

Based on the test results in guinea pigs, TODI should be classified as Skin Sens. 1A (hazard statement H317: May cause an allergic skin reaction) and an SCL of 0.001% should be assigned in line with the recommendations in Table 3.9 of the CLP guidance (ECHA, 2017a).

10.8 Germ cell mutagenicity

10.8.1 Evaluation strategy

Some *in vitro* and *in vivo* studies are available to evaluate TODI mutagenicity. However, other data exists on similar substances which can be used to bring useful information for the evaluation of mutagenicity potential of TODI.

Concerning carcinogenicity, no data on TODI is available. The only repeated study available is a 28-day study by oral route which is too short to highlight carcinogenic potential (Anonymous, 1998b).

Therefore, based only on data from TODI, no robust assessment of mutagenic and carcinogenic potential is possible.

Consequently, an evaluation strategy using read-across of human and non-human data from structurally similar substances to the target substance has been performed to assess the potential of TODI to cause germ cell mutagenicity and carcinogenicity. This is described below.

MDI and TDI, commonly used diisocyanates, are classified as Carc. 2 according to CLP Regulation. These substances form MDA and TDA by hydrolysis (in a similar way as TODA is formed from TODI). MDA and

TDA have an harmonized classification as Carc. 1B and Muta. 2 and TODA has an harmonized classification as Carc. 1B. These data suggest that TODI needs to be assessed for the classification of these endpoints.

The approach used by DE for respiratory sensitisation (10.6.2) cannot be used mainly due to the lack of a known mechanism of action linked to the isocyanate group. Moreover, considering the existing harmonised classification of the metabolites substances TODA, MDA and TDA, the DS extends the list of substances included in the evaluation.

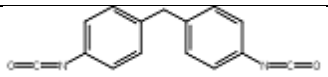
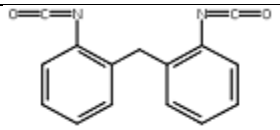
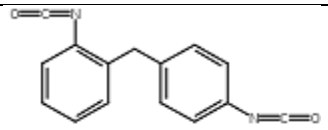
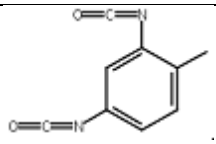
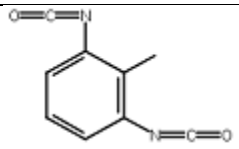
Considering therefore that:

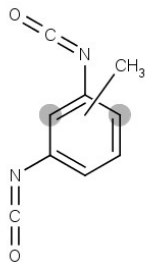
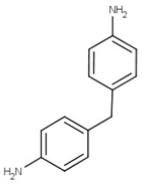
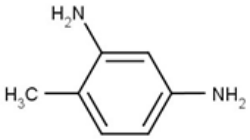
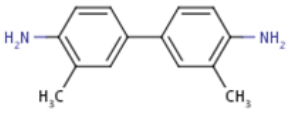
- **no robust dataset is available on mutagenicity of TODI;**
- rapid and complete hydrolysis of isocyanate substances is expected;
- **data on mutagenicity and carcinogenicity are available for other substances which belong to the diisocyanates group and their hydrolysis products;**
- **a mechanism of carcinogenicity for MDI is proposed (increase regenerative proliferation of type-II cells is considered to be the cause of the pre-neoplastic changes in rats, which is a known chronic reaction of rat lung to irritating substances),**

an assessment of the mutagenicity and carcinogenicity of TODI in a weight of evidence approach seems adequate.

Table 612 provides information on the identity and harmonised classification of the source substances.

Table 12: Diisocyanates and metabolites used for evaluation strategy with a harmonised classification (excluding polymers).

EC Name	Abbreviation	EC No.	CAS No.	Structure	Classification
methylenediphenyl diisocyanate	MDI (group)	247-714-0	26447-40-5		Carc 2 H351
4,4'-methylenediphenyl diisocyanate	4,4'-MDI	202-966-0	101-68-8		Carc 2 H351
2,2'-methylenediphenyl diisocyanate	2,2'-MDI	219-799-4	2536-05-2		Carc 2 H351
o-(pisocyanatobenzyl)phenyl isocyanate	2,4'-MDI	227-534-9	5873-54-1		Carc 2 H351
4-methyl-m-phenylene diisocyanate	2,4-TDI	209-544-5	584-84-9		Carc 2 H351
2-methyl-m-phenylene diisocyanate	2,6-TDI	202-039-0	91-08-7		Carc 2 H351

EC Name	Abbreviation	EC No.	CAS No.	Structure	Classification
m-tolylidene diisocyanate	80/20 TDI or 65/35 TDI	247-722-4	26471-62-5		Carc 2 H351
4,4'-methylenedianiline	MDA	202-974-4	101-77-9		Carc 1B H350 Muta 2 H341
4-methyl-m-phenylenediamine	TDA	202-453-1	95-80-7		Carc 1B H350 Muta 2 H341
4,4'-bi-o-toluidine	TODA	204-358-0	119-93-7		Carc 1B H350

As described in the Table 614, all members of the group are monomeric diisocyanates, i.e. they share the structural feature of two isocyanate functional groups, or monomeric diamines, which are the hydrolysis products of the former.

Unfortunately, the classifications of these substances are old, and ground for these classifications cannot be found. However, TDI and MDI were assessed by IARC in monograph volume 71 (1999) and TODA in monograph 1 (1987). TDI isomers are possibly carcinogenic to humans (Group 2B) based on inadequate evidence in humans and sufficient evidence in experimental animals. MDI (industrial preparation) is not classifiable as to its carcinogenicity to humans (Group 3) based on inadequate evidence in humans and limited evidence in experimental animals. TODA was classified possibly carcinogenic to humans (Group 2B) based on no adequate data in humans and sufficient evidence in experimental animals.

Three *in vitro* genetic toxicity studies with TODI (Ames test, Gene cell mutation and chromosomic aberration, with and without simulated metabolic activation) are available, detecting mutations and clastogenic potential (Table 13).

Table 13: Summary table of mutagenicity/genotoxicity tests *in vitro*

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
OECD test guideline 471 (bacterial reverse mutation	TODI with a purity >99.9% The vehicle was DMSO.	The test strains S. typhimurium TA 1535, TA 1537, TA 1538, TA 98, TA 100, TA 102, TA 104 and E. coli WP2 uvr A as well as E. coli WP2 uvr A pKM 101 were examined at 10, 20, 50,	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).	Anonymous / JETOC (1996)

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
assay)		100, 200, 500, 1000, 2000 µg TODI/plate with and without metabolic activation.		
OECD test guideline 476 (In vitro gene mutation test in mammalian cells)	TODI with a purity >99.9% The vehicle used was acetone.	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)	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).	Anonymous (1999a)
Similar to OECD test guideline 473	TODI with a purity of 99.8%. The vehicle was DMSO.	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.	Slightly positive results were obtained with metabolic activation at 0.6 mg/mL.	Anonymous / JETOC (1996)

Moreover, as described in Table 14, two different *in vivo* genetic toxicity studies with TODI detecting mutations and aneugenic activity (UDS and micronuclei) are available.

Table 14: Summary table of mutagenicity/genotoxicity tests in mammalian somatic or germ cells *in vivo*

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
OECD test Guideline 474 (Mammalian Erythrocyte	TODI with a purity > 99.9%. The vehicle was	Albino Crl:CD-1TM (ICR) BR mice (males/females) were exposed by intraperitoneal administration to the test	No significant increase in the frequency of micronuclei in polychromatic erythrocytes of mice was observed under the conditions of the test. The test was	Anonymous (1998a)

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Micronucleus Test)	arachis oil.	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.	considered negative.	
GLP-compliant unscheduled DNA synthesis (DNA damage and/or repair) conducted in accordance with OECD test Guideline 486 (Test with Mammalian Liver Cells in vivo)	TODI with a purity of 99.8% (range 99.5-100%). The vehicle was arachis oil.	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.	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.	Anonymous (1999b)

10.8.2 Short summary and overall relevance of the provided information on germ cell mutagenicity

TODI was tested in three *in vitro* genetic toxicity studies (Ames test, Gene cell mutation and chromosomic aberration, with and without simulated metabolic activation) and two different *in vivo* genetic toxicity studies (UDS and micronuclei).

In these assays, the tested substance TODI has a high purity (typical purity 99.8% with a range of 99.5%-100%).

In the Ames test on 6 bacterial strains, positive results were obtained in the presence of metabolic activation for two strains (TA 98 and TA 1538 at concentrations of 10 to 1000 µg/plate).

In an *in vitro* gene mutation test in mammalian cells, 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).

A Chromosome Aberration Test in CHL cells was performed to assess the mutagenicity potency of TODI. The reported data of this Chromosome Aberration Test shows, that under the experimental conditions described, TODI induced chromosome aberration after metabolic activation at 0.6 mg/mL.

TODI is unstable in water and, therefore, DMSO and acetone were used in *in vitro* tests and arachis oil in *in vivo* tests. The impact of the vehicle on the test results was however not studied such as the stability of TODI in organic solvents and the identity of relevant degradation products.

Diisocyanates were shown to be unstable in aprotic polar solvents such as dimethylsulfoxide (DMSO), resulting in the formation of amines. 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. Even if there is no harmonised classification for mutagenicity, data found in the literature for TODA are equivocal (NTP report n°390; You et al. (1993); HSDB data bank; IARC monography on benzidine and derivatives (2010)). Therefore, no clear conclusion on genotoxicity mechanism can be drawn based on these *in vitro* tests related to TODA.

Concerning *in vivo* tests, TODI will likely react with the vehicle (arachis oil) to form a long fatty chain with TODA in one extremis. This may affect the results of the micronucleus study to an unknown extent (considering that intraperitoneal administration was used), and which will likely affect the results of the UDS study by preventing gastro-intestinal absorption and distribution of the substance to the target tissues. In a 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 (Anonymous, 1998).

In conclusion, 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. Moreover, this method is not considered suitable to assess genotoxic carcinogens as it is considered of low sensitivity.

Even if data are available on TODI, mutagenicity data of structurally similar MDI (a diisocyanate) can be addressed. It appears that most of the available test results of *in vitro* genotoxicity assays for 4,4'-MDI rather reflect the properties of reaction products formed under specific assay conditions than the ones of the parent compound.

A key study was performed in accordance with the OECD 489 to assess the potential of aerosolized 4,4'-MDI to cause DNA damage to the lung and liver of male Wistar rats following a single, 6-hour nose-only inhalation exposure to the concentrations of 2, 5, and 11 mg/m^3 (achieved 2.5, 4.9, and 12 mg/m^3). The tested substance did not cause a significant increase in DNA damage in the lung (as evaluated in cells obtained from bronchoalveolar lavage, BAL cells), liver, and stomach under the test conditions. Therefore, 4,4'-MDI was concluded to be negative for the *in vivo* Comet assay under the test conditions.

It can be concluded that under the key study test conditions MDI did not show genotoxic potential, therefore the concern for genotoxic mode of action was not confirmed for this substance (Anonymous, 2016).

10.8.3 Comparison with the CLP criteria

Toxicological results	**CLP criteria**
No human data is available. Thus, a classification category 1A is not appropriate for TODI.	The classification in Category 1A is based on positive evidence from human epidemiological studies.

Testing *in vitro*: Bacterial reverse mutation assays: Positive Tests involving mammalian cells: - Positive (*In vitro* Mammalian Cell Gene Mutation Test) - Positive (*In Vitro* Mammalian Chromosomal Aberration Test) Testing *in vivo* (experiments in mammals): - Negative (Mammalian Erythrocyte Micronucleus Test) - Negative (UDS test) In conclusion, no positive *in vivo* study are available for TODI. In a grouping approach with other diisocyanates such as structurally similar MDI. It appears that most of the available test results of *in vitro* genotoxicity assays for 4,4'-MDI rather reflect the properties of reaction products formed under specific assay conditions than the ones of the parent compound. MDI was not classified as genotoxic by Estonia in 2018. Then, TODI cannot be classified as a Germ cell mutagen according to CLP Regulation.	The classification in Category 1B is based on: — positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals; or — positive result(s) from *in vivo* somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/genotoxicity tests in germ cells *in vivo*, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or — positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people. The classification in Category 2 is based on: — positive evidence obtained from experiments in mammals and/or in some cases from *in vitro* experiments, obtained from: — somatic cell mutagenicity tests *in vivo*, in mammals; or — other *in vivo* somatic cell genotoxicity tests which are supported by positive results from *in vitro* mutagenicity assays. Note: Substances which are positive in *in vitro* mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification as Category 2 mutagens. If there are positive in vitro data from mammalian mutagenicity assays, structural similarities not sufficient for grouping/read-across may still warrant classification.

10.8.4 Conclusion on classification and labelling for germ cell mutagenicity

In conclusion, the available data do not allow classifying TODI for mutagenicity.

10.9 Carcinogenicity

10.9.1 Short summary and overall relevance of the provided information on carcinogenicity

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

For **MDI**, tumours in the lungs were observed in rodents in a chronic toxicity/carcinogenicity inhalation study. No carcinogenicity studies by oral or dermal route are available.

A reliable 2-year chronic toxicity/carcinogenicity inhalation study in rats Wistar with pMDI (1990) is available where formation of a pulmonary adenocarcinoma in one male as well as pulmonary adenomas, described as rare in this strain, in males (6/60) and females (2/59) exposed to 6.03 mg/m^3 of pMDI was found. A non-genotoxic mode of action for tumours formation was claimed by the Registrant(s) due to observation of chronic inflammation/irritation in the lungs following lifetime inhalation exposure.

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

Feron et al. (2001) performed a comparison of the pulmonary effects described in female rats after chronic inhalation exposure to either polymeric or monomeric MDI (Reuzel et al., 1994 and a chronic inhalation study, 1995). The major pulmonary effects observed included interstitial fibrosis, hyperplasia and bronchiolo-alveolar adenomas, the latter occurring at low incidence in the high exposure groups of both studies (i.e. total inhalation exposures of 17728 and 17575 mg MDI h/m³). Both studies also report the presence of particle-laden macrophages, predominantly in the alveoli close to the alveolar ducts which in some cases, particularly in high dose groups, were associated with areas of fibrosis. It was concluded that the results of the two studies could be combined to serve as a basis for human risk assessment of MDI.

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

Two hypothesis were proposed to explain the carcinogenicity mechanism:

Oncogenesis based on irritation and an epigenetic mechanism,

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), 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. 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 (RAR, 2005). MDI was also evaluated in an *in vivo* mammalian alkaline comet assay (OECD 489) on Wistar rat via inhalation route, with examination of lungs and liver. Negative results were obtained.

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

Considering the reactivity of TODI and the absence of study on metabolism, it can be considered 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.

TODA has a harmonized classification as Carc. 1B H350 and a classification as Carc. 2B by IARC. In a 14-month study of NTP by oral route with 3,3'-dimethylbenzidine dihydrochloride (CAS 612-82-8, analogue to TODA – NTP, 1991) on F344/N rats, 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 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. Tumours 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. 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 and TODA.

10.9.2 Comparison with the CLP criteria

For potential classification on carcinogenicity, criteria from CLP-guidance (ECHA, 2017c) were used. Particularly, as there is no data on the substance itself, criteria for classification based on data from similar substances/read across were applied.

A chemical that has not been tested for carcinogenicity may in certain instances be classified as a carcinogen based on tumour data from a structurally similar chemical with which it is predicted to have similar carcinogenic activity. Such an approach must always be based on a robust and transparent argument to support this supposition. There may also be evidence demonstrating similarity in terms of other important factors such as toxicokinetics or mutagenic activity etc. (OECD 2004, 2005, 2007; Guidance on IR&CSA, Section R.6, QSARs and grouping of chemicals).

In the absence of carcinogenicity data, read-across can be used to support a classification for carcinogenicity when the chemical in question is similar to a known or suspected carcinogen (Category 1A, 1B or 2). The similarity between chemicals is considered in terms of structural features, physico-chemical properties and overall toxicological profile.

In general the chemicals will share a common structural element or functional group (i.e., a toxophore) that has been shown to be integral to the underlying mechanism of carcinogenicity for chemicals with this toxiphore in well conducted studies. These toxiphores can be identified through expert judgement or through automated systems such as (Q)SARs. The read-across should also consider the physico-chemical properties of the chemical and data from other toxicity studies to judge the similarity between the chemicals in terms of bioavailability by relevant routes of exposure and toxicokinetics. The toxicity profile from other studies should also be compared (e.g., acute and repeated-dose toxicity and mutagenicity) and should share similarities in nature and severity. Data from shorter term toxicity studies may be useful, particularly for non-genotoxic carcinogens, to indicate that the chemicals cause the same underlying pathological changes (e.g., hyperplasia), and act via a common mode of action. Any predictions made on the basis of read-across should take into account the totality of data on the chemicals in question, including the physico-chemical properties, toxicological profile, toxicokinetics, structural analogy and the performance of any (Q)SAR models used, in a weight of evidence approach driven by expert judgement. The final decision must be clear, scientifically defensible and transparent.

The specific category depends on the category of the known carcinogen and the degree of confidence in the robustness of the read-across prediction. The category will not be higher than the chemical used to read-across from, but normally may be the same. However a lower category may be applied if the read-across highlights a possible carcinogenic hazard, and thus supports a classification, but there is uncertainty as to the robustness of the read-across prediction or there is evidence, for instance from mechanistic or other studies, that the chemical may be of lower concern for carcinogenicity.

If a chemical is similar to a substance known to be carcinogenic and shares the toxiphore that is considered to be causally related to carcinogenicity, then it is unlikely that there will be sufficient confidence in a prediction of no hazard (for instance based on arguments relating to differences in physico-chemical or steric properties), to justify no classification in the absence of supporting negative experimental data. However, the bioavailability of the toxiphore will need evaluation (Guidance on IR&CSA R.6).

Based on the classification 1B of the hydrolysis product of TODI, TODA, it can be concluded that a classification as category 1B carcinogen could be proposed for TODI.

10.9.3 Conclusion on classification and labelling for carcinogenicity

In this context, a classification as category 1B carcinogen is proposed for TODI according to CLP regulation.

10.10 Reproductive toxicity

Not relevant for this dossier

10.11 Specific target organ toxicity-single exposure

Not relevant for this dossier

10.12 Specific target organ toxicity-repeated exposure

Not relevant for this dossier

10.13 Aspiration hazard

Not relevant for this dossier

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not relevant for this dossier

12 EVALUATION OF ADDITIONAL HAZARDS

Not relevant for this dossier

13 ADDITIONAL LABELLING

According to the CLP regulation, Annex II, section 2.4, the following special rule for supplemental label elements shall apply for mixtures containing m-XDI:

"Unless already identified on the label of the packaging, mixtures containing isocyanates (as monomers, oligomers, prepolymers, etc., or as mixtures thereof) shall bear the following statement:

EUH204 — 'Contains isocyanates. May produce an allergic reaction."

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15 LIST OF ABBREVIATIONS

AB: Antibodies

ADME: Absorption, distribution, metabolism, and excretion

AE: Aerosol

AHR: Airway hyperresponsiveness

AOP: Adverse outcome pathway

BAL(F): Bronchoalveolar lavage (fluid)

BHR: Bronchial hyperresponsiveness

BT: Biuret

CLH: Harmonised classification and labelling

CLP: Classification, labelling, and packaging

DO: Dog

DS: Dossier submitter

DSC: Differential scanning calorimetry

DH: Dunkin-Hartley

ECHA: European Chemicals Agency

ERR: Exposure-Reponse-Relationship

ESH: English smooth-hair

F: Female

FEF_{25-75}: Forced expiratory flow between 25 and 75% of FVC

FEV_1: Forced Expiratory Volume in one second

FEV_1%: FEV_1/FVC x 100

FVC: Forced vital capacity

GLP: Good laboratory practice

GP: Guinea pig

GPSA: Guinea pig serum albumin

HDI: Hexamethylene diisocyanate

HH: Human health

HMDI: "Hydrated MDI", 4'-methylenedicyclohexyl diisocyanate

HO: Head-only

IC: Isocyanurate

IDE: Intradermal

IF: Inflammation

IgE/IgG: Immunoglobulin E/G

INA: Intranasal

INH: Inhalation

IPDI: Isophoronediisocyanate

IPE: Intraperitoneal

IR & CSA: Information requirements and chemical safety assessment

ITR: Intratracheal

IUCL: Only IUCLID summary available

IVE: Intravenous

JEM: Job exposure matrix

LLNA: Local lymph node assay

LOD: Limit of detection

MDI: 4,4'-Methylenediphenyl-diisocyanate

M: Male

MIE: Molecular initiating event

MMF: Maximum mid-expiratory flow

MO: Mouse

NCO: Isocyanate functional group

NDI: 1,5-Naphthylene-diisocyanate

NO: Nose-only

n.s.: Not significant

OA: Occupational asthma

OR: Odds Ratio

OECD: Organization for Economic Co-Operation and Development

OVA: Ovalbumin

PEF(R): Peak expiratory flow (rate)

PHDI: Polymeric HDI

PIPDI: Polymeric IPDI

PMDI: Polymeric MDI

PR: Prevalence ratio

PU: Polyurethane

QSAR: Quantitative Structure-Activity Relationship(s)

RA: Rat

RB: Rabbit

REACH: Registration, evaluation, authorisation and restriction of chemicals

RF: Respiratory function

RR: Relative Risk

RS: Respiratory sensitisation

SCU: Subcutaneous

SS: Skin sensitisation

TDI: Toluyenediisocyanate, mixed isomers, isomer ratio 80:20 (2,4:2,6)

TDI_{UC}: TDI of unclear composition

TMI: Toluylenemono-isocyanate

m-TMXDI: 1,3-Bis(1-isocyanato-1-methyl-ethyl)benzene

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

TOE: Toepad inoculation

TOP: Topical

TWA: Time-weighted average

VP: Vapour

WB: Whole-body