

**Committee for Risk Assessment  
RAC**

Annex 1  
**Background document**  
to the Opinion proposing harmonised classification  
and labelling at EU level of

**2,4,6-triisopropyl-*m*-phenylene diisocyanate**

**EC Number: 218-485-4**  
**CAS Number: 2162-73-4**

CLH-O-0000006862-68-01/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

**Adopted**  
**17 September 2020**



# CLH report

## Proposal for Harmonised Classification and Labelling

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

### International Chemical Identification:

*2,4,6-Triisopropyl-m-phenylene diisocyanate;*

*[TRIDI]*

**EC Number:** 218-485-4

**CAS Number:** 2162-73-4

**Index Number:** n.a.

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## CONTENTS

<b>1</b>	<b>IDENTITY OF THE SUBSTANCE .....</b>	<b>1</b>
1.1	NAME AND OTHER IDENTIFIERS OF THE SUBSTANCE.....	1
1.2	COMPOSITION OF THE SUBSTANCE .....	1
<b>2</b>	<b>PROPOSED HARMONISED CLASSIFICATION AND LABELLING .....</b>	<b>2</b>
2.1	PROPOSED HARMONISED CLASSIFICATION AND LABELLING ACCORDING TO THE CLP CRITERIA .....	2
<b>3</b>	<b>HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING .....</b>	<b>3</b>
<b>4</b>	<b>JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL .....</b>	<b>4</b>
<b>5</b>	<b>IDENTIFIED USES .....</b>	<b>4</b>
5.1	GENERAL .....	4
5.2	CONSUMER USES .....	4
5.3	ARTICLE SERVICE LIFE .....	4
5.4	WIDESPREAD USE BY PROFESSIONAL WORKERS .....	5
5.5	FORMULATION OR RE-PACKING.....	5
5.6	USES AT INDUSTRIAL SITES .....	5
5.7	MANUFACTURE.....	5
<b>6</b>	<b>DATA SOURCES.....</b>	<b>5</b>
<b>7</b>	<b>PHYSICOCHEMICAL PROPERTIES.....</b>	<b>5</b>
<b>8</b>	<b>EVALUATION OF PHYSICAL HAZARDS .....</b>	<b>7</b>
<b>9</b>	<b>TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION) .....</b>	<b>7</b>
<b>10</b>	<b>EVALUATION OF HEALTH HAZARDS.....</b>	<b>7</b>
10.1	ACUTE TOXICITY - ORAL ROUTE .....	7
10.2	ACUTE TOXICITY - DERMAL ROUTE .....	7
10.3	ACUTE TOXICITY - INHALATION ROUTE.....	7
10.4	SKIN CORROSION/IRRITATION .....	7
10.5	SERIOUS EYE DAMAGE/EYE IRRITATION .....	7
10.6	RESPIRATORY SENSITISATION.....	7
10.6.1	<i>Endpoint definition and evaluation strategy .....</i>	<i>7</i>
10.6.2	<i>Justification of the category approach.....</i>	<i>8</i>
10.6.3	<i>Data retrieval, evaluation, and presentation strategy.....</i>	<i>10</i>
10.6.4	<i>Human data.....</i>	<i>10</i>
10.6.5	<i>Animal data.....</i>	<i>11</i>
10.6.6	<i>Short summary and overall relevance of the provided information on respiratory sensitisation .....</i>	<i>16</i>
10.6.7	<i>Comparison with the CLP criteria .....</i>	<i>16</i>
10.6.8	<i>Conclusion on classification and labelling for respiratory sensitisation .....</i>	<i>17</i>
10.7	SKIN SENSITISATION .....	24
10.7.1	<i>Short summary and overall relevance of the provided information on skin sensitisation .....</i>	<i>27</i>
10.7.2	<i>Comparison with the CLP criteria .....</i>	<i>27</i>
10.7.3	<i>Conclusion on classification and labelling for skin sensitisation .....</i>	<i>27</i>
10.8	GERM CELL MUTAGENICITY .....	28
10.9	CARCINOGENICITY .....	28
10.10	REPRODUCTIVE TOXICITY.....	28
10.11	SPECIFIC TARGET ORGAN TOXICITY-SINGLE EXPOSURE .....	28
10.12	SPECIFIC TARGET ORGAN TOXICITY-REPEATED EXPOSURE .....	28
10.13	ASPIRATION HAZARD.....	28
<b>11</b>	<b>EVALUATION OF ENVIRONMENTAL HAZARDS.....</b>	<b>28</b>
<b>12</b>	<b>EVALUATION OF ADDITIONAL HAZARDS .....</b>	<b>29</b>
<b>13</b>	<b>ADDITIONAL LABELLING .....</b>	<b>29</b>
<b>14</b>	<b>REFERENCES .....</b>	<b>29</b>
<b>15</b>	<b>LIST OF ABBREVIATIONS.....</b>	<b>31</b>

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIIISOPROPYL-*M*-PHENYLENE DIISOCYANATE

## 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

<b>Name(s) in the IUPAC nomenclature or other international chemical name(s)</b>	2,4-Diisocyanato-1,3,5-triisopropylbenzene
<b>Other names (usual name, trade name, abbreviation)</b>	Isocyanic acid, 2,4,6-triisopropyl- <i>m</i> -phenylene ester 2,4-Diisocyanato-1,3,5-tris(1-methylethyl)benzene 1,3,5-Triisopropylbenzene 2,4-diisocyanate 2,4,6-Triisopropyl- <i>m</i> -phenylene diisocyanate 2,4,6-Triisopropyl- <i>m</i> -phenylene isocyanate TRIDI
<b>ISO common name (if available and appropriate)</b>	-
<b>EC number (if available and appropriate)</b>	218-485-4
<b>EC name (if available and appropriate)</b>	2,4,6-Triisopropyl- <i>m</i> -phenylene diisocyanate
<b>CAS number (if available)</b>	2162-73-4
<b>Other identity code (if available)</b>	-
<b>Molecular formula</b>	C <sub>17</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub>
<b>Structural formula</b>	
<b>SMILES notation (if available)</b>	CC(C)C1=C(C(=C(C(=C1)C(C)C)N=C=O)C(C)C)N=C=O
<b>Molecular weight or molecular weight range</b>	286.37 g/mol
<b>Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)</b>	-
<b>Description of the manufacturing process and identity of the source (for UVCB substances only)</b>	-
<b>Degree of purity (%) (if relevant for the entry in Annex VI)</b>	-

### 1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

<b>Constituent (Name and numerical identifier)</b>	<b>Concentration range (% w/w minimum and maximum in multi-constituent substances)</b>	<b>Current CLH in Annex VI Table 3.1 (CLP)</b>	<b>Current self- classification and labelling (CLP)</b>
2,4,6-triisopropyl- <i>m</i> -phenylene diisocyanate EC No. 218-485-4 CAS No. 2162-73-4	80 -100	-	Skin Irrit. 2 ; H315 Resp. Sens. 1; H334 STOT SE 3; H335 Acute Tox. 4; H332 Acute Tox. 1; H330 Eye Irrit. 2; H319 Carc. 2; H351 Skin Sens. 1; H317

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIISOPROPYL-*M*-PHENYLENE DIISOCYANATE

**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 TRIDI

	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	2,4,6-triisopropyl- <i>m</i> -phenylene diisocyanate	218-485-4	2162-73-4	Resp. Sens. 1	H334	GHS08 Dgr	H334			
Resulting Annex VI entry if agreed by RAC and COM					Skin Sens. 1	H317		H317			

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIISOPROPYL-M-PHENYLENE DIISOCYANATE

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	Harmonised classification proposed	Yes
Serious eye damage/eye irritation		
Respiratory sensitisation	Hazard class not assessed in this dossier	No
Skin sensitisation		
Germ cell mutagenicity		
Carcinogenicity		
Reproductive toxicity		
Specific target organ toxicity-single exposure		
Specific target organ toxicity-repeated exposure		
Aspiration hazard		
Hazardous to the aquatic environment		
Hazardous to the ozone layer		

### 3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Not applicable

## **RAC general comment**

The Dossier Submitter (DS) noted that according to Article 36 of the CLP regulation, respiratory sensitisation is an endpoint for which Harmonised Classification and Labelling (CLH) is warranted, and skin sensitisation is closely linked to respiratory sensitisation. Namely, all currently known low molecular weight chemical respiratory sensitisers are also skin sensitisers.

The CLH report has been created based on data submitted by the lead registrant in the REACH registration dossier for 2,4,6-triisopropyl-*m*-phenylene diisocyanate (TRIDI), and further relevant data were retrieved as part of a general literature search in the context of the restriction proposal for diisocyanates recently submitted to ECHA by the Dossier Submitter (DS). In addition, SCOPUS and PubMed databases were searched for relevant literature, for the period 2015-2017 and the information found was added to the initial CLH report.”.

RAC agrees with the DS’s proposal to add the following EUH statement: EUH204; Contains isocyanates. May produce an allergic reaction.

## **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.

## **5 IDENTIFIED USES**

A summary of the information available on ECHA’s public website (accessed 2017-12-14) is given below<sup>1</sup>.

### **5.1 General**

This substance is manufactured and/or imported in the European Economic Area in 100 - 1000 tonnes per year. This substance is used at industrial sites and in manufacturing.

### **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**

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. ECHA has no public registered data indicating whether or into which articles the substance might have been processed.

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<sup>1</sup> 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.



#### 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 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. ECHA has no public registered data on the types of manufacture using this substance. This substance is used in the following activities or processes at workplace: transfer of chemicals, closed processes with no likelihood of exposure, closed, continuous processes with occasional controlled exposure, closed batch processing in synthesis or formulation and laboratory work. Release to the environment of this substance can occur from industrial use: as an intermediate step in further manufacturing of another substance (use of intermediates) and for thermoplastic manufacture.

#### 5.7 Manufacture

This substance is used in the following activities or processes at workplace: transfer of chemicals, closed processes with no likelihood of exposure, closed, continuous processes with occasional controlled exposure, closed batch processing in synthesis or formulation, transfer of substance into small containers and laboratory work. Release to the environment of this substance can occur from industrial use: manufacturing of the substance.

### 6 DATA SOURCES

This report has been created based on the data submitted by the lead registrant in the REACH registration dossier for TRIDI. In addition, further relevant data on TRIDI and related diisocyanates (cf. section 10.6) were retrieved as part of a general literature search in the context of the restriction proposal for diisocyanates recently submitted to ECHA by the DS.

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	Liquid	Sensorial observation
Melting/freezing point	No melting of crystalline subcomponents between -90 °C and 50 °C; Cooling run: no crystallisation; glass transition temperature (amorphous components) at -56 °C.	Experimental result [EU Method A.1 (Melting / Freezing Temperature): differential scanning calorimetry (DSC)]
Boiling point	305.07 °C at 99.8 kPa	Experimental result [VP 2/A: differential scanning calorimetry]
Relative density	1.046 (at 20 °C)	Experimental result

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIISOPROPYL-*M*-  
PHENYLENE DIISOCYANATE

Property	Value	Comment (e.g. measured or estimated)
		[ASTM D 7042; equivalent to ISO 3104 or ASTM D445]
<b>Vapour pressure</b>	0.19 Pa (at 20 °C)	Estimated value [EEC-directive 92/69/EEC, method A.4. (Grain Watson estimation; calculation based on the lowest possible boiling temperature)]
<b>Surface tension</b>	N.a. (water solubility is below 1 mg/L at 20 °C; based on structure, surface activity is not expected)	-
<b>Water solubility</b>	N.a. (substance reacts with water; hydrolytically unstable)	-
	0.005141 mg/L (at 25 °C) (based on a estimated logPow value of 7.56)	Estimated value [QSAR estimation: WSKOW v1.41 (EPIWIN software by US-EPA)]

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIIISOPROPYL-*M*-PHENYLENE DIISOCYANATE

Property	Value	Comment (e.g. measured or estimated)
<b>Partition coefficient n-octanol/water</b>	LogPow: 7.56	Estimated value [QSAR estimation: KOWWIN v1.67 (EPIWIN software by US-EPA)]
<b>Granulometry</b>	N.a. (liquid)	-
<b>Stability in organic solvents and identity of relevant degradation products</b>	N.a. (stability in organic solvents is not a critical property of the substance)	-
<b>Dissociation constant</b>	N.a. (hydrolytically unstable)	-
<b>Viscosity</b>	Dynamic viscosity (at 20 °C) = 59.35 ± 0.37 mPa s Dynamic viscosity (at 40 °C) = 19.82 ± 0.05 mPa s	Experimental result [OECD Test Guideline 114 (Viscosity of Liquids): rotational viscometer (dynamic)]

## 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 TRIDI are available. In the registration dossier, the lead registrant has provided a general statement pointing out the assumed potential of TRIDI for rapid hydrolysis, fast absorption via inhalation and low dermal absorption by reference to the structural analogue toluylene diisocyanate (TDI). On the other hand, the potential for respiratory and skin sensitisation is acknowledged (Chemservice, 2011). Based on the latter, the DS concludes that whatever the amount of absorption which may occur via the dermal or inhalation routes is able to cause protein-hapten complex formation to such a degree that sensitisation can take place.

## 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).

## ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIIISOPROPYL-M-PHENYLENE DIISOCYANATE

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 TRIDI, the substance addressed by this dossier, data with respect to RS are scarce. For TRIDI, 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 TRIDI. 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))

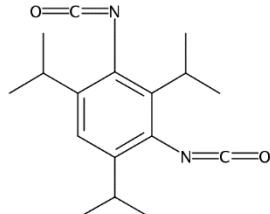

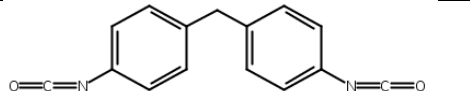
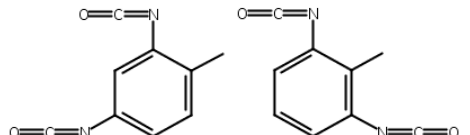
The approach relates to RAAF Scenario 6 (human health), i.e. the read-across hypothesis for the category is based on different compounds which have qualitatively similar properties, with no relevant variations in properties observed among source substances and the same strength predicted for the target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

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 TRIDI has been characterised above. Table 6 provides information on the identity of the category source substances HDI, MDI, and TDI.

**Table 6: Overview of target and category source substances used for read-across to m-TMXDI**

EC Name; trivial name used in this report	EC No. CAS no.	CLH for sensitisation (Annex VI to CLP)	Structure
2,4,6-Triisopropyl-m-phenylene diisocyanate; TRIDI	218-485-4 2162-73-4	-	
Hexamethylene diisocyanate; HDI	212-485-8 822-06-0	Resp. Sens. 1 Skin Sens. 1	
4,4'-Methylenediphenyl diisocyanate; MDI <sup>§</sup>	202-966-0 101-68-8		
m-Tolyldiene diisocyanate (80/20 mixture of 2,4-TDI and 2,6-TDI isomers); TDI <sup>§</sup>	247-722-4 26471-62-5		

<sup>§</sup> 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.

<sup>2</sup> 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. It is also evident that 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 Annex 1.

### 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 1.

### 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 electrophils 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.

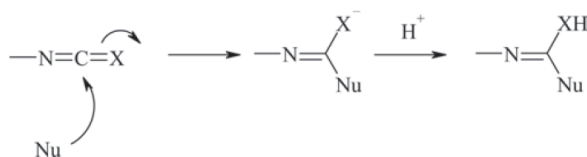


Figure 1: Acylation reaction for isocyanates (X = oxygen). Reproduced from (Enoch et al., 2011)

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.

## ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIIISOPROPYL-M-PHENYLENE DIISOCYANATE

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, the DS 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

The DS 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, the DS 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. The DS 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 the DS as follows:

- Identify all studies in humans and animals for TRIDI, 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<sup>3</sup>), however, since the definition from the CLP regulation given 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 TRIDI).
- 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 TRIDI).
- 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).

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

## ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIIISOPROPYL-M-PHENYLENE DIISOCYANATE

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<sub>1</sub>), 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 TRIDI

No relevant data for TRIDI 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 TRIDI 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).

## ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRISOPROPYL-M-PHENYLENE DIISOCYANATE

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 TRIDI 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 TRIDI 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 the DS, 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



## ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIIISOPROPYL-*M*-PHENYLENE DIISOCYANATE

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 linguistic 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	
TRIDI	-	-	-	-
HDI	-	3	-	3
MDI	6	-	6	12
TDI	14	7	-	21
<b>Total</b>	20	10	6	36

### 10.6.5.1 Animal data for the target substance TRIDI

For TRIDI, 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 15 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
<b>Guinea pigs</b>												
ESH	F	TDI	-	-	VP	HO	8	2	3	3	AB	(Karol, 1983)
			IDE	TDI-GPSA			12	5		5	SS	
			INH	TDI-GPSA/TMI-GPSA			8				RF	
			12									
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		VP								
		TDI-GPSA										

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRISOPROPYL-*M*-PHENYLENE DIISOCYANATE

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
DH	F	MDI	INH	MDI	AE	NO	16	5	3	18	AB	(Rattray et al., 1994)
?	?	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	1344	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)
<b>Mice</b>												
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)
<b>Rats</b>												
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  $\geq 0.12$  ppm TDI, again specific antibodies were found (at concentrations  $\geq 0.36$  ppm); moreover, contact hypersensitivity was observed as a result of intradermal challenge with TDI-guinea pig serum albumin conjugate (TDI-GPSA) at concentrations of  $\geq 0.12$  ppm. Finally, following a specific bronchial provocation challenge with TDI-GPSA, a significant increase in respiratory rate (RR) was reported at  $\geq 0.36$  ppm (Karol, 1983).

Botham et al. (1988) reported the production of TDI-specific IgE- and IgG<sub>1</sub> 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<sup>3</sup> MDI vapour and found an increased production of specific IgG<sub>1</sub> 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  $\geq 0.12$  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  $\geq 0.02$  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  $\geq 0.2$  ppm (Aoyama et al., 1994).

## ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIISOPROPYL-M-PHENYLENE DIISOCYANATE

Pauluhn sensitised guinea pigs via inhalation by a single 15 min exposure to 135 mg MDI/m<sup>3</sup> or to 45 mg TDI/m<sup>3</sup>. Upon challenge with the same diisocyanate, either unbound or conjugated to GPSA at approximate concentrations of 12 (MDI) or 4 mg/m<sup>3</sup>, 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).

Ratray and co-workers reported a slight increase in IgG<sub>1</sub> levels in female Dunkin-Hartley guinea pigs 18 d after five 3 h/d exposures to atmospheres containing ca. 20 mg MDI/m<sup>3</sup> (Ratray et al., 1994).

In another study in guinea pigs, the animals were exposed via inhalation to 132 mg MDI aerosol/m<sup>3</sup> 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<sup>3</sup>, 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/m<sup>3</sup>). 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<sup>3</sup>) 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<sub>1</sub> 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<sup>4</sup>. 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

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<sup>4</sup> 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.

## ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIIISOPROPYL-M-PHENYLENE DIISOCYANATE

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).

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 TRIDI, 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 TRIDI 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 criteria 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).

## ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIIISOPROPYL-M-PHENYLENE DIISOCYANATE

Since for TRIDI, 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 TRIDI 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 analogue 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 and
- a category approach using read-across of human and non-human data from the source substances HDI, MDI, and TDI to the target substance TRIDI,

the DS concludes that TRIDI 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.

## RAC evaluation of respiratory sensitisation

### Summary of the Dossier Submitter’s proposal

The DS proposed to classify 2,4,6-triisopropyl-*m*-phenylene diisocyanate (TRIDI) as Resp. Sens. 1; H334. Currently, TRIDI does not have a harmonised classification.

There are no specific human or animal data on respiratory sensitisation available for TRIDI. Therefore, the proposed harmonised classification was based on read across.

Only the three most commonly used source substances were used for read across, as most of the published literature on diisocyanates is related to these: hexamethylene diisocyanate (HDI; CAS number 822-06-0), 4,4'-methylenediphenyl diisocyanate (MDI, CAS number 101-68-8) and *m*-tolylidene diisocyanate (TDI; CAS number 26471-62-5; 80/20 mixture of 2,4-TDI and 2,6-TDI isomers). They all have harmonised classifications as Resp. Sens. 1; H334. In addition, the DS noted that several other diisocyanates have also been self-classified as respiratory sensitisers. The DS was not aware of any monomeric diisocyanates for which data convincingly show that the substance is not a respiratory (and skin) sensitiser. For HDI, MDI

and TDI, there is an abundance of publicly available human and non-human data.

**Human data for the read across source substances HDI, MDI and TDI**

More than 100 case reports and epidemiological studies were evaluated by the DS, an overview is available in Annex I of the CLH report (tables 2-8). The literature consistently demonstrates the potential of HDI, MDI and TDI to cause respiratory sensitisation in humans.

According to the DS, the case reports provide overwhelming proof that humans exposed to the source substances may suffer from a broad spectrum of respiratory effects including asthma and pathological changes of the airways. In addition, 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 enable an assessment of the frequency of occurrence of respiratory sensitisation in the human population because they feature only a small number of patients. It is also not known which fraction of all exposed individuals is affected and which fraction of the affected is reported. The case reports are therefore not suited for potency sub-categorisation. In addition, no harmonised approach for sub-categorising respiratory sensitisers is currently available.

According to the DS, despite the large number of available epidemiological studies, none of them are suitable for deriving a reliable Exposure-Response-Relationship 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. In addition, both dermal exposure and inhalation peak exposure are likely to contribute to the induction of sensitisation.

Patients with diisocyanate-induced asthma display both early (seconds to minutes) and delayed (up to several hours) hypersensitivity. However, the prevalence of delayed responses is as high as 70% (Niimi *et al.*, 1996). A particular concern is 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. In addition, patients often develop persistent bronchial hyper-responsiveness (often also the more general term "airway hyper-responsiveness/hyper-reagibility" 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).

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

There are no internationally recognised *in vivo* test methods for identification of respiratory sensitisation. Animal studies were considered by the DS to be relevant for the classification only if the induction route was truly via the inhalation route. Studies using other routes of induction or mixed routes were discarded. Furthermore, studies were considered unreliable and excluded from the assessment in case any of the following information was missing or incomplete: identity of the test substance, physical state of the test substance as applied (aerosol or vapour), inhalation route protocol followed (whole-body or head-/nose-only), confirmation of the presence of a negative control, and number of animals per dose group. In addition, the DS noted that animal study designs for respiratory sensitisation have been manifold, involving a variety of species, protocols, and target endpoints, and a standardised

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIIISOPROPYL-M-PHENYLENE DIISOCYANATE

protocol with regulatory acceptance is still missing. Therefore, the DS noted that a negative result from an animal experiment on respiratory sensitisation 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 by the DS for further processing. Where several experiments were reported in one study report, only those with effects were processed further.

For HDI, MDI and TDI, 36 experiments from 18 study reports qualified for further evaluation and are summarised in the table below. These experiments were performed in guinea pigs (6 with MDI, 14 with TDI), mice (3 with HDI, 7 with TDI) and rats (6 with MDI). The DS concluded that inhalation exposure to the three source substances was shown to trigger respiratory sensitisation as demonstrated by the production of specific antibodies, impairment of respiratory function, and characteristic inflammation markers in bronchoalveolar lavage fluid (BALF). Observed respiratory symptoms (increased respiratory rate, effects on respiratory flow, laboured breathing etc.) resemble those seen in humans with asthma. In addition, skin sensitisation has also been observed following induction via inhalation route. However, 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.

**Table.** Summary by the DS of the animal studies evaluating the potential of the source substances HDI, MDI, and TDI to cause respiratory sensitisation in rodents following exposure via the inhalation route (sorted by species and year; originally Table 10 in the CLH report).

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIIISOPROPYL-M-PHENYLENE DIISOCYANATE

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
<b>Guinea pigs</b>												
ESH	F	TDI	-	-	VP	HO	8	2	3	3	AB	(Karol, 1983)
			IDE	TDI-GPSA			12	5		5	SS	
			INH	TDI-GPSA/ TMI-GPSA			8				RF	
							12					
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)
		TDI		MDI-GPSA								
DH	F	MDI	INH	MDI	AE	NO	16	5	3	18	AB	(Rattray et al., 1994)
?	?	MDI	INH	MDI	AE	NO	16	1	0.25	21/ 28	AB/RF	IUCL: (Bayer, 1995)
DH	F	TDI	-	-	VP	WB	20	1	48	3	RF	(Gagnaire et al., 1996)
									168	8		
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)



ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIISOPROPYL-M-PHENYLENE DIISOCYANATE

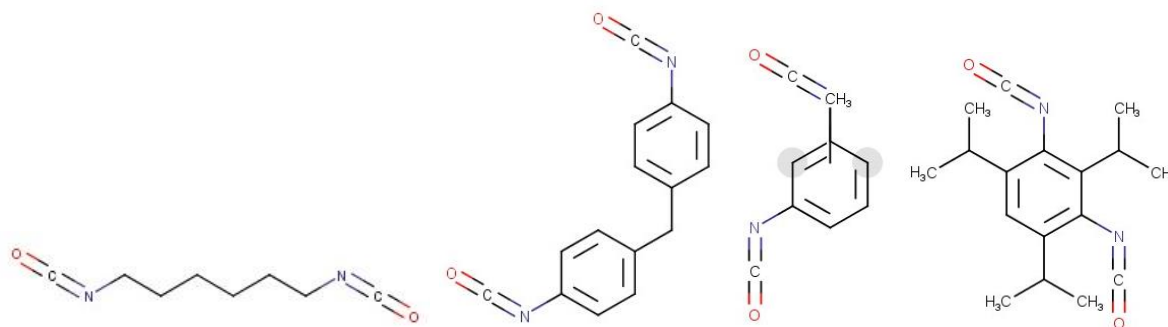
Strain	Sex	“Induction” Agent	“Elicitation” Route	“Elicitation” Agent	Physical state	Inhalation type	Animals/group	No. of “induction” exposures	Hours/exposure	Total days	Critical effect	Reference		
<b>Mice</b>														
C57BL/6	F	TDI	INH	TDI	VP	NO	5	30	4	56	AB/IF/RF	(Matheson et al., 2005a)		
C57BL/6	F	TDI	INH	TDI	VP	HO	5	1	2	1	AB/IF/RF	(Matheson et al., 2005b)		
								30	4	56				
BALB/c	F	TDI	INH	TDI	VP	WB	6-8	1	4	14	AB/IF	(Ban et al., 2006)		
BALB/c	M	HDI	-	-	VP	NO	6	3	0.75	5	IF	(Arts et al., 2008; de Jong et al., 2009)		
									1.5					
		3												
		0.75												
		1.5												
3														
<b>Rats</b>														
Wistar	F	MDI	-	-	AE	WB	20	8	17	610	RF	IUCL: (Hoymann et al., 1995)		
								12					436	
								80			65		728	IF
											260			
											436			
80	520													

AB=antibodies; AE=aerosol; DH=Dunkin-Hartley; ESH=English smooth-hair; HO=head-only; IDE=intradermal; IF=inflammation; INH=inhalation; IPE=intraperitoneal; NO=nose-only; RF=respiratory function; SS=skin sensitisation; TOP=topical; WB=whole-body; VP=vapour

**Read across from HDI, MDI and TDI to TRIDI**

The read across was founded on the category approach and structural similarity to monomeric diisocyanates, according to the ECHA Read Across Assessment Framework (RAAF) Scenario 6 (human health). In this scenario, the read across hypothesis was based on different compounds that have qualitatively similar properties, with no relevant variations in properties observed among source substances and the same strength predicted for the target substance. All assessment elements (AEs) relevant to the RAAF Scenario 6 (human health) were considered by the DS.

The three source substances and the target substance TRIDI, all share the structural feature of two isocyanate functional groups, while the part of the molecular structure that links the two isocyanate groups are variable (see figure below).



**Figure.** The structures of HDI, MDI, TDI and TRIDI, respectively, from left to right.

The isocyanate functional group is a well-known structural alert for respiratory sensitisation, and therefore also commonly used in respiratory sensitisation prediction tools. It has been hypothesised, and to a certain degree shown, that similarly to skin sensitisation, covalent binding of electrophiles to proteins in the lung marks a molecular initiating event and that for isocyanates, an acylation type reaction between electrophilic N=C=O functional groups and nucleophilic protein moieties may occur, leading to protein adducts (Enoch *et al.*, 2009; 2011; 2014). Furthermore, it has been shown that a higher occupational asthma hazard is caused by low molecular weight agents that can form two or more bonds with human macromolecules, and that e.g. diisocyanates rank high in this respect (Agius *et al.*, 2000). The potential reactivity of HDI, MDI and TDI towards amino acids has been shown in chemico (Lalko *et al.*, 2013).

Moreover, the DS noted that at least the qualitative respiratory sensitising potential of HDI, MDI and TDI appears to be dependent on the diisocyanate structure. The variations in the molecular structure connecting the two isocyanate groups are of less importance, although they may have an impact on the physical-chemical and ADME properties of the compounds, and therefore influence their relative potencies (not addressed in the dossier).

### Comments received during consultation

Two MSCAs commented during the consultation, both supported the proposed classification as Resp. Sens. 1; H334.

### Assessment and comparison with the classification criteria

There are no validated test methods for respiratory sensitisation, and therefore compounds are typically classified for Resp. Sens. based on human data, with supportive evidence from e.g. animal data. Furthermore, there is no specific human or animal data available on TRIDI that could be used to assess respiratory sensitisation. However, data on skin sensitisation from closely related substances (discussed below) demonstrates that TRIDI has sensitising properties.

For the source substances HDI, MDI and TDI, numerous case reports and epidemiological studies consistently demonstrate potential to cause respiratory sensitisation in humans. *In vivo* studies provide additional support. Consequently, all three source substances have existing harmonised classification as Resp. Sens. 1; H334, as do also many other diisocyanates. Current mechanistic knowledge on the effects of diisocyanates shows that the effects depend

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIISOPROPYL-M-PHENYLENE DIISOCYANATE

on the diisocyanate group, while the rest of the molecular structure can vary considerably. In other words, the diisocyanate structure itself is widely considered an alert for respiratory sensitisation.

For TRIDI, the read across performed by the DS considers all of the AEs relevant for scenario 6 of the RAAF (Appendix F).

The CLP criteria for classification of a substance as the respiratory sensitiser are the following:

**Hazard category and sub-categories for respiratory sensitisers**

Category	Criteria
Category 1	Substances shall be classified as respiratory sensitisers (Category 1) where data are not sufficient for sub-categorisation in accordance with the following criteria:
Category	Criteria
	(a) if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity; and/or (b) if there are positive results from an appropriate animal test.
Sub-category 1A:	Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitisation rate in humans based on animal or other tests <sup>(1)</sup> . Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitisation rate in humans based on animal or other tests <sup>(1)</sup> . Severity of reaction may also be considered.

In addition, CLP Regulation, Annex I, section 3.4.2.1.2.3 states that the evidence required to demonstrate respiratory sensitisation 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).

## ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIIISOPROPYL-M-PHENYLENE DIISOCYANATE

Regarding *in vivo* studies, section 10.6.5 of the same Annex states: "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").

Overall, RAC considers the weight of evidence assessment by the DS adequate. In addition, RAC agrees with the justification for a category approach using read across (based on human and non-human data) from the known Cat. 1 respiratory sensitisers HDI, MDI and TDI to the target substance TRIDI. The read across by the DS is acceptable and performed according to RAAF. RAC also agrees that it is not possible to sub-sub-categorise TRIDI into 1A or 1B, as no reliable data on the potency of either TRIDI or the source substances HDI, MDI or TDI are available.

In conclusion, RAC agrees with the DS that classification as **Resp. Sens. 1**; H334 is warranted for TRIDI.

### 10.7 Skin sensitisation

To the knowledge of the DS, there are no data in humans or animals demonstrating the potential of TRIDI to cause skin sensitisation. Above, for the endpoint respiratory sensitisation, already a category read-across approach to the three most commonly marketed diisocyanates has been applied. A justification for this read-across approach has been given above (section 10.6.2), which in much the same way applies to skin sensitisation and is therefore not repeated here.

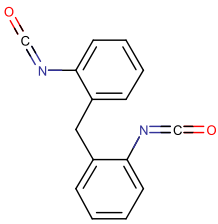
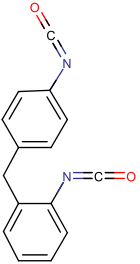
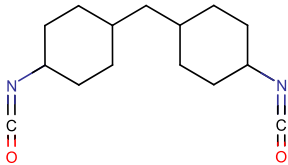
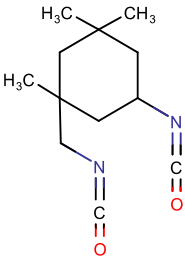
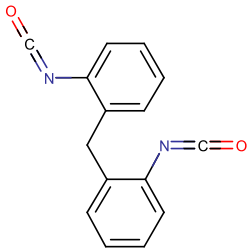
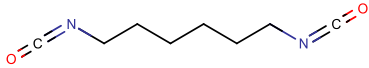
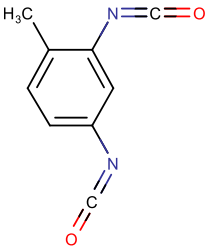
Table 9 shows that not only HDI, MDI, and TDI, but in fact 14 out of 17 diisocyanates currently listed as respiratory sensitisers in CLP Annex VI are also classified as skin sensitisers. In addition, in parallel with the present dossier, the German CA has prepared four further CLH dossiers demonstrating – based on substance-specific data - that the diisocyanates m-TMXDI (EC 220-474-4), m-XDI (EC 222-852-4), TODI (EC 202-112-7), and NDI (EC 221-641-4, which is in fact the only one of the three substances being already included in Annex VI, but only with CLH for RS) are all strong or even extreme skin sensitisers in addition to being respiratory sensitisers.

As has already been stated in section 10.6.2 above, the available evidence demonstrates that the presence of two isocyanate groups already sufficiently indicates sensitisation potential, whereas the nature of the chemical structural moiety connecting the two isocyanate groups is of less importance, at least for the monomeric diisocyanates listed in Table 9.

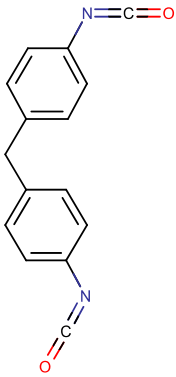
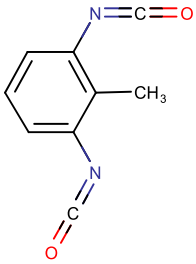
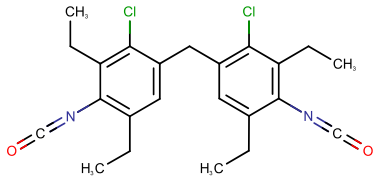
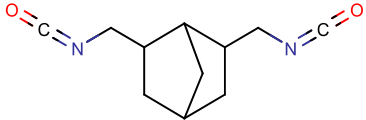
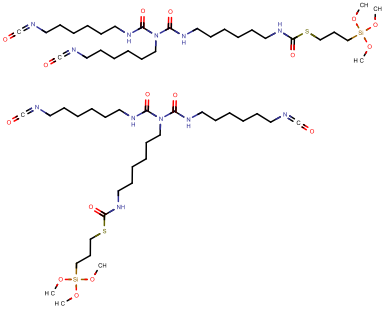
Table 9: List of current entries in Annex VI of the CLP regulation for diisocyanates with classification as both Resp. Sens. 1 and Skin Sens. 1

EG	CAS	Structure	Name	Index No.
247-722-4	26471-62-5		m-tolylidene diisocyanate; toluene-diisocyanate	615-006-00-4

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIISOPROPYL-*M*-PHENYLENE DIISOCYANATE

EG	CAS	Structure	Name	Index No.
247-714-0	26447-40-5		methylenediphenyl diisocyanate	615-005-00-9
227-534-9	5873-54-1		o-(p-isocyanatobenzyl)phenyl isocyanate; diphenylmethane-2,4'-diisocyanate	615-005-00-9
225-863-2	5124-30-1		4,4'-methylene di(cyclohexyl isocyanate); dicyclohexylmethane-4,4'-di-isocyanate	615-009-00-0
223-861-6	4098-71-9		3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate; isophorone di-isocyanate	615-008-00-5
219-799-4	2536-05-2		2,2'-methylene diphenyl diisocyanate; diphenylmethane-2,2'-diisocyanate	615-005-00-9
212-485-8	822-06-0		hexamethylene di-isocyanate	615-011-00-1
209-544-5	584-84-9		4-methyl-m-phenylene diisocyanate; toluene-2,6-di-isocyanate	615-006-00-4

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIISOPROPYL-*M*-PHENYLENE DIISOCYANATE

EG	CAS	Structure	Name	Index No.
202-966-0	101-68-8		4,4'-methylenediphenyl diisocyanate; diphenylmethane-4,4'-diisocyanate	615-005-00-9
202-039-0	91-08-7		2-methyl-m-phenylene diisocyanate; toluene-2,4-diisocyanate	615-006-00-4
420-530-1	-		4,4'-methylene bis(3-chloro-2,6-diethylphenylisocyanate)	615-045-00-7
411-280-2	74091-64-8		2,5-bis-isocyanatomethylbicyclo[2.2.1]heptane	615-029-00-X
402-290-8			S-(3-trimethoxysilyl)propyl 19-isocyanato-11-(6-isocyanatohexyl)-10,12-dioxo-2,9,11,13-tetraazanonadecanethioate	607-184-00-7

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

The DS concludes that there is sufficient evidence from structural analogue diisocyanates to classify TRIDI as a skin sensitiser. It is however not possible to assign a sub-category for potency. It is stressed that also the lead registrant for this substance has self-classified TRIDI as Skin Sens. 1 in the C&L Inventory.

### 10.7.2 Comparison with the CLP criteria

Article 5, 1. c) of the CLP regulation foresees the possibility to use “any other information generated in accordance with section 1 of Annex XI to Regulation (EC) No 1907/2006” for “the purposes of determining whether the substance entails a physical, health or environmental hazard”. Since Annex XI inter alia allows for read-across assessments, the approach followed in this dossier (in light of the absence of any experimental data for TRIDI) is covered by the legal text.

### 10.7.3 Conclusion on classification and labelling for skin sensitisation

Based on read-across to a number of diisocyanates TRIDI should be classified as Skin Sens. 1 (hazard statement H317: May cause an allergic skin reaction).

## RAC evaluation of skin sensitisation

### Summary of the Dossier Submitter’s proposal

Since no information on the skin sensitising potential of TRIDI in humans or animals is available, the DS applied read across approach, as they did for respiratory sensitisation endpoint.

Read across approach is based on the category approach and structural similarity to monomeric diisocyanates, according to the ECHA RAAF Scenario 6 (human health). The read across hypothesis is based on different compounds that have qualitatively similar properties, with no relevant variations in properties observed among source substances and the same strength predicted for the target substance.

The justification for the read across for respiratory sensitisation endpoint provided in the sections above (*RAC evaluation of respiratory sensitisation*) applies in much the same way to skin sensitisation. Namely, the available evidence demonstrates that the presence of two isocyanate groups already sufficiently indicates sensitisation potential, whereas the nature of the chemical structure connecting the two isocyanate groups is of less importance. The three most commonly used diisocyanate substances, which all have harmonised classifications as Resp. Sens. 1; H334, and Skin. Sens. 1; H317, were used as source substances, because most of the published literature on diisocyanates is related to these (HDI, MDI and TDI). In addition, as shown in Table 9 of the CLH Report, there are more diisocyanates that are classified both as Resp. Sens. 1 and Skin Sens. 1 (including o-(p-isocyanatobenzyl)phenyl isocyanate, 4,4'-methylenedi(cyclohexyl isocyanate), 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, 4-methyl-m-phenylene diisocyanate, 2-methyl-m-phenylene diisocyanate, 4,4'-methylene bis(3-chloro-2,6-diethylphenylisocyanate), 2,5-bis-isocyanatomethylbicyclo[2.2.1]heptane, S-(3-trimethoxysilyl)propyl 19-isocyanato-11-(6-isocyanatohexyl)-10,12-dioxo-2,9,11,13-tetraazanonadecanethioate).

The DS concluded that there is sufficient evidence from structural analogue diisocyanates to classify TRIDI as a skin sensitiser, and that it should be classified as **Skin Sens. 1**; H317. It is, however, not possible to assign a sub-category for potency due to a lack of reliable data that would allow sub-categorisation. The DS noted that also the lead registrant for this substance

has self-classified TRIDI as Skin Sens. 1 in the C&L Inventory.

### **Comments received during consultation**

Two comments were received during the consultation (from MSCAs), both supportive of the DS's proposal.

### **Assessment and comparison with the classification criteria**

RAC notes that in addition to read across from the diisocyanates mentioned above, RAC proposed to classify m-XDI (EC 222-852-4) and NDI (EC 221-641-4) as strong or even extreme skin sensitizers, based on substance-specific animal data. Furthermore, in the REACH Registration dossier, a QSAR analysis was presented (OECD Toolbox 2.2). From this, TRIDI has been predicted as a skin sensitizer, with a reliability score of 2 (reliable with restrictions). Namely, the target chemical was not in the applicability domain because of its logK<sub>ow</sub>. However, the REACH Registrant considered that the similarity of category members regarding protein binding mechanisms was sufficiently demonstrated because the isocyanate functional group is crucial for exerting their sensitization activity and therefore they considered the prediction to be meaningful and acceptable.

In conclusion, RAC agrees with the DS that there is sufficient evidence from structural analogue diisocyanates to classify TRIDI as a skin sensitizer, and that it should be classified as **Skin Sens. 1**.

RAC also agrees that available data do not allow for sub-classification. Specific concentration limit was not proposed either.

### **10.8 Germ cell mutagenicity**

Not relevant for this dossier

### **10.9 Carcinogenicity**

Not relevant for this dossier

### **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 TRIDI:

*“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.’”*

### 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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## ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIIISOPROPYL-M-PHENYLENE DIISOCYANATE

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## ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIIISOPROPYL-M-PHENYLENE DIISOCYANATE

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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

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2,4,6-TRIIISOPROPYL-*M*-PHENYLENE DIISOCYANATE

CLP: Classification, labelling, and packaging	IUCL: Only IUCLID summary available	RS: Respiratory sensitisation
DO: Dog	IVE: Intravenous	SCU: Subcutaneous
DS: Dossier submitter	JEM: Job exposure matrix	SS: Skin sensitisation
DSC: Differential scanning calorimetry	LLNA: Local lymph node assay	TDI: Toluyenediisocyanate, mixed isomers, isomer ratio 80:20 (2,4:2,6)
DH: Dunkin-Hartley	LOD: Limit of detection	TDI <sub>UC</sub> : TDI of unclear composition
ECHA: European Chemicals Agency	MDI: 4,4'-Methylenediphenyl-diisocyanate	TMI: Toluylenemono-isocyanate
ERR: Exposure-Reponse-Relationship	M: Male	m-TMXDI: 1,3-Bis(1-isocyanato-1-methyl-ethyl)benzene
ESH: English smooth-hair	MIE: Molecular initiating event	TOE: Toepad inoculation
F: Female	MMF: Maximum mid-expiratory flow	TOP: Topical
FEF <sub>25-75</sub> : Forced expiratory flow between 25 and 75 % of FVC	MO: Mouse	TWA: Time-weighted average
FEV <sub>1</sub> : Forced Expiratory Volume in one second	NCO: Isocyanate functional group	VP: Vapour
FEV <sub>1</sub> %: FEV <sub>1</sub> /FVC x 100	NDI: 1,5-Naphthylene-diisocyanate	WB: Whole-body
FVC: Forced vital capacity	NO: Nose-only	
GLP: Good laboratory practice	n.s.: Not significant	
GP: Guinea pig	OA: Occupational asthma	
GPSA: Guinea pig serum albumin	OR: Odds Ratio	
HDI: Hexamethylene diisocyanate	OECD: Organization for Economic Co-Operation and Development	
HH: Human health	OVA: Ovalbumin	
HMDI: "Hydrated MDI", 4'-methylenedicyclohexyl diisocyanate	PEF(R): Peak expiratory flow (rate)	
HO: Head-only	PHDI: Polymeric HDI	
IC: Isocyanurate	PIPDI: Polymeric IPDI	
IDE: Intradermal	PMDI: Polymeric MDI	
IF: Inflammation	PR: Prevalence ratio	
IgE/IgG: Immunoglobulin E/G	PU: Polyurethane	
INA: Intranasal	QSAR: Quantitative Structure-Activity Relationship(s)	
INH: Inhalation	RA: Rat	
IPDI: Isophoronediiisocyanate	RB: Rabbit	
IPE: Intraperitoneal	REACH: Registration, evaluation, authorisation and restriction of chemicals	
IR & CSA: Information requirements and chemical safety assessment	RF: Respiratory function	
ITR: Intratracheal	RR: Relative Risk	