Committee for Risk Assessment

RAC

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

Adopted

17 September 2020

17 September2020

CLH-O-0000006862-68-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **2,4,6-triisopropyl-*m*-phenylene diisocyanate**

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

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

The proposal was submitted by **Germany** and received by RAC on **3 July 2019.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **26 August 2019**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **25 October 2019**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Tiina Santonen**

Co-Rapporteur, appointed by RAC: **Veda Varnai**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **17 September 2020** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	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-m-phenylene diisocyanate	218-485-4	2162-73-4	Resp. Sens. 1 Skin Sens. 1	H334 H317	GHS08 Dgr	H334 H317	EUH204		
RAC opinion	TBD	2,4,6-triisopropyl-m-phenylene diisocyanate	218-485-4	2162-73-4	Resp. Sens. 1 Skin Sens. 1	H334 H317	GHS08 Dgr	H334 H317	EUH204		
Resulting Annex VI entry if agreed by COM	TBD	2,4,6-triisopropyl-m-phenylene diisocyanate	218-485-4	2162-73-4	Resp. Sens. 1 Skin Sens. 1	H334 H317	GHS08 Dgr	H334 H317	EUH204		

GROUNDS FOR ADOPTION OF THE OPINION

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.

HUMAN HEALTH HAZARD EVALUATION

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 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).*

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)
?	?	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)
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	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			
		TDI							0.75			
									1.5			
									3			
Rats												
Wistar	F	MDI	-	-	AE	WB	8	436	17	610	RF	IUCL: (Hoymann et al., 1995)
							12					
							20	65		98	IF	
								260		365		
								436		371		
							80	520		728		

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).

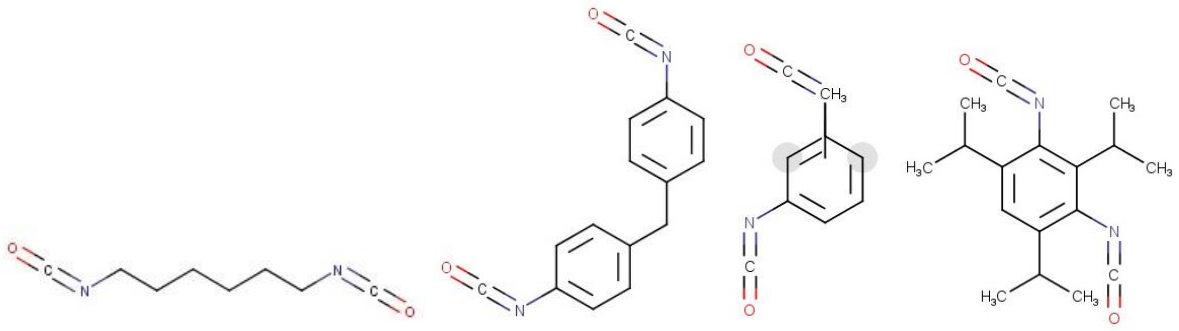

Figure. *The structures of HDI, MDI, TDI and TRIDI, respectively, from left to right.*

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 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 ([1]). 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 ([1]). 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).

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 agrees with the weight of evidence assessment of the DS and 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.

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 sensitisers, 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 sensitiser, with a reliability score of 2 (reliable with restrictions). Namely, the target chemical was not in the applicability domain because of its $\log K_{OW}$. 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 sensitiser, 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.

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**".*

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).