Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

1,3-bis(1-isocyanato-1-methylethyl)benzene

EC Number: 220-474-4
CAS Number: 2778-42-9

CLH-O-0000006861-70-01/F

Adopted

17 September 2020

17 September 2020

CLH-O-0000006861-70-01/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: **1,3-bis(1-isocyanato-1-methylethyl)benzene**

EC Number: **220-474-4**

CAS Number: **2778-42-9**

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	1,3-bis(1-isocyanato-1-methylethyl)benzene	220-474-4	2778-42-9	Resp. Sens. 1 Skin Sens. 1A	H334 H317	GHS08 Dgr	H334 H317	EUH204		
RAC opinion	TBD	1,3-bis(1-isocyanato-1-methylethyl)benzene	220-474-4	2778-42-9	Resp. Sens. 1 Skin Sens. 1A	H334 H317	GHS08 Dgr	H334 H317	EUH204		
Resulting Annex VI entry if agreed by COM	TBD	1,3-bis(1-isocyanato-1-methylethyl)benzene	220-474-4	2778-42-9	Resp. Sens. 1 Skin Sens. 1A	H334 H317	GHS08 Dgr	H334 H317	EUH204		

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

1,3-bis(1-isocyanato-1-methylethyl)benzene (m-TMXDI) is used in the production of polymers and has no current entry in Annex VI to the CLP Regulation.

The CLH report has been prepared based on data submitted by the lead registrant in the REACH registration dossier for the 1,5-naphthylene diisocyanate (NDI), 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; Germany). In addition, SCOPUS and PubMed databases were searched for relevant literature, covering the period 2015 to 2017.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of respiratory sensitisation

Summary of the Dossier Submitter's proposal

The DS proposed to classify 1,3-bis(1-isocyanato-1-methylethyl)benzene (m-TMXDI) as Resp. Sens. 1; H334. Currently, m-TMXDI has no harmonised classification in Annex VI to the CLP Regulation.

There are no specific reliable respiratory sensitisation data available for m-TMXDI that would be sufficient on their own to evaluate the need for classification. Therefore, the proposed harmonised classification was based on a weight of evidence assessment of the available data and 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 also several other diisocyanates have been self-classified as respiratory sensitisers. The DS is 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 target substance m-TMXDI

The DS identified only one report addressing potential respiratory sensitisation in humans by m-TMXDI. Grammer *et al.* (1993) reported an evaluation of 96 workers from facilities manufacturing or using m-TMXDI. While ca. 40% of the workers reported to have experienced irritation of the upper respiratory tract and/or the eyes, no workers with new asthma or other severe respiratory symptoms were identified. Two workers reported exacerbation of a previously existing asthmatic disease. Serological assessments showed m-TMXDI-specific IgE antibodies in one worker and m-TMXDI-specific IgG antibodies in eight workers. Overall, 12% of the workers exposed to estimated maximum concentrations of 0.4 to 10.2 ppb tested positive for m-TMXDI-specific antibodies.

However, the DS identified several significant limitations in the report, including the following:

- the symptoms were only self-reported and respiratory function tests were not performed;
- there was no follow-up of the workers who tested positive for specific antibodies;
- no information was provided on the possible origin of asthma in the two reported exacerbation cases;
- low estimated exposure levels and unknown true exposure level;
- no information on whether all the surveyed workers had worked in the factory over the whole study period (1984-1988);
- no information on whether during this period workers had left the factory, in particular after the early phase of factory setup, which was identified by the authors as a phase of potentially higher exposure, and if so, whether these workers had shown symptoms of respiratory disease.

The DS concluded that as evidence of immunological reactions in several workers was shown, the results do not demonstrate the absence of a potential of m-TMXDI to cause respiratory sensitisation in humans. They also concluded that the results are not suitable to rank m-TMXDI as a "low" or "lower than other diisocyanates" potency respiratory sensitiser, as the authors of the study had concluded.

Animal data on the read across target substance m-TMXDI

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 inhalation. Studies using other routes of induction or mixed routes were discarded. Furthermore, studies were considered unreliable and excluded from the assessment if 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 protocol followed (whole-body or head-/nose-only), confirmation of the presence of a negative control, and number of animals per dose group.

Regarding m-TMXDI, all studies meeting the above criteria (inhalation route, reliability) were included, regardless of whether an effect was observed or not. Three inhalation studies performed in guinea pigs were identified and assessed by the DS, summarised in the table below. For all of these studies, only IUCLID summaries submitted by the REACH lead registrant were available. Two of these studies were considered not reliable (quality issues in design and reporting, assessed only a limited spectrum of effect parameters). The third study (Union Carbide, 1988) was considered reliable with restrictions.

The DS concluded that overall, beyond a weak indication of possible antibody formation of unknown type, none of these studies can reliably contribute to the identification of m-TMXDI as a respiratory sensitiser. They also noted that they be used to prove the absence of respiratory sensitisation potential in humans. As mentioned before, due to lack of a standardised animal test design with regulatory acceptance, negative findings from such experiments cannot be used to exclude the need for classification and labelling for RS.

Table. *Summary by the DS of the animal studies on sensitisation after induction via inhalation with m-TMXDI (from Table 9 in the CLH report).*

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, vehicle	Study protocol	Results	Reference
Not applicable Range-finding study GLP: no data Reliability 3 (not reliable): Only IUCLID summary available, inconsistencies in reporting the treatment of control groups, spectrum of effect parameters assessed did not include more sophisticated respiratory function tests (only respiratory rate was measured). Reportedly, antibody analysis was performed, but results were not provided in the summary.	Guinea-pig, English Smooth-Haired, F, 8/group	Induction: m-TMXDI, no vehicle Challenge: m-TMXDI-Guinea-pig serum albumin (GPSA) conjugate in GPSA	Induction (days 1-5): 3 h/d with an atmospheric concentration of 24 µg/L by inhalation Challenge (day 8): Intradermal injection 25 µL of 0.0225 or 0.225 % solution of m-TMXDI-GPSA Skin reactions were evaluated after 24 and 48 h Terminal sacrifice on day 10	*"No evidence of increase in respiratory rate was seen in controls. Labored respiration and nasal oral discharge occurred in treated groups during the induction exposures. Slightly reduced body weights were observed. Lung weights and the histological appearance of the lungs of animals remained comparable with those of the controls. Slightly prominent bronchial and cervical lymph nodes were apparent macroscopically. Intradermal challenges with test material elicited clear erythemal response compared with controls."*	(Bio-Research Laboratories, 1984a)
Not applicable GLP: claimed Reliability 3 (not reliable): Only IUCLID summary available Only one treatment group, spectrum of effect parameters assessed did not include more sophisticated respiratory function tests (only respiratory rate was measured). Reportedly, antibody analysis was performed, but results were not provided in the summary.	Guinea-pig, English Smooth-Haired, F, 12/group	Induction: m-TMXDI, no vehicle Challenge: m-TMXDI-Guinea-pig serum albumin (GPSA) conjugate in GPSA	Induction (inhalation): 5 x 3 h/d to 36 µg/L air Rest period of 10-14 d Inhalation challenge: 20 min exposures to 15-20 µg/L m-TMXDI-GPSA/L air on days 22, 23, and 26 Intradermal challenge: Injection of 100 µL of 0.0333 % solution of m-TMXDI-GPSA on day 24 Skin reactions were evaluated after 6, 22 and 46 h Terminal sacrifice on day 26	*„Lethargy as well as nasal and oral discharge were observed in treated groups during the induction exposures. Body weights, lung weights and the histological appearance of the lungs of animals remained comparable with those of the controls. Intradermal and respiratory challenges with test material did not elicit any response indicative of sensitization."*	(Bio-Research Laboratories, 1984b)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, vehicle	Study protocol	Results	Reference
Not applicable GLP: claimed Reliability 2 (reliable with restrictions): Spectrum of effect parameters assessed did not include more sophisticated respiratory function tests (only respiratory rate was measured). High mortality (4/12 animals on days 2 (2 animals), 19 and 25)	Guinea pig, Hartley, F, 12	Induction: m-TMXDI, no vehicle Challenge: m-TMXDI-Guinea-pig serum albumin (GPSA) conjugate in GPSA	Induction (inhalation): 3 h/d to 30 µg/L TMXDI aerosol for 5 d Challenge (inhalation) on days 22, 23 and 26: 20 min to air followed by 20 min to 15-20 µg/L GPSA; recovery period of 30 min followed by 20 min to TMXDI-GPSA Day of sacrifice on day 26	*"Clinical signs of periocular, perioral, and perinasal wetness were observed along with respiratory difficulties and diminished motor activity in TMXDI-exposed animals. Four of the twelve TMXDI-exposed animals died during the study. Histopathologic examination of the lungs of TMXDI-exposed animals surviving until the end of the study showed a greater incidence and degree of alveolar histiocytosis than the lungs of control animals.* *A pulmonary hypersensitivity response was defined as a sustained increase (> 36 %) over the mean pre-exposure rate. An immediate pulmonary hypersensitivity response measured in terms of increased respiratory rates was not elicited from any of the guinea pigs upon inhalation challenge.* ***Low, but positive antibody titers for TMXDI were observed in exposed guinea pigs****."*	(Union Carbide, 1988)

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. The literature outlined in tables 2-8 of Annex I of the CLH report consistently demonstrate 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 allow for an assessment of the frequency of occurrence of respiratory sensitisation in the human population; they feature only a small number of patients and it is 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 sub-categorisation. In addition, no harmonised approach for sub-categorising respiratory sensitisers is available yet.

According to the DS, despite the large number of available epidemiological studies, none of them is eligible 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.

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

The same criteria as described above (under *Animal data for the target substance m-TMXDI*) were used by the DS to select the studies that were considered relevant and reliable for the classification. In addition, regarding the source substances, 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, 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 broncho-alveolar 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. 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 from 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 m-TMXDI

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 relevant to the RAAF Scenario 6 (human health) were considered by the DS.

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

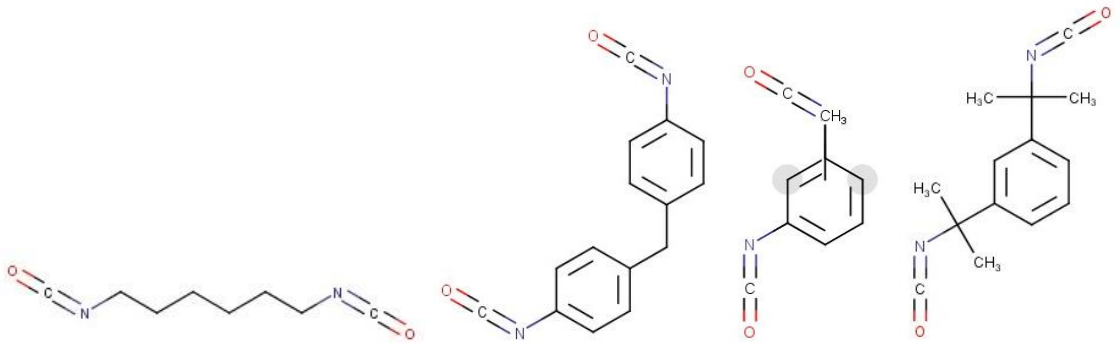

Figure. *The structures of HDI, MDI, TDI and m-TMXDI, respectively, from left to right.*

The isocyanate functional group is a well-known structural alert for respiratory sensitisation, and therefore commonly used also 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 highly 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

Three MSCAs commented during the consultation. All of them supported the proposed classification as Resp. Sens. 1; H334.

Assessment and comparison with the classification criteria

There is no validated test method for respiratory sensitisation, and therefore compounds are typically classified for Resp. Sens. based on human data, with supportive evidence from e.g. animal data.

For m-TMXDI, specific antibody formation in humans (workers) and an indication of possible antibody formation of unknown type in guinea pigs has been shown. While these data provide support for the proposed classification, they are not sufficient on their own to warrant classification for respiratory sensitisation. Furthermore, data on skin sensitisation (discussed below) demonstrates that m-TMXDI 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 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 m-TXMDI, the read across performed by the DS considers all of the assessment elements relevant for scenario 6 of the RAAF (Appendix F).

CLP, 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 accepts the weight of evidence assessment by the DS and agrees with the justification for a category approach using read across (based on human and non-human data) from the known respiratory sensitisers HDI, MDI and TDI to the target substance m-TMXDI. RAC also agrees that it is not possible to sub sub-categorise m-TMXDI into 1A or 1B, as no reliable data on the potency of either m-TMXDI 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 m-TMXDI.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

No information on the skin sensitising potential of m-TMXDI in humans is available.
One animal study is available (Biosphere Research Centre. Cytec Industries, unpublished, BRC, 1981), similar to the Buehler test (OECD TG 406), for which GLP compliance has been claimed.

The study was performed in Hartley guinea pigs of unspecified gender, 10 per group. Induction was performed by epicutaneous (non-occlusive) application of m-TMXDI (purity 91.58%) at 0.36 molar concentration (around 9% w/v) in olive oil, and challenge and re-challenge with 0, 0.10, 0.05, 0.025, 0.0125 and 0.00625 molar dilutions (units expressed as percentage in the CLH Report), 5 and 14 days after single induction application, epicutaneously (open application). Isophoronediisocyanate (IPDI) was used as a positive control. Prior to the induction application, the primary irritation potential was determined.

The DS recognised significant deviations from OECD TG 406 protocol, and other limitations in the study methodology and reporting, as follows:

- only a summary of the study is available;
- only 10 animals per group were used;
- exposure was non-occlusive;
- there was only one induction application;
- challenge was performed earlier than days 27-29;
- irritant doses were also used for challenge (the concentration used for the challenge exposure should be the highest non-irritating dose);
- individual scores for skin changes after challenge or re-challenge are not given in the summary;
- upon re-challenge (24h or 48h post-challenge), no positive reactions were reported;
- positive control (IPDI) gave only lower or no positive results upon re-challenge.

The DS pointed out that although the reason for negative results in re-challenge is unclear, the positive control gave only lower or no positive results upon re-challenge which might indicate experimental problems at the re-challenge step. Furthermore, the deviations from OECD TG 406, including only one instead of three induction exposures, non-occlusive exposure and early challenge, could decrease the sensitivity of the test, and a negative test result would not have been acceptable in this case.
Due to clear positive results obtained (table below), the DS rated the study as "reliable with restrictions" or Klimisch score 2, and proposed **Skin Sens. 1A** (H317: May cause an allergic skin reaction). Namely, according to the criteria given in Table 3.4.3 of the CLP regulation, skin sensitisers fall into category 1A based on the results from a Buehler test, if 60% or more of the animals show a positive response at a topical induction concentration of > 0.2 to ≤ 20%. This criterion was fulfilled for four of the five challenge doses tested (0.0125% - 0.1%) at the first reading, and for all tested doses at the second reading.

***Table**. Results from a study on skin sensitisation with m-TMXDI (BRC, 1981) (Table 12 from CLH Report)*

Reading	Challenge dose level	No. with reactions (%)
1 (24 h post-challenge)	0.1 and 0.05%	10 (100)*
	0.025%	7 (70)*
	0.0125%	9 (90)
	0.00625%	5 (50)
2 (48 h post-challenge)	0.1, 0.05, 0.025 and 0.0125%	10 (100)
	0.00625%	7 (70)
Re-challenge (24 h post-challenge)	0.1, 0.05, 0.025, 0.0125 and 0.00625%	0 (0)
Re-challenge (48 h post-challenge)	0.1, 0.05, 0.025, 0.0125 and 0.00625%	0 (0)

* According to the summary in the REACH registration dossier, these doses were slightly irritant (grade 1 erythema) in 2/5 females and irritant (grade 2 erythema) in 1/5 males tested during the primary skin irritation phase.

***Table**. Mean skin irritation scores (BRC, 1981) (Table 12 in Annex 1; the values have been reproduced by the DS from the summary presented in the REACH registration dossier)*

Primary Skin Irritation Phase:												
Concentration	0.1		0.05		0.025		0.0125		0.00625		0.0*	
	Er	Ed	Er	Ed	Er	Ed	Er	Ed	Er	Ed	Er	Ed
IPDI (24 h)	0.6	0.0	0.4	0.0	0.2	0.0	0.2	0.0	0.2	0.0	0.2	0.0
IPDI (48 h)	0.2	0.0	0.2	0.0	0.2	0.0	0.2	0.0	0.2	0.0	0.0	0.0
11583B15 (24 h)	0.8	0.0	0.2	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
11583B15 (48 h)	0.4	0.0	0.2	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Challenge Phase:												
IPDI (24 h)	2.7	0.5	2.1	0.0	1.5	0.0	1.1	0.0	0.9	0.0	0.0	0.0
IPDI (48 h)	1.9	0.0	1.9	0.0	1.7	0.0	1.2	0.0	0.9	0.0	0.0	0.0
11583B15 (24 h)	2.3	0.2	2.1	0.2	0.7	0.0	1.1	0.0	0.5	0.0	0.0	0.0
11583B15 (48 h)	2.1	0.0	2.0	0.0	1.0	0.0	1.2	0.0	0.8	0.0	0.2	0.0
Rechallenge Phase:												
A-IPDI (24 h)	0.9	0.0	0.8	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0
A-IPDI (48 h)	0.7	0.0	0.6	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
B-IPDI (24 h)	0.5	0.0	0.3	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
B-IPDI (48 h)	0.4	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
11583B15 (24 h)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
11583B15 (48 h)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

11583B15 = m-TMXDI; A: Animals treated with IPDI during induction; B: Animals treated with m-TMXDI during induction; * Vehicle (olive oil) only; Er: Erythema; Ed: Oedema

A specific concentration limit (SCL) was not proposed by the Dossier Submitter.

Comments received during consultation

Three comments were received during the consultation (from MSCAs). Although they pointed out limitations of the study and some further unclarities in the study reporting, all were supportive of the DS's proposal.

Assessment and comparison with the classification criteria

The results of BRC (1981) study, presented in two tables above, indicate strong sensitising potential for m-TMXDI (positive reaction in up to 100% of the animals tested, both at the 24h and 48h reading). Mean scores for the challenge phase stated in the table above showed that the reaction did not diminish at the second reading, indicating a sensitisation rather than irritation reaction. Based on these results, classification as Skin Sens. Cat. 1A would be warranted, according to the criteria given in Table 3.4.3 of the CLP Regulation. However, the study had numerous limitations, which are listed above. Additionally, while the induction dose was expressed only as a molar concentration, as commented during the Consultation, it is not clear in which units the challenge and re-challenge doses were expressed – percentage (e.g. % w/v), percentage molar concentration or molar dilution, since all these units are used interchangeably in the CLH Report, Annex 1 and the REACH registration dossier. Further clarification on this issue is not possible, since only a summary from the REACH registration dossier is available.

RAC, therefore, considers that an assessment of the skin sensitisation potential of m-TMXDI cannot be based solely on this study, and has conducted a weight-of-evidence approach in which read across from other diisocyanates have also been used.

RAC has conducted the same read across procedure as done for respiratory sensitisation endpoint for this substance, i.e. based on the category approach and structural similarity to monomeric diisocyanates, according to the 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). Moreover, as shown in Table 9 of the CLH Report for 2,4-diisocyanato-1,3,5-triisopropylbenzene (TRIDI), 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).

In addition, based on substance-specific animal data, RAC proposes to classify m-XDI (EC 222-852-4) and NDI (EC 221-641-4) as strong or even extreme skin sensitisers.

In conclusion, based on weight-of-evidence approach, which took into account:

- that the data for m-TMXDI as such, although uncertain, support 1A (i.e. strong positive response in a Buehler-like study (BRC, 1981) with significant limitations);
- read across from the known Cat. 1 skin sensitisers HDI, MDI and TDI, to the target substance m-TMXDI;
- strong or even extreme skin sensitising property of m-XDI and NDI, for which Skin Sens. Cat. 1A has been proposed by RAC, based on substance-specific experimental data;
- the close structural similarity between m-TMXDI and the strong sensitiser m-XDI;

- the likelihood that all isocyanates are strong sensitisers;[1]

RAC considers that classification as **Skin Sens. Cat. 1A**; H317 is warranted for m-TMXDI.

An SCL is not proposed, since RAC considers that the limitations in the experimental data for m-TMXDI (BRC, 1981) render it insufficiently reliable to support setting an SCL.

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****."*

Additional references

ECHA 2018. Committee for Risk Assessment (RAC) Committee for Socio-economic Analysis (SEAC) Annex to the Background document to the Opinion on the Annex XV dossier proposing restrictions on diisocyanates.

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).

[1] RAC notes that subcategorisation (1A) is not proposed for another diisocyanate evaluated by RAC, 2,4,6-triisopropyl-m-phenylene diisocyanate (TRIDI), due to complete lack of experimental data for this substance. In the case of m-TMXDI, however, experimental data exist, and although there are numerous limitations, the data indicate strong sensiting potential of m-TMXDI, as stated above.