Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

1,3-bis(isocyanatomethyl)benzene

EC Number: 222-852-4
CAS Number: 3634-83-1

CLH-O-0000006846-62-01/F

Adopted

17 September 2020

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CLH-O-0000006846-62-01/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(isocyanatomethyl)benzene**

EC Number: **222-852-4**

CAS Number: **3634-83-1**

The proposal was submitted by **Germany** and received by RAC on **12 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(isocyanatomethyl) benzene	222-852-4	3634-83-1	Resp. Sens. 1 Skin Sens. 1A	H334 H317	GHS08 Dgr	H334 H317		Skin Sens. 1A; H317: C ≥ 0,001 %	
RAC opinion	TBD	1,3-bis(isocyanatomethyl) benzene	222-852-4	3634-83-1	Resp. Sens. 1 Skin Sens. 1A	H334 H317	GHS08 Dgr	H334 H317	EUH204	Skin Sens. 1A; H317: C ≥ 0,001 %	
Resulting Annex VI entry if agreed by COM	TBD	1,3-bis(isocyanatomethyl) benzene	222-852-4	3634-83-1	Resp. Sens. 1 Skin Sens. 1A	H334 H317	GHS08 Dgr	H334 H317	EUH204	Skin Sens. 1A; H317: C ≥ 0,001 %	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

1,3-bis(isocyanatomethyl)benzene (m-XDI) has no current entry in Annex VI to the CLP Regulation. The substance is used for manufacture of plastic products and is self-classified as Resp. Sens. 1, and/or Skin Sens. 1 or Skin Sens. 1A.

The Dossier Submitter (DS) mentioned 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 the data submitted by the lead registrant in the REACH registration dossier for m-XDI, 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 DS.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of respiratory sensitisation

Summary of the Dossier Submitter's proposal

The DS proposed to classify m-XDI as Resp. Sens. 1 (H334). Currently, m-XDI does not have a harmonised classification. Its self-classification and labelling according to CLP is variously: Flam Liq. 3, Acute Tox. 1 or 2 (H330), Acute Tox. 3 (H331), Skin Corr. 1B (H314), Skin Irrit. 2 (H315), Eye Dam. 1 (H318), Eye Irrit. 2 (H319), Resp. Sens. 1 (H334), Skin Sens. 1A/1 (H317), STOT SE 1 (H370, respiratory tract, inhalation), STOT SE 3 (H335, inhalation), STOT RE 1 (H372, respiratory tract, inhalation), Aquatic Chronic 3 (H412).

There is no specific human or animal respiratory sensitisation (RS) data available for m-XDI. Therefore, the proposed harmonised classification was based on read across.

Only the three most commonly used source substances were used for read across from, as most of the published literature on diisocyanates is related to them: 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). The DS noted that several other diisocyanates also have a (self-)classification as respiratory sensitiser. 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 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, and they all have harmonised classifications as Resp. Sens. 1 (H334).

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. 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 the respiratory symptoms may eventually be reversed upon removal of exposure, an irreversible remodelling of the airways will eventually take place if 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 individuals 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 eligible for deriving a reliable Exposure-Response-Relationship (ERR) due to limitations of the studies. This is also inherent in the aetiology of the disease. No study overcomes the problem that sensitive predictive markers for diisocyanate sensitisation are missing and cannot currently be assessed appropriately. In addition, dermal exposure and inhalation peak exposure are both 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% of patients. 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. Complete recovery of lung function may never be achieved and 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.

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

There are no internationally recognised *in vivo* identification methods for 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 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, while a standardised protocol with regulatory acceptance is still missing. Therefore, while a negative result from an animal experiment on respiratory sensitisation is deemed as not sufficient to exclude the need for classification and labelling, the read across assessment concentrated on data providing a positive indication of respiratory sensitisation. HDI, MDI, and TDI studies reporting one or more relevant effects were selected for further processing, as outlined in the table below. 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, as 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). The observed respiratory symptoms (increased respiratory rate, effects on respiratory flow, laboured breathing etc.) resembled those seen in humans with asthma. In addition, skin sensitisation has been observed following induction via inhalation. However, the interdependencies and quantitative contributions 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)

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
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-XDI

The read-across of hazard data 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). The read-across hypothesis is that different compounds have qualitatively similar properties with no relevant variations in properties observed among source substances, and the same potency is 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-XDI all share the structural feature of two isocyanate (-N=C=O) functional groups while the part of the molecular structure that links the two isocyanate groups are variable (see figure below).

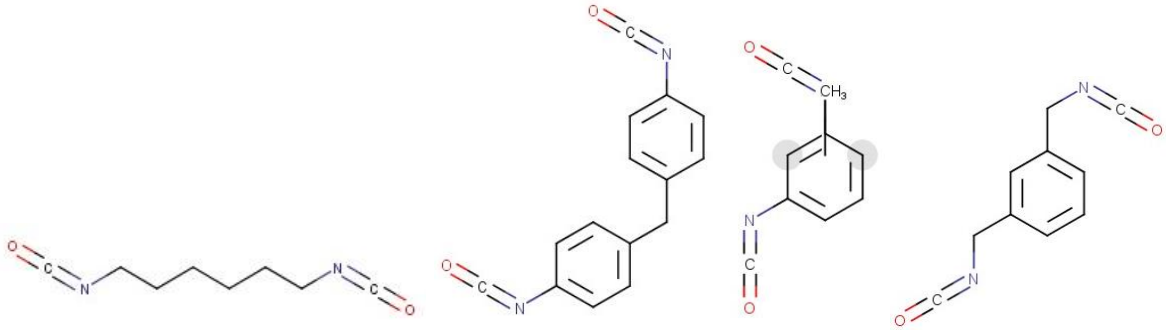

Figure The structures of HDI, MDI, TDI and m-XDI, respectively, from left to right.

The isocyanate (-N=C=O) 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 for respiratory sensitisers that, similarly to skin sensitisation, covalent binding of electrophiles to proteins in the lung marks a molecular initiating key event. For isocyanates, an acylation type reaction between electrophilic NCO chemical functional groups and nucleophilic protein moieties may occur, leading to protein adducts (Enoch *et al.*, 2011; Enoch *et al.*, 2009; Enoch *et al.*, 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

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

For the source substances HDI, MDI and TDI, numerous case reports and epidemiological studies consistently demonstrate their 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 accepted as an alert for respiratory sensitisation.

For m-XDI, the read across performed by the DS considered all of the assessment elements relevant for scenario 6 of the RAAF (Appendix F).

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:

In addition to the CLP criteria for classification of a substance as a respiratory sensitiser, the CLP Regulation Annex I section 3.4.2.1.2.3 also 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 considers the weight of evidence assessment by the DS to be adequate. In addition, the Committee 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 m-XDI. 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 m-XDI into 1A or 1B, as no reliable data on the potency of either m-XDI 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-XDI.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

No information on the skin sensitising potential of m-XDI in humans is available.

Four studies in guinea pigs are presented in the CLH report: one Guinea pig maximisation test (GPMT) study (Huntingdon, 1997), and three equivalent or similar to GPMT studies (Huntingdon, 1980; Safepharm, 1992, 1998). Out of these, only Huntingdon (1997) GPMT study was

considered reliable (with restrictions, since no purity information was provided, and only summary was available), while other three studies were considered by the DS as unreliable (reliability 3) due to limitations in methodology and reporting.

The Huntingdon (1997) Guinea Pig Maximisation test (GPMT) was available to the DS only as a summary, provided by the REACH lead registrant for m-XDI. According to the summary, it is a GLP study, performed in 10 male Dunkin-Hartley Guinea pigs. The highest intradermal (0.01% in Alembicol D[1]) and topical induction concentrations (100%) applied in the range-finding study were chosen for the main experiment, since they caused only mild to moderate skin irritation and were well tolerated systemically. For topical challenge 15% and 7.5% (the highest non-irritant concentration and one lower concentration) were applied. Appropriate negative control was included (5 animals), and positive controls (hexyl cinnamic aldehyde, benzocaine, and 2-mercaptobenzothiazole) periodically checked the strain. Slight irritation was observed in test and control animals after intradermal inductions, and slight erythema after topical applications. No systemic effects were noted.

Positive reaction (necrosis, thickening, dryness and sloughing of the epidermis) occurred in all tested animals (10/10), at both challenge doses. Negative control animals did not show a positive reaction. Results were identical at 24 and 48 h post-challenge.

The DS concluded that a reliable GPMT demonstrated the potential of m-XDI to act as a skin sensitiser with extreme potency in guinea pigs (100% sensitisation rate at intradermal induction concentrations ≤ 0.1%, according to Table 3.7 of the CLP Guidance, 2017[2]), and proposed **Skin Sens. 1A**, with a Specific Concentration Limit (SCL) of 0.001% (as recommended for extreme potency skin sensitisers in Table 3.9 of the CLP guidance).

The other three available animal tests, for which also only summaries (as again provided by the REACH lead registrant for m-XDI) were available to the DS, were considered unreliable due to deficiencies in reporting and/or design. Nevertheless, their results were consistent with the proposed classification.

In the Huntingdon (1980) non-GLP, non-Guideline study, which was similar to a GPMT (OECD TG 406), dosing was performed by 0.01% m-XDI intradermal injections, topical induction with undiluted substance, and epi-cutaneous challenge with 20% m-XDI in acetone. Nine out of 10 exposed guinea pigs had a positive reaction (and none of 5 negative controls), which would trigger Skin Sens. 1A. However, elementary information on study methodology is missing, such as whether and which adjuvant was used, size of the treated area, and duration of topical exposure.

GLP has been claimed for the Safepharm (1992) GPMT study, although no purity and batch number of m-XDI were given. After intradermal induction with 0.1% of the test substance in Arachis oil BP (with Freund's Complete Adjuvant), topical induction with 75% test material, and epicutaneous challenge with 50% and 75% test material, all treated guinea pigs showed a positive sensitisation reaction 24 h and 48 h post-challenge, which would support Skin Sens. 1A classification. Nevertheless, skin erythema was also noted in negative controls, which could indicate irritation. As erythema scores were not reported, uncertainty remains about whether the test was performed in accordance with OECD TG 406, which requires non-irritant doses for the topical challenge.

[1] Fractionated coconut oil.

[2] ECHA Guidance on the Application of the CLP Criteria, Version 5.0, July 2017.

The Safepharm (1998) study under GLP test was similar to OECD TG 406/EU B.6 (GPMT). In the study, m-XDI produced a sensitisation rate of 100% with an intradermal induction dose of 0.01% test substance in Arachis oil BP (with Freund's Complete Adjuvant), topical induction with undiluted test material, and re-challenge with 50% and 25% test material. The study, however, has serious deficiencies in design and reporting (i.e. results of the first challenge are not reported; re-challenge was performed with concentrations other than those used in the first challenge and much later than recommended in OECD TG 406, without explanation; 48 h after re-challenge, erythema could not be scored due to undisclosed "adverse reactions").

Comments received during consultation

Three comments were received during the consultation from MSCAs, all supportive of the DS's proposal.

Assessment and comparison with the classification criteria

RAC agrees with the DS that the Huntingdon (1980), and Safepharm (1992 and 1998) studies are not reliable enough to be used for classification and labelling, but their results are in line with DS's proposed classification.

RAC considers that for regulatory purposes, summary of the key study Huntingdon (1997), a GLP study performed in accordance with OECD TG 406 (GPMT guideline), provides enough information on study methodology and results. The 2nd ATP[1] and ECHA CLP Guidance indicate that Skin Sens. sub-category 1A is applicable when there are ≥ 30% responding animals at ≤ 0.1% intradermal induction dose in a Guinea pig maximisation test. RAC, therefore, agrees with the DS that the results of this study justify **classification of m-XDI as Skin Sens. sub-category 1A (H317)**, since 100% tested animals had a positive reaction to m-XDI following 0.01% intradermal induction dose.

According to ECHA CLP Guidance (Table 3.7) this magnitude of response indicates a skin sensitiser with extreme potency. Therefore, an **SCL of 0.001%**, as proposed by the DS, is considered warranted (ECHA CLP Guidance, Table 3.9).

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, pre-polymers, etc., or as mixtures thereof) shall bear the following statement: **EUH204 — Contains isocyanates. May produce an allergic reaction***".*

[1] Commission Regulation (EU) No 286/2011 of 10 March 2011 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures.

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).