Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

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

EC Number: 202-112-7
CAS Number: 91-97-4

CLH-O-0000006965-60-01/F

Adopted

18 March 2021

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 3,3'-DIMETHYLBIPHENYL-4,4'-DIYL DIISOCYANATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: 3,3'-dimethylbiphenyl-4,4'-diyl diisocyanate; [TODI]
EC number: 202-112-7
CAS number: 91-97-4
Dossier submitters: Germany and France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
06.05.2020	Belgium	ISOPA Aisbl	Industry or trade association	1
Comment received				
We believe that the references made to TDI and MDI are not justifiable.				
Dossier Submitter's Response				
Thank you for your comment, we believe that the strategy based on read across is sufficiently described in the document. Without sufficient amount of details in your comments, we can not answered more precisely.				
RAC's response				
Regarding skin sensitisation endpoint, the conclusion on classification (Skin Sens. 1A) is based on actual data for TODI, i.e. a GPMT assay, since, despite its limitations, the study is considered to provide enough information on study methodology and results. Also for carcinogenicity RAC considered read-across to MDI/TDI justified.				

Date	Country	Organisation	Type of Organisation	Comment number
24.04.2020	Germany		MemberState	2
Comment received				
The formation of the hydrolytic product, TODA, should be mentioned as an additional outcome of the hydrolysis test performed with TODI within section 9 (TOXICOKINETICS). For consistency reasons "DS" should be used in the complete (background) document. While the abbreviation DS (dossier submitter) had been used throughout the entire dossier, in section 10.6 (RS) and 10.7 (SS), the narrative perspective is often DE (BAuA,				

DE MSCA).
No details on carcinogenicity studies are presented neither within the dossier nor within annex I. The presentation of studies relevant for the purpose of classification with sufficient amount of details is mandatory to allow for a proper evaluation of the proposal.

Dossier Submitter's Response

Thank you for your comment.
The only repeated study available on TODI in the dossier is a 28-days study by oral route which is too short to highlight carcinogenic endpoint (anonymous, 1998b). Consequently, based only on data from TODI, no assessment of carcinogenic potential is possible. Therefore, evaluation strategy using read-across of human and non-human data based on structurally similar substances to the target substance has been performed.
We proposed only a brief summary of data of the similar substances (MDI, TODA), as these substances have already an harmonised classification and were robustly assessed by different organisms (IARC MONOGRAPHS VOLUME 71; ECB, Risk Assessment Report methylenediphenyl diisocyanate (MDI), 2005; NTP Report on Carcinogens Background Document for Dyes Metabolized to 3,3'-Dimethylbenzidine; WHO, Concise International Chemical Assessment Document 27 DIPHENYLMETHANE DIISOCYANATE (MDI), 2000).

We can nevertheless give below more details of these studies, as summarised by other organisms:

Reuzel et al., 1994: Groups of 60 male and 60 female Wistar rats, six weeks of age, were exposed to target concentrations of 0 (controls), 0.2, 1.0 or 6.0 mg/m^3 (analytical value, 0.19, 0.98 or 6.03 mg/m^3) respirable (particle size, 93.5% < 4.2 µm) polymeric 4,4'-methylenediphenyl diisocyanate (pMDI) aerosol (31.0–31.7% (w/w) isocyanate content, 0.06–0.12% hydrolysable chlorine, 0.20–0.37% total chlorine, 0.0001–0.0069% chlorobenzene, 0.003–0.005% phenyl isocyanate, 44.8–50.2% monomeric 4,4'-methylenediphenyl diisocyanate, 0.01% sediment content) for 6 h per day on five days per week for two years. The exposure concentrations were selected based on results of a 13-week study. Complete histological examination was performed and almost all organs and all grossly observed lesions were examined histologically. Survival at 104 weeks of study was 38/60, 38/60, 42/60 and 36/60 control, low-dose, mid-dose and high-dose in males and 41/60, 42/60, 48/60 and 50/60 control, low-dose, mid-dose and high-dose in females. In the high-dose group, pulmonary adenomas were found in 6/60 males ($p < 0.05$ by two-sided Fisher's exact test) and 2/59 females, and pulmonary adenocarcinoma was found in 1/60 males. No lung tumours were found in other groups. Accumulation of alveolar macrophages containing pMDI-associated refractile yellowish material, localized fibrosis, alveolar duct epithelialization and increased incidences of calcareous deposits and localized alveolar bronchiolization were observed in the lungs of the high-dose group.

Hoymann et al., 1995: chronic inhalation study conducted with 99.5% pure monomeric 4,4'-MDI. Female Wistar rats (80 per exposure group) were exposed (whole body) to MDI in aerosol at 0.23, 0.70, or 2.05 mg/m^3 (MMAD about 1 µm) for 17 h per day, 5 days per week, for up to 24 months. A separate group of 20 per exposure level was examined histopathologically at 12 months. Smaller numbers of animals were assessed at various time points for lung function and for examination of bronchioalveolar lavage (BAL) fluid for cell counts and protein and enzyme determinations. Statistically significant concentration-related pulmonary lesions included (1) an increase in focal/multifocal alveolar and bronchioalveolar hyperplasia, (2) interstitial fibrosis, and (3) an accumulation of particle-laden and pigmented macrophages. Alveolar cell hyperplasia, considered preneoplastic, exhibited a concentration–response trend, with the incidence

reaching significance in the high-exposure group. These effects correlated with pulmonary function deficits (FEF25 [forced expiratory flow from 25% of the forced vital capacity, or FVC] and carbon monoxide diffusion), particularly in the high-exposure group. All groups exhibited significantly increased relative lung weights at all time periods (more than 60% at 20 months), with significant increases in hydroxyproline in BAL fluid (more than 70% at 12 months). In contrast to the results reported by Reuzel et al. (1994b) for PMDI, there was no apparent effect of monomeric MDI on nasal tissues at any exposure level. In one high-dose animal, a bronchioloalveolar adenoma was observed. Because of the concentration-related lung effects, 0.23 mg/m3 is considered a LOAEL. There is no NOAEL in this study.

NTP 1991: Groups of 70, 45, 75, and 70 male and female F344/N rats, five weeks old at the time of study initiation, were given drinking water containing 3,3′-dimethylbenzidine dihydrochloride at 0, 30, 70, or 150 ppm for up to 14 months. Although initially planned as a two-year study, this experiment was terminated early because of reduced survival associated with the appearance of treatment-related neoplasms. A scheduled interim sacrifice and histopathological assessment (10 controls and 10 high-dose animals of each sex) was conducted during the ninth month of the study. Although the incidences of tumors observed in 3,3′-dimethylbenzidine-dosed rats were not significantly elevated at the interim sacrifice, the appearance of any of these neoplasms after only nine months suggested a treatment-associated early onset of some tumors.
Tumor incidences were unequivocally increased in a dose-related manner after 14 months of 3,3′-dimethylbenzidine dihydrochloride administration. Administration of DMB dihydrochloride increased the incidences of a wide array of malignant and benign tumors in both sexes of F344/N rats. Under the conditions of the experiment, 3,3′-dimethylbenzidine dihydrochloride was clearly carcinogenic to male and female Fischer 344/N rats.

Tumor type	Daily dose (ppm)			
	0	30	70	150
	Tumor incidences/number examined[a]			
Males				
Skin: Basal cell adenoma or carcinoma	0/60	11/45**	54/75**	30/60**
Sebaceous gland adenoma	0/60	0/45	7/75*	5/60*
Squamous cell papilloma or carcinoma	0/60	2/45	17/75**	27/60**
Keratoacanthoma	1/60	1/45	8/75*	5/60*
Zymbal gland: Adenoma or carcinoma	1/60	3/45	32/75**	36/60**
Preputial gland: Adenoma or carcinoma	2/60	4/45	6/75	9/60*
Liver: Neoplastic nodule or hepatocellular carcinoma	0/60	0/45	35/75**	33/60**
Oral cavity: Squamous cell papilloma or carcinoma	0/60	0/45	4/75	5/60*
Small intestine: Adenomatous polyp or adenocarcinoma	0/60	0/45	4/75	8/60*
Large intestine: Adenomatous polyp or adenocarcinoma	0/60	0/45	6/75*	15/60**
Lung: Neoplasms	1/60	0/45	8/75*	6/60*
Females				
Skin: Basal-cell adenoma or carcinoma	0/60	3/45	10/75**	9/60**
Squamous cell papilloma or carcinoma	0/60	3/45	9/75*	12/60**
Zymbal gland: Adenoma or carcinoma	0/60	6/45*	32/75**	42/60**
Clitoral gland: Adenoma or carcinoma	0/60	14/45**	42/75**	32/59**
Liver: Neoplastic nodule or hepatocellular carcinoma	0/60	0/45	7/74*	4/60*
Oral cavity: Squamous cell papilloma or carcinoma	0/60	3/45	9/75*	13/60**
Small intestine: Adenomatous polyp or adenocarcinoma	0/60	1/45	3/75	5/60*
Large intestine: Adenomatous polyp or adenocarcinoma	0/60	1/45	7/75*	4/60*
Mammary gland: Adenocarcinoma	0/60	1/45	3/75	6/60*

RAC's response

Thank you for the comments. RAC agrees that detailed information on the carcinogenicity studies is needed.

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2020	Sweden		MemberState	3

Comment received

Read-across justification is required endpoint by endpoint. In the current CLH-report there is no justification presented for mutagenicity or carcinogenicity. It could have been made clearer that the Evaluation strategy, under the section of Germ cell mutagenicity, also applies for carcinogenicity (if this is the case). However, robust justifications for the appropriateness of applying read-across for both these hazard classes are still lacking.

Dossier Submitter's Response

Thank you for your comment.

We confirm that the justification of the read acros strategy presented in the chapter 10.9.2 also apply to carcinogenicity. As mentioned, the approach as the one used for respiratory sensitisation cannot be used due to the lack of a known mechanism of action

linked to the isocyanate group. We therefore based the justification on the structural similarity of substances.
RAC's response
Thank you for the comment. RAC agrees with the comment.

Date	Country	Organisation	Type of Organisation	Comment number
07.05.2020	Germany	Nisso Chemical Europe GmbH	Please select organisation type..	4
Comment received				
The present CLH report focuses on the harmonization of the C&L with regard to skin and respiratory sensitization as well as mutagenicity and carcinogenicity. In the joint registration also a classification for acute toxicity (Cat.4, H332) and aquatic toxicity (Aquatic Acute 1 and Chronic 1, H400 and H410) has been proposed. In the C&L inventory database on ECHA homepage different classifications are contained regarding aquatic toxicity. The purpose of the CLH process should be to come up with a harmonized C&L for all relevant endpoints. Therefore, Nisso Chemical Europe GmbH (NCE) requests to update the CLH report and to include the endpoints acute toxicity and acute and chronic aquatic toxicity in order to come to a harmonized classification with respect to all relevant endpoints.				
Dossier Submitter's Response				
Thank you for your comment. At this step, the CLH report cannot be modified anymore. In this assessment, the choice was made to focus on priority endpoints as defined by the CLP regulation. Moreover, as indicated on ECHA website, as all notifiers agree on the acute classification (Acute Tox. 4) in their self classification, there would be limited interest of an harmonised classification on a management point of view.				
RAC's response				
Thank you for the comment. RAC evaluation is limited to the endpoints covered in CLH report.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
24.04.2020	Germany		MemberState	5
Comment received				
While the DE-CA generally acknowledges concerns regarding potential carcinogenic properties of TODI, we do not support the proposal in its current form for the following reasons. Given the lack of data showing carcinogenic properties of TODI in both humans and experimental animals, classification is proposed based on data from a structural analogue. The eMSCA first considers MDI as a valid source substance due to structural similarity. This structural similarity, namely the two isocyanate functional groups (see 10.6.2.2), has been linked to a mode of carcinogenic action (MoCA) by the eMSCA. Given their potential to react with proteins, diisocyanates induce pathological changes within the lung eventually leading to the formation of lung tumours following exposure by inhalation. The eMSCA and others consider this particular MoCA as non-genotoxic. MDI carries the harmonised classification CARC 2 and so do the other diisocyanates in the group (Table				

12). The guidance on the application of the CLP criteria states: "…the existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (e.g., hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation) may lead to a downgrading of a Category 1 to Category 2 classification." Hence, a classification of isocyanates into category 2 based on a secondary, non-genotoxic MoCA (irritation and proliferation) is comprehensible. Allocating TODI to category 1B may, therefore, not be justified.

In a second step, the eMSCA considers TODA as another valid source substance. This is based on an available hydrolysis test conducted with TODI, showing pH- and temperature-dependent hydrolysis and the formation of the hydrolytic product TODA- an aromatic diamine. TODA carries the harmonised classification CARC 1B. Only one study conducted with a TODA analogue is mentioned in the CLH dossier. Details are not provided. The study shows the formation of tumours in numerous tissues following oral administration of the test substance. This may be indicative of a genotoxic mode of action. However, as discussed in section 10.8, the available mutagenicity data on TODA are equivocal. TODA does not have a harmonised classification on germ cell mutagenicity. Moreover, in the light of the fact that toxicokinetic data are not available for TODI, the extent to which TODA is formed in vivo or whether it is formed at all remains obscure. No data on MDA, the presumed metabolite of MDI, are presented within the carcinogenicity section. MDA carries a harmonised classification too (CARC 1B). If such data exist, it would be helpful to support the hypothesis, that in vivo formation of aromatic diamines are involved in cancer formation. Based on the studies mentioned within the section, tumour formation appears to be very different when comparing MDI with TODA (lung tumours based on irritation and proliferation for MDI vs. tumours scattered throughout the entire body for TODA) which may be a result of the different routes of substance application (inhalation vs. oral) or different MoCA. In the absence of convincing evidence regarding the in vivo formation of TODA and a plausible MoCA, classification into category 1B may not be justified.

Taking together, the DE-CA is of the opinion that TODI should be classified based on read-across to MDI, justifying category 2. Classification based on read-across to data conducted with the potential metabolite TODA may not be justified due to the missing evidence of in vivo formation derived from toxicokinetic studies and uncertainty as to whether a genotoxic MoCA exists.

Dossier Submitter's Response

France : Thank you for your comment.
We understand your point of view, and agree that this is a borderline case between category 1B and 2 that probably need to be debated during the RAC meeting.
Due to the lack of data on metabolism and carcinogenicity of TODI, the incomplete information about the conversion by hydrolysis of TODI into TODA, we have decided to choose the more conservative option which was based on the assumption that TODI is completely metabolized to form TODA and therefore the C&L for TODA (Carc. 1B) is applicable to TODI (worst case assumption).
Details of the study on TODA have been added in the response of comment 2.
Moreover, for consistency, as we chose to base our proposal of classification on TODA classification, we did not take into consideration the MoCA of MDI and did not downgrade the classification.

RAC's response
Thank you for the comments. RAC agrees that read across should be from MDI/TDI rather than from TODA.

Date	Country	Organisation	Type of Organisation	Comment number
07.05.2020	Germany	Nisso Chemical Europe GmbH	Please select organisation type..	6

Comment received

A harmonized classification for carcinogenicity Cat. 1B is proposed in the CLH report based on the assumption that TODI completely metabolizes to form TODA and therefore the C&L for TODA (Carc. 1B) is applicable to TODI (worst case assumption).
Nisso Chemical Europe GmbH strongly disagrees with the proposed harmonized classification and labeling for carcinogenicity Cat.1B (H350).
According to the CLH report MDI and TODI share a similar hydrolysis behavior. The unique feature common to all diisocyanates is that they consist of two N=C=O (isocyanate) functional groups attached to an aromatic or aliphatic parent compound. Because of the highly unsaturated nature of the isocyanate functional group, the diisocyanates readily react with nucleophiles. Thus, a complete hydrolysis of TODI to TODA in vivo as postulated in the CLH report should not be anticipated for the most relevant exposure route, i.e. inhalation exposure. In the 28-day oral repeated dose toxicity study performed with TODI insoluble degradation products of the substance have been reported to be present in the stomach of the rats assuming the formation of polyureas. Moreover, the reaction of an amine with isocyanate is faster than the hydrolysis reaction of water with isocyanate, which leads primarily to reactions forming polyureas [2] and not the formation of the free diamine.
For the group members MDI and TDI data from in vivo metabolism studies are available. The initial metabolism profiles differ substantially between oral and inhalation exposure. In the lung (pH approx. 7), TDI-vapor conjugates with proteins, whereas in the stomach (pH below 2) protein binding is reduced and hydrolysis and formation of polyurea is facilitated [2]. Radiolabelled 2,6-TDI isomer in corn oil was dosed by oral gavage to rats and excreta were collected. In the high dose group polymerized solid mass was present in the stomach and the stomach became greatly distended. Further studies show that TDI polymerized in the acid environment of the stomach to solid polyureas and therefore the oral dose route leads to polymerization reaction of TDI before absorption into the body. In analogy to TDI, for diisocyanates it is expected that oral gavage dosing will result in reaction with stomach contents and polymerization to solid polyureas [2].
When rats were exposed for 4 hours to [14C]-2,4-TDI vapors the majority of the label associated with the blood (74-87%) was recovered in the plasma. Plasma profiles showed that 97-100% of this radioactivity existed in the form of biomolecular conjugates. The majority of the radioactivity present in the low molecular weight fraction was not identifiable as TDA but was spread across a number of unidentified components. The authors concluded that conjugation was the predominant reaction and that free TDA was not a primary in vivo reaction product following inhalation of 2,4-TDI vapor [2]. Similar results have been reported for MDI after inhalation exposure to rats [1, 3]. MDI-metabolite formation is described to proceed via formation of a labile isocyanate glutathione (GSH)-adduct and transfer to a more stable adduct with larger proteins. No free MDA was detected in feces, urine or bile. Only conjugated metabolites have been detected. The initial metabolism of MDI is dominated by reaction with GSH. This is in contrast to its diamine MDA, which showed a metabolism dominated by direct acetylation and further glucuronidation and sulfatation. Moreover, in none of the metabolism studies

(in vitro and in vivo) with MDI free MDA has been found. For MDA the main excretion product upon exposure was MDA and N-Acetyl-MDA. Also for TODA based dyes the main excretion products in rats have been identified as TODA and N-Acetyl-TODA [4] indicating a similar metabolism of these diamines.
Based on the available metabolism data on diisocyanates it can be concluded that metabolism is complex and clearly not dominated by simple hydrolysis to the corresponding diamines, neither after inhalation nor after oral exposure. Thus, a complete transformation of TODI to TODA can be excluded and consequently read-across from TODA to TODI is not justified.
MDI was carcinogenic in rats after inhalation exposure. A non-genotoxic mode of action for tumor formation was proposed [5] and confirmed recently [1]. MDI is classified for carcinogenicity Cat. 2. MDA is a genotoxic carcinogen classified for mutagenicity Cat. 2 and carcinogenicity Cat. 1B. TDI was carcinogenic only after oral exposure [6]. No treatment-related tumor was observed in mice or rats following inhalation exposure to rats and mice [2]. As described in the NTP study report [6] the pattern of multifocal tumors following oral exposure was similar to the carcinogenic responses produced by the hydrolysis product TDA. In the CoRAP evaluation report on TDI [2] it is concluded that "the results of the studies using oral administration are compromised by severe deficiencies in test substance handling that led to the fact that the sample administered also contained other unidentified breakdown and reaction products of TDI, possibly including TDA. […] Therefore, these studies are considered "invalid" by Klimisch criteria. Furthermore, the addition of TDI directly into the acidic environment of the stomach, bypassing the oral cavity, is an unrealistic exposure scenario which leads to generation of the diamine which would not occur in normal handling and use." Thus, TDI is classified for carcinogenicity Cat. 2 and not classified for mutagenicity. In contrast, TDA is classified for carcinogenicity Cat. 1B and mutagenicity Cat. 2.
In conclusion, diisocyanates differ from the corresponding diamines with respect to carcinogenicity and mutagenicity, which is also reflected in different classification of both substance groups, i.e. MDI and TDI are classified for carcinogenicity Cat. 2 and not classified for mutagenicity, whereas the diamines MDA and TDA are classified as Cat. 1B carcinogen and Cat 2 mutagen.
In summary, the read-across from TODA to TODI for the endpoint carcinogenicity is not justified for the following reasons.
- The mode of action leading to respiratory sensitization of diisocyanates necessitates the reaction of the isocyanate group with proteins. Consequently, a complete hydrolysis of TODI to TODA as assumed in the CLH report can be ruled out.
- In vivo toxicokinetic data show differences in metabolism and excretion between diisocyanates and the corresponding diamines and data on MDI and TDI demonstrate that free diamines do not occur. Thus, read-across should be done within the group of diisocyanates or diamines, but not between diisocyanates and diamines.
- The mutagenic and carcinogenic potential of diisocyanates differs from the respective diamines. TDI and MDI are not classified for mutagenicity and only for carcinogenicity Cat. 2 whereas their respective diamines MDA and TDA are classified for mutagenicity Cat. 2 and carcinogenicity Cat. 1B. This further demonstrates that diisocyanates do not behave like the diamines in vivo. Consequently, read-across from TODA to TODI cannot be justified and should not be done.
Based on the above considerations NCE proposes to address the endpoint carcinogenicity for TODI by read-across from the structurally most similar diisocyanate MDI as already done in the CLH report for the endpoints mutagenicity and sensitization. Thus, NCE proposes for TODI a harmonized classification and labeling for carcinogenicity Cat. 2 in the absence of any substance-specific carcinogenicity data.

References:
[1] CoRAP Substance Evaluation Report, 4,4'-methylenediphenyl diisocyanate (MDI), EC No 202-966-0, November 2018
[2] CoRAP Substance Evaluation Report, m-tolylidene diisocyanate (TDI), EC No. 247-722-4, November 2013
[3] Gledhill A et al., Absorption, distribution, metabolism and excretion of an inhalation dose of [14C] 4,4-methylenediphenyl diisocyanate in the male rat, Xenobiotica, March 2005; 35(3): 273-292
[4] NTP Report No. 390, TOXICOLOGY AND CARCINOGENESIS STUDIES OF 3,3`-DIMETHYLBENZIDINE DIHYDROCHLORIDE (CAS NO. 612-82-8) IN F344/N RATS (DRINKING WATER STUDIES), June 1991
[5] EU Risk Assessment Report, 3rd Priority List, Volume 59, 4,4'-methylenediphenyl diisocyanate (MDI), Joint Research Center, 2005
[6] NTP Report No. 251, TOXICOLOGY AND CARCINOGENESIS STUDIES OF COMMERCIAL GRADE 2,4 (80%)-AND 2,6 (20%)TOLUENE DIISOCYANATE (CAS NO. 26471-62-5) IN F344/N RATS AND B6ClF1 MICE (GAVAGE STUDIES), August 1986

Dossier Submitter's Response

France: Thank you for your comment. See response to comment 5.

RAC's response

Thank you for the comments. RAC agrees that read across should be from MDI/TDI rather than from TODA.

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2020	Germany	Freudenberg Sealing Technologies GmbH	Company-Downstream user	7

Comment received

The French Competent Authority proposes a harmonized classification as Carc. 1B. Since there is no experimental data available on the carcinogenic potential of TODI, the Carc. 1B proposal is based on a read across approach from the diamine TODA (classified as Cat. 1B carcinogen) to the diisocyanates TODI assuming that 'TODI will be totally metabolised in TODA in organisms'.
Freudenberg Sealing Technologies GmbH is of the opinion that the read across is scientifically not justified and disagrees with the classification proposal for Carc. 1B.
Due to the impact of COVID-19 the comment could not be finalized within the commenting deadline. Additional comments are to follow until May 22, as agreed with ECHA.
ECHA note: on May 20 the comment submitter provided the public attachment linked to this comment.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment Freudenberg Sealing Technologies_update_2020-05-20.pdf

Dossier Submitter's Response

France: Thank you for your comment. See responses to comment 5

RAC's response

Thank you for the comments. RAC agrees that read across should be from MDI/TDI rather than from TODA.

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2020	Sweden		MemberState	8
Comment received				
The SE CA considers that the level of detail and lack of robust justification for the read-across applied prevents us from being able to make a conclusion on the proposed classification. - Why is there no data on carcinogenicity of MDI (source substance) presented in a table and detailed more carefully in the summary section to allow an independent assessment? There seems to be in total 3 inhalation toxicity studies in rats available of MDI. - Why is there no data on carcinogenicity of TODA (metabolite and source substance) presented in a table and detailed more carefully in the summary section to allow an independent assessment? The comparison with criteria for the classification of TODI is not clear to us. There are statements of evidence for carcinogenicity of the structural analogue MDI presented and for the metabolite TODA. However, in the conclusion it seems as if the information from both these source substances was not used in a total WoE for classification of TODI in category 1B, but only from TODA? We think that some elaboration on this would be beneficial for the understanding of the reasoning behind the conclusion on classification. In particular since the TODA Carc. 1B classification is based on a study, not on the substance itself, but on an analogue.				
Dossier Submitter's Response				
France: Thank you for your comment. See responses to comments 2 and 5				
RAC's response				
Thank you for the comments. RAC agrees that the read across needs better justification. RAC is of the opinion that read across should be from MDI/TDI rather than from TODA.				

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2020	Japan	Nippon Soda Co., Ltd.	Company-Manufacturer	9
Comment received				
Nippon Soda Co. Ltd. disagrees with the proposed harmonised classification and labelling of TODI for Carc.1B based on the read-across to the diamine TODA. This classification is based on the assumption of completely hydrolysis of TODI to TODA, which does not take into account the available data on in vivo metabolism for the structurally very similar MDI. In vivo metabolism studies following inhalation exposure to MDI and TDI, which is the most relevant route for occupational exposure to diisocyanates, TDA or MDA could not be detected. This is mainly due to the fact that diisocyanates react rapidly with glutathion forming GSH conjugates [1,2,3]. MDI is not mutagenic [1] and is reported to follow a non-genotoxic mode of action regarding carcinogenicity after inhalation exposure to rats [3] leading to the classification as Carc. 2. In contrast, MDA is classified for Carc.1B and is a mutagen (Cat.2). For TDI no carcinogenicity was reported after inhalation exposure, only after oral exposure to rats and mice [4]. However, the oral studies are rated as not reliable [2] as a breakdown of TDI to TDA in the vehicle corn oil was assumed [2,4]. TDA is classified as mutagen Cat. 2 and Carc. 1B. In contrast, TDI is classified for Carc. 2 and not classified for mutagenicity.				

In summary, the proposed worst case assumption that TODI is completely metabolized in organisms to TODA is not justified. Based on the above information, it can be concluded that diisocyanates do not behave like the diamines in vivo and the read-across approach form TODA to TODI proposed for the endpoint carcinogenicity cannot be supported. Furthermore, it is rather inconsequent to accept the read-across from MDI for the endpoint mutagenicity but not for the endpoint carcinogenicity. Based on this, Nippon Soda Co. Ltd. proposes a harmonized classification and labeling as Carc. 2 for TODI based on the read-across to the structurally very similar MDI. References: [1] CoRAP Substance Evaluation Report, 4,4'-methylenediphenyl diisocyanate (MDI), EC No 202-966-0, November 2018 [2] CoRAP Substance Evaluation Report, m-tolylidene diisocyanate (TDI), EC No. 247-722-4, November 2013 [3] EU Risk Assessment Report, 4,4'-methylenediphenyl diisocyanate (MDI), 2007 [4] NTP Report No. 251, TOXICOLOGY AND CARCINOGENESIS STUDIES OF COMMERCIAL GRADE 2,4 (80%)-AND 2,6 (20%)TOLUENE DIISOCYANATE (CAS NO. 26471-62-5) IN F344/N RATS AND B6ClF1 MICE (GAVAGE STUDIES), August 1986A.
Dossier Submitter's Response
France: Thank you for your comment. Concerning the route of exposure, even if we agree that the inhalation is probably the most relevant one, the classification process have to take into account all existing route of exposure in its assessment. See response to comment 5
RAC's response
Thank you for the comments. RAC agrees that read across should be from MDI/TDI rather than from TODA.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
24.04.2020	Germany		MemberState	10
Comment received				
The DE-CA is in support of the conclusion drawn by the eMSCA that the available data do not trigger a classification as germ cell mutagen. While positive results from in vitro studies and insufficient data from in vivo experiments give rise to concern regarding mutagenic properties of the TODI, the data do not support a harmonised classification. However, we noticed a couple of minor issues. (1) Section 10.8 should exclusively cover the assessment of the mutagenic properties. In its current form, both mutagenicity and carcinogenicity are addressed together. We do not see the rationale behind the chosen approach for it is not known whether the MoCA is based on genotoxicity or not. (2) Some of the references to the tables within the text are faulty (e.g. Table 612, Table 614). (3) As there are indeed data on the target substance (according to or similar to an OECD test guideline), an assessment strategy may start with these data followed by supporting data from category members and potential metabolites. (4) Table 12 may be divided in (a) diisocyanates and (b) potential metabolites with reference to their respective parent compound. (5) A discussion regarding the formation of aromatic amines with respect to their known				

mutagenic properties may be worth adding. (6) It may be useful to address all members of the category regarding their mutagenic potential in analogy to the approach chosen for RS and skin sensitisation. According to table 12, both MDA and TDA carry a harmonised classification as Muta 2. (7) A data matrix would be helpful. (8) In section 10.8.3, the conclusion reads as follows: "In a grouping approach with other diisocyanates such as structurally similar MDI. It appears that most of the available test results of in vitro genotoxicity assays for 4,4'-MDI rather reflect the properties of reaction products formed under specific assay conditions than the ones of the parent compound.". It may be worth adding that due to a lack of proper ADME data for different routes of application, it is not known under which conditions these reaction products are formed in vivo or whether they are formed at all. (9) The studies listed in Table 14 should be assessed in more detail. Important information is missing such as: deviations, number of animals used, positive/negative control, cytotoxicity (indicator of bone marrow exposure) within the MN test, etc.
Dossier Submitter's Response
Thank you for your comment, your carefull reading of the report, and your support of classification proposal.
RAC's response
Thank you for your comment, RAC agrees with the no-classification conclusion.

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2020	Sweden		MemberState	11
Comment received				
The SE CA agrees that no classification of TODI for germ cell mutagenicity is warranted. Some specific comments: It is not clear why no detailed description of the Comet assay of MDI (Anonymous, 2016) was presented in the CLH-report if read-across from this study was applied. To us, this study seems also as a relevant follow up on the observed increases of mutant frequencies of TODI in the OECD 476 study, which is otherwise lacking for TODI (only an in vivo micronucleus assay via i.p. administration available). There is also no study summary available in Annex I. Thus, it is not possible to make an independent assessment of this study. In the comparison with criteria for germ cell mutagenicity, the conclusion should be made that there are positive in vitro mutagenicity tests of TODI, both for gene mutations and chromosomal aberrations. But the available in vivo micronucleus test of TODI was negative (but also unclear if bone marrow was reached) and there is no structural similarity to a known germ cell mutagen. Therefore, category 2 classification is not possible. In addition, there was a positive in vitro gene mutation study but there was no relevant in vivo study of TODI available to follow up on the gene mutation concern (other than the Comet assay on MDI that was negative) and there is no structural similarity to a known germ cell mutagen and therefore category 2 is not warranted.				
Dossier Submitter's Response				
Thank you for your comment and support.				
RAC's response				
Thank you for your comment, RAC agrees with the no-classification conclusion.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 3,3'-DIMETHYLBIPHENYL-4,4'-DIYL DIISOCYANATE

Date	Country	Organisation	Type of Organisation	Comment number
07.05.2020	Germany	Nisso Chemical Europe GmbH	Please select organisation type..	12
Comment received				
NCE agrees with the proposal not to classify TODI for mutagenicity. It has been emphasized in the CLH report that most of the available test results of in vitro mutagenicity assays for TODI rather reflect the properties of reaction products formed under specific assay conditions than the ones of the parent compound. The CLH report points out that the mutagenicity studies performed with TODI in vitro utilized inappropriate vehicles and it is not possible to conclude whether the positive results observed in the in vitro tests are due to TODI and/or TODA and/or other degradation products. Therefore, data from the structurally similar diisocyanate MDI have been evaluated in a read-across approach to come to a final conclusion regarding the mutagenic potential of TODI. Results from an OECD TG 489 study confirmed that the structurally closely related diisocyanate MDI did not cause a significant increase in DNA damage in the lung, liver, and stomach after inhalation exposure. Overall, it was concluded that MDI does not show a genotoxic potential (eMSCA Estonia, 2018 [1]). The CLH report came to the conclusion that based on the available in vivo results for TODI and the results from the read-across from MDI, TODI does not have to be classified for mutagenicity. There is no data available regarding mutagenicity of the hydrolysis product TODA. For MDA a harmonized classification and labeling for mutagenicity Cat. 2 is available. This indicates that the toxicity potential of MDI is different from the diamine MDA. It is assumed that TODA differs also from TODI in this regard. Reference: [1] CoRAP Substance Evaluation Report, 4,4'-methylenediphenyl diisocyanate (MDI), EC No 202-966-0, November 2018				
Dossier Submitter's Response				
Thank you for your comment and support.				
RAC's response				
Thank you for your comment, RAC agrees with the no-classification conclusion.				

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
07.05.2020	Germany	Nisso Chemical Europe GmbH	Please select organisation type..	13

Comment received

NCE agrees with the proposed harmonized classification and labeling for skin and respiratory sensitization (Resp. Sens. 1 and Skin Sens. 1A, H317 and H334).
The presented data in the CLH report outline a common underlying mechanism for substances possessing isocyanate groups and highlight the reactivity of these towards proteins in general. As stated, "the isocyanate functional group marks a well-known structural alert for respiratory sensitization 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 of proteins" (CLH report, p. 11). In light of this plausible mechanism NCE wants to emphasize that in order to induce respiratory sensitization TODI must react directly with proteins and therefore will not be totally metabolized in vivo to its diamine TODA as proposed in the section on carcinogenicity of the CLH report. This is also evidenced by the fact that the diisocyanates MDI, TDI and HDI are well known respiratory sensitizers, whereas the corresponding diamines MDA, TDA and HDA are not; they are only skin sensitizers (MDA and TDA) or even not sensitizing at all (HDA). In summary, the isocyanate moiety in TODI is essential for the induction of respiratory sensitization, leading to the conclusion that the assumption of a complete metabolism of TODI to TODA as stated in the CLH report is not justified.

Dossier Submitter's Response

DE-CA: Thank you for your comment and support of the proposed harmonized classification for skin and respiratory sensitisation.
For your comment on metabolism please see Comment 5 and the corresponding response. No valid test on skin sensitisation is available for HDA.

RAC's response

Thank you for your comment and support of the proposed harmonized classification for skin and respiratory sensitisation.

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2020	Sweden		MemberState	14

Comment received

As stated in section 3.4.2.1 of Annex I to the CLP Regulation, classification for respiratory sensitisation is typically based on human data with supportive evidence from e.g. animal data. No human or animal data is available for TODI and although the CLP criteria cannot directly be applied, the Swedish CA supports the category approach for read-across taken by the Dossier Submitters. Hence, classification of TODI as Resp. Sens. 1, H334 is supported based on sufficient evidence of the hazardous property, including the following pieces of information;
1) TODI contains the diisocyanate structure which is an alert for respiratory sensitisation (REACH guidance on IR/CSA, Table R.7.3-3, and OECD QSAR toolbox),

2) read-across of data from structurally related diisocyanates HDI, MDI and TDI, clearly showing the respiratory sensitisation potential of the source substances in humans. 3) supporting evidence by read-across of animal data from structurally similar diisocyanates HDI, MDI and TDI, clearly showing their respiratory sensitisation potential.
Dossier Submitter's Response
DE-CA: Thank you for your comment and support.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
07.05.2020	Germany	Nisso Chemical Europe GmbH	Please select organisation type..	15
Comment received				
NCE agrees with the proposed harmonized classification and labeling for skin sensitization (Skin Sens. 1A, H317).				
Dossier Submitter's Response				
DE-CA: Thank you for your comment and support.				
RAC's response				
Thank you for your comment and support.				

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2020	Sweden		MemberState	16
Comment received				
Skin Sensitisation: The proposal to classify TODI as a skin sensitizer is based on a GPMT study in which it was reported that an intradermal induction dose of 0.01% resulted in 80-90% sensitization rate. The Swedish CA hence agrees with the proposed classification as Skin Sens 1A, H317 with a specific concentration limit of 0.001%.				
Dossier Submitter's Response				
DE-CA: Thank you for your comment and support.				
RAC's response				
Thank you for your comment and support.				

PUBLIC ATTACHMENTS
1. Comment Freudenberg Sealing Technologies_update_2020-05-20.pdf [Please refer to comment No. 7]