Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

1,5-naphthylene diisocyanate

EC Number: 221-641-4
CAS Number: 3173-72-6

CLH-O-0000006855-63-01/F

Adopted

17 September 2020

17 September 2020

CLH-O-0000006855-63-01/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: **1,5-naphthylene diisocyanate**

EC Number: **221-641-4**

CAS Number: **3173-72-6**

The proposal was submitted by **Germany** and received by RAC on **19 June 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	615-007-00-X	1,5-naphthylene diisocyanate	221-641-4	3173-72-6	Acute Tox. 4* Skin Irrit. 2 Eye Irrit. 2 Resp. Sens. 1 STOT SE 3 Aquatic Chronic 3	H332 H315 H319 H334 H335 H412	GHS08 GHS07 Dgr	H332 H315 H319 H334 H335 H412			
Dossier submitters proposal	TBD	1,5-naphthylene diisocyanate [containing < 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]	221-641-4	3173-72-6	**Add** Skin Sens. 1A **Remove** Acute Tox. 4*	**Add** H317 **Remove** H332		**Add** H317 **Remove** H332			
	TBD	1,5-naphthylene diisocyanate [containing ≥ 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]	221-641-4	3173-72-6	**Add** Skin Sens. 1A **Modify** Acute Tox. 2	**Add** H317 **Modify** H330	**Add** GHS06 **Remove** GHS07	**Add** H317 **Modify** H330		**Add** Inhalation: ATE = 0,27 mg/L (dusts or mists)	
RAC opinion	TBD	1,5-naphthylene diisocyanate [containing < 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]	221-641-4	3173-72-6	**Add** Skin Sens. 1A **Remove** Acute Tox. 4*	**Add** H317 **Remove** H332		**Add** H317 **Remove** H332			
	TBD	1,5-naphthylene diisocyanate [containing ≥ 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]	221-641-4	3173-72-6	**Add** Skin Sens. 1A **Modify** Acute Tox. 2	**Add** H317 **Modify** H330	**Add** GHS06 **Remove** GHS07	**Add** H317 **Modify** H330		**Add** Inhalation: ATE = 0,27 mg/L (dusts or mists)	
Resulting Annex VI entry if agreed by COM	TBD	1,5-naphthylene diisocyanate [containing < 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]	221-641-4	3173-72-6	STOT SE 3 Skin Irrit. 2 Eye Irrit. 2 Resp. Sens. 1 Skin Sens. 1A Aquatic Chronic 3	H335 H315 H319 H334 H317 H412	GHS07 GHS08 Dgr	H335 H315 H319 H334 H317 H412			
	TBD	1,5-naphthylene diisocyanate [containing ≥ 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]	221-641-4	3173-72-6	Acute Tox. 2 STOT SE 3 Skin Irrit. 2 Eye Irrit. 2 Resp. Sens. 1 Skin Sens. 1A Aquatic Chronic 3	H330 H335 H315 H319 H334 H317 H412	GHS06 GHS08 Dgr	H330 H335 H315 H319 H334 H317 H412	EUH204	Inhalation: ATE = 0,27 mg/L (dusts or mists)	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

The current harmonised classification for 1,5-naphthylene diisocyanate (NDI), which is used in the plastics industry as a curing agent, was transposed from the previous legislation (the Dangerous Substances Directive, Dir. 67/548/EEC) to Annex VI of the CLP Regulation, but further details are not available.

The CLH report has been created based on data submitted by the lead registrant in the REACH registration dossier, 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). Also, SCOPUS and PubMed databases were searched for relevant literature.

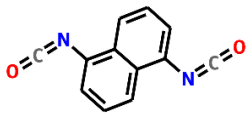

Figure: NDI structure

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

NDI's current Annex VI entry for acute toxicity is Acute Tox. 4*; H332. The DS proposed to modify this classification into a **split entry** as follows:

- 1,5-naphthylene diisocyanate [containing **< 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]: no classification**
- 1,5-naphthylene diisocyanate [containing **≥ 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]: Acute Tox. 2; H330**. Inhalation: ATE = 0,27 mg/L (dusts or mists).

According to the REACH registration dossier, the substance is solid at 20°C and has a very low vapour pressure (8.0 x 10^{-4} Pa at 25.0°C). The particle size distribution of the registered substance is:

Particle size	Amount
> 875 µm	82.0 %
> 100 - < 875.0 µm	16.7 %
> 50 - < 100 µm	1.0 %
< 50 µm	0.3 %

This was measured by a dry dispersion technique by combined manual sieving at 875 µm and laser diffraction. It was observed that significant amounts of the substance stick to the vibrational feeding system, which was used for laser diffraction analysis. Additionally, agglomeration of fine particles in the vibrational feeder was likely to occur due to the cohesive nature of the substance.

In the REACH registration dossier, the lead registrant provided the following statement with relevance to available toxicokinetic information for NDI regarding the inhalation route: "*Experimental toxicokinetic studies were not performed. NDI is a white to yellowish organic solid with a very low vapour pressure under normal ambient conditions (8 x 10^{-6} hPa at 25°C), therefore inhalation exposure to the vapour is expected to be negligible. Currently available data on particle size during worst-case end-use of NDI indicate a thoracic percentage of 0.02% that can be inhaled by humans and may reach the thoracic region.*" (Bayer, 2010).

For evaluation of acute inhalation toxicity, three studies in Wistar rats were available, summarised in the table below. The DS only had access to the study summaries in the registration dossier. Therefore, the excerpts reported below are from the study summaries provided by the lead registrant for NDI under REACH, or reproduced by the DS from the summary in the REACH registration dossier with slight editorial modifications.

***Table*:** *Summary by the DS of the animal studies for acute inhalation LC_{50} determination (originally Table 6 in the CLH proposal). The texts referred to are in the original CLH proposal*

<table>
<tr><th>Method, guideline, deviations</th><th>Species, strain, sex, no/group</th><th>Test substance, duration of exposure, form, dose levels, and particle size, results</th><th>Reference</th></tr>
<tr><td>OECD 403/EU B.2

GLP claimed

Reliability 2 (reliable with restrictions): Only summary available

Key study</td><td>Rat, Wistar, 5M+ 5F per group</td><td>NDI, aerosol (dust), 1 x 4 h, nose-only

<table>
<tr><td>Dose level (mg/m³)</td><td>0</td><td>96</td><td>189</td><td>238</td><td>314</td><td>384</td><td>541</td></tr>
<tr><td>MMAD (µm)</td><td>NA</td><td>3.1</td><td>3.2</td><td>4.0</td><td>3.6</td><td>3.8</td><td>3.1</td></tr>
<tr><td>GSD (µm)</td><td>NA</td><td>1.6</td><td>1.7</td><td>2.1</td><td>1.5</td><td>1.5</td><td>1.6</td></tr>
<tr><td>Mortality (no. dead/no. exposed)
M
F</td><td>
0/5
0/5</td><td>
0/5
0/5</td><td>
0/5
0/5</td><td>
3/5
3/5</td><td>
3/5
3/5</td><td>
4/5
4/5</td><td>
4/5
4/5</td></tr>
<tr><td>Mortality (%, M+F combined)</td><td>0</td><td>0</td><td>0</td><td>60</td><td>60</td><td>80</td><td>80</td></tr>
</table>
LC_{50} (4h) = 0.27 mg/L

Cf. text for further details (including clinical signs)</td><td>(Bayer, 1995a)</td></tr>
</table>

<table>
<tr><th>Method, guideline, deviations</th><th>Species, strain, sex, no/group</th><th>Test substance, duration of exposure, form, dose levels, and particle size, results</th><th>Reference</th></tr>
<tr><td>Non-guideline

GLP claimed

Reliability 2 (reliable with restrictions): Only summary available, observation time post-exposure: 7 d (instead of 14 d as recommended by OECD TG 403), MMAD outside the range recommended by OECD TG 403

Supporting study</td><td>Rat, Wistar, 18 M/group</td><td>NDI, aerosol (dust), 1 x 4 h, nose-only

<table>
<tr><td>Dose level (mg/m³)</td><td>0</td><td>56</td><td>140</td><td>148</td><td>240</td><td>245</td><td>1 050</td></tr>
<tr><td>MMAD (µm)</td><td>NA</td><td>3.1</td><td>4.1§</td><td>6.9§</td><td>5.4§</td><td>9.0§</td><td>10.1§</td></tr>
<tr><td>GSD (µm)</td><td>NA</td><td>1.9</td><td>1.9</td><td>2.4</td><td>2.1</td><td>2.5</td><td>2.8</td></tr>
<tr><td>Mortality (no. dead/no. exposed)</td><td>0/18</td><td>0/18</td><td>2/18</td><td>0/18</td><td>7/18</td><td>0/18</td><td>18/18</td></tr>
<tr><td>Mortality (%)</td><td>0</td><td>0</td><td>11</td><td>0</td><td>39</td><td>0</td><td>100</td></tr>
</table>

LC_{50} (4 h) not calculated

Cf. text for further details (including clinical signs)</td><td>(Bayer, 2003)</td></tr>
</table>

<table>
<tr><td>Similar to OECD 403/EU B.2

GLP claimed

Reliability 2 (reliable with restrictions): Only summary available, MMAD outside the range recommended by OECD TG 403

Supporting study</td><td>Rat, Wistar, 5M+5F per group</td><td>NDI, aerosol (dust), 1 x 1 h, nose-only

<table>
<tr><td>Dose level (mg/m³)</td><td>0</td><td>1 285</td><td>2 075</td></tr>
<tr><td>MMAD (µm)</td><td>NA</td><td>4.6§</td><td>8.1§</td></tr>
<tr><td>GSD (µm)</td><td>NA</td><td>1.6</td><td>1.7</td></tr>
<tr><td>Mortality (no. dead/no. exposed)
M
F</td><td>
0/5
0/5</td><td>
1/5
0/5</td><td>
0/5
0/5</td></tr>
<tr><td>Mortality (%, M+F combined)</td><td>0</td><td>10</td><td>0</td></tr>
</table>

For details regarding clinical signs, cf. text.</td><td>(Bayer, 1995b)</td></tr>
</table>

§ Outside the range recommended by OECD TG 403 (1-4 µm).

Bayer (1995a) was identified as the **key study** by the DS and used as the basis for the classification proposal. In this study, using 1 x 4h nose-only exposure to aerosol (dust), mortality was seen at concentrations of 238 mg/m^3 and above (see table above). Decreased body weights were observed in all groups exposed to the test compound. None of the rats in the control group exhibited any clinical signs. In the test substance groups, clinical signs were observed in all rats at all tested dose levels. They included bradypnea, laboured breathing pattern, nose/snout area

with red encrustations, reduced motility, flaccid appearance, ungroomed hair-coat and piloerection. In addition, rales, salivation, serous discharge from nose, cyanosis and apathy were seen at 189 mg/m^3 and above. At 96 mg/m^3 and above, also a concentration-dependent decrease of body temperature was recorded. The onset and duration of the clinical signs was 4h – 11 days in all dose groups and both sexes. The onset of mortality, where it occurred, was 1 – 2 days. Gross pathology findings in the animals sacrificed during the observation period of 4 weeks included white foamy discharge from snout, red encrustation in the muzzle area, lungs with dark-red colourations and spongy (oedematous) appearance, foam in trachea, distended hydrothorax, lobulation of liver, and pale parenchymatous organs. In rats sacrificed at the end of the observation period, an increased incidence of macroscopical findings was observed on lungs. However, the findings appeared not to be induced in a clear concentration-dependent manner. The LC_{50} value (aerosol, 4h) was determined as 270 mg/m^3 for male and female rats combined. In this study, the particle sizes varied between 3.1 – 4.0 µm (mass median aerodynamic diameter (MMAD), geometric standard deviations (GSD), between 1.5 – 2.1 µm).

The other two available studies were considered by the DS as supporting, but important in demonstrating a dependency of NDI associated mortality on the particle size distribution. These studies were not used for classification directly because they either applied only 1h exposure and/or used test materials with MMADs outside the range recommended in OECD TG 403. However, they were seen by the DS as relevant for the evaluation whether the split-entry concept for acute toxic substances via the inhalation route is applicable to NDI.

The non-guideline, 1 x 4h, nose-only study (Bayer, 2003) focused on an analysis of bronchoalveolar lavage (BAL) parameters rather than lethality. In the 56, 140, 148, 240, 245 and 1050 mg/m^3 exposure groups, the MMAD (GSD) were 3.1 (1.9), 4.1 (1.9), 6.9 (2.4), 5.4 (2.1), 9.0 (2.5) and 10.1 (2.8) µm, respectively. Except for the 56 mg/m^3 group, all of these distributions were outside the MMAD range recommended in OECD TG 403. All rats in the control group tolerated the exposure without clinical signs. In all exposure groups, mean body weights were markedly different from the control group. The clinical signs were similar to those reported in Bayer (1995a), again visible in all rats in each test compound group, and mostly comparable across all of the exposure groups. In this study, the onset and duration of the clinical signs was 0 – 7 days. The onset of mortality, when it occurred, was 0 – 2 days. In gross pathology, in all groups exposed to the test substance, concentration dependent macroscopic alterations of the respiratory tract were observed.

Moreover, in Bayer (2003), BAL fluid was collected on post-exposure days 1, 3, and 7 and analysed for indicators of inflammatory response and lower respiratory tract damage as well as for interactions with pulmonary phospholipids. According to the registration dossier, *absolute lung weights were significantly increased in all […] exposure groups*. Despite the increase, observed lung weights of the exposure groups were indistinguishable from the control group on day 7. From all endpoints, increase in protein was most prominent. The conclusion by the lead registrant on the BAL results was that the influx of protein into the alveoli and the elevated lung weights were dependent upon the actually respirable mass (total mass concentration x fraction penetrating the alveolar region; approximate cut-off for rats is 5 µm) rather than total concentration.

The DS noted that while Bayer (2003) is not a suitable study as a basis for classification as such, it demonstrated that acute toxicity of NDI is a function of not only the total air concentration, but in particular of the particle size distribution. An external concentration of 140 mg/m^3 NDI (MMAD: 4.1 µm) resulted in 11% mortality, while a concentration of 148 mg/m^3 NDI (MMAD: 6.9 µm) did

not cause any mortality (see table above). Likewise, 240 mg/m^3 NDI (MMAD: 5.4 µm) was lethal for 39%, while all of the animals survived exposure to 245 mg/m^3 NDI (MMAD: 9.0 µm). Overall, the DS agreed that these results suggest a strong dependency of NDI associated lethality on the particle size distribution of the test material, and that Pauluhn (2004) demonstrated the correlation of BAL fluid parameters with particle MMAD.

In the third study (Bayer, 1995b), the study design was similar to OECD TG 403, but with an exposure duration of 1 x 1h only, creating a high degree of uncertainty (see table above). In addition, the MMADs of the test materials used were clearly outside the range recommended by OECD TG 403 (1 – 4 µm): in the 1285 and 2075 mg/m^3 exposure groups, the MMAD (GSD) were 4.6 (1.6) and 8.1 (1.7) µm. The results were summarised by the registrant as follows: "*Aerosol (dust) concentrations up to 1 285 mg/m^3 did induce test substance related mortality (males: 1 out of 5 rats died; females: no mortality). Exposure to the limit concentration of 2075 mg/m^3 test compound was tolerated without mortality. Mortality occurred on post-exposure day ten. Necropsy findings support the conclusion that a causal relationship between lethality and lung damage existed. Exposure to concentrations of 1285 mg/m^3 and higher were followed by concentration-dependent signs suggestive of irritation of the respiratory tract (e.g. bradypnoea, dyspnoea, laboured breathing pattern, rales, nose/snout area with red encrustations, serous discharge from nose, cyanosis) and non-specific signs such as reduced motility and flaccid muscle tone. The duration of signs (maximum duration up to day 9) was dependent on respiratory signs"* (Bayer, 1995b).

Split-entry

In section 3.1.2.3.2 (p. 242), the ECHA Guidance on the Application of the CLP Criteria (v5.0, 2017) notes: *"The use of highly respirable dusts and mists is ideal to fully investigate the potential inhalation hazard of the substance. However, it is acknowledged that these exposures may not necessarily reflect realistic conditions. For instance, solid materials are often micronised to a highly respirable form for testing, but in practice exposures will be to a dust of much lower respirability. Similarly, pastes or highly viscous materials with low vapour pressure need strong measures to be taken to generate airborne particulates of sufficiently high respirability, whereas for other materials this may occur spontaneously. In such situations, specific problems may arise with respect to classification and labelling, as these substances are tested in a form (i.e. specific particle size distribution) that is different from all the forms in which these substances are placed on the market and in which they can reasonably be expected to be used.*

A scientific concept has been developed as a basis for relating the conditions of acute inhalation tests to those occurring in real-life, in order to derive an adequate hazard classification. This concept is applicable only to substances or mixtures which are proven to cause acute toxicity through local effects and do not cause systemic toxicity (Pauluhn, 2008)" (ECHA, 2017).

In Pauluhn (2008), further guidance on the applicability of the EU split–entry concept is provided. In this context, criteria are defined which are supportive or prohibitive for its use (see table below). Relevant findings for NDI from the two 4h acute toxicity tests via the inhalation route are summarised by the DS in next table below (the DS's comparison between the criteria from Pauluhn (2008) and relevant findings for NDI…), and compared with the above mentioned criteria. This latter table also shows the DS's conclusions on whether each finding is considered supportive or prohibitive for the use of the split-entry concept.

Table: *Criteria supportive of or prohibitive for the use of the split-entry concept (by default all criteria refer to findings from an acute 4h inhalation study using the OECD (2007) protocol), from Pauluhn (2008), originally Table 9 in the CLH proposal*

	Mandatory endpoint	RT (ET-TB)	Pulmonary (alveolar)	Supportive of the use of split-entry	Prohibitive for the use of split-entry
Non-inhalation route (acute)	Yes	-	-	Low toxicity	High toxicity
MMAD				< approx. 4 µm	>> 4 µm
Irritation/inflammation		Minimal	Yes	Yes	-
Lethality dependent on particle size		-	-		No
Onset of lethality				Immediate (up to day 7)	If delayed in onset (≥ 8d)
Respiratory distress		Minimal	Yes	Yes	
Evidence on severe non-respiratory tract toxicity	-	-	-	No	Yes, if not secondary
Necropsy findings in succumbed rats	Yes			Hepatisation, lung enlarged, oedema	No findings in lungs
Increase in BAL protein	Supportive		Yes	Yes	-
Histopathology				Major lesions restricted to lower RT	Major lesions distributed throughout RT
Severe extrapulmonary organ damage	-		-	No	Yes

MMAD: mass median aerodynamic diameter of particulate atmosphere in the vicinity of the breathing zone of animals and measured by cascade impactor, post-exposure days are relative to day 0 (exposure day); RT: respiratory tract; ET: extrathoracic region (pharynx, nasal passages); TB: tracheobronchial region; - : not applicable.

Table: *The DS's comparison between the criteria from Pauluhn (2008) and relevant findings for NDI (originally Table 10 in the CLH proposal)*

Criterion	Data for NDI			DS's conclusion for NDI
	Bayer, 2003	Bayer, 1995a	Other study	
Lethality dependent on particle size	56 mg/m³ (3.1 µm MMAD): no mortality 140 mg/m³ (4.1 µM MMAD): 2/18 dead 148 mg/m³ (6.9 µm MMAD): no mortality 240 mg/m³ (5.4 µm MMAD): 7/18 dead 245 mg/m³ (9.0 µm MMAD): no mortality 1050 mg/m³ (10.1 µm MMAD): 18/18 dead	96 mg/m³ (3.1 µm MMAD): no mortality 189 mg/m³ (3.2 µm MMAD): no mortality 238 mg/m³ (4.0 µm MMAD): 6/10 dead 314 mg/m³ (3.6 µm MMAD): 6/10 dead 384 mg/m³ (3,8 µm MMAD): 8/10 dead 541 mg/m³ (3,1 µm MMAD): 8/10 dead	Not applicable	Supportive
Onset of lethality	Onset of lethality: days 0-2	Onset of lethality: days 1-2		
Respiratory distress	Onset of clinical signs: Day 0 Signs: bradypnoe, laboured breathing pattern, breathing sounds, stridor, nasal discharge (serous), nostrils: reddened, red encrustations, dyspnoe	Onset of clinical signs: 4 h Signs: bradypnoe, laboured breathing pattern, rales, nose/snout area with red encrustations, serous discharge from nose		
Evidence on severe non-respiratory tract toxicity	No effects reported (decrease of rectal body temperature not considered severe)	No effects reported (decrease of rectal body temperature not considered severe)		
Necropsy findings in succumbed rats	"Absolute lung weights were significantly increased in all exposure groups."	Lungs with dark-red colourations and spongy (oedematours) appearance		
Increase in BAL protein	"From all endpoints the increase in protein was most prominent. […] this endpoint is considered to be the most sensitive one to assess early changes."	BALF not examined		
Histopathology	Data not available	Data not available		Criterion cannot be evaluated.
Severe extrapulmonary organ damage	Severe extrapulmonary organ damage not reported	Severe extrapulmonary organ damage not reported (lobulation of liver/pale parenchymatous organs not considered severe)		Supportive

The DS concluded that there is sufficient supportive evidence from the toxicological data that the split-entry concept is applicable to NDI. In addition, according to the CLP Regulation, Annex I, Table 3.1.1, NDI meets Category 2 criteria for acute toxicity via the inhalation route as the calculated LC_{50} was 0.27 mg/L. With regard to the split-entry concept, the DS proposed to establish a split entry for NDI in analogy to tolylfluanid (index numbers 613-116-00-7/613-116-01-4) and several per(oxo)borates (index numbers 005-017-00-7/005-017-01-4, 005-018-00-2/005-018-01-X, and 005-019-00-8/005-019-01-5):

- If NDI contains < 0.1% (w/w) of particles with an aerodynamic diameter of below 50 µm, no classification for acute toxicity via the inhalation route is warranted.
- If NDI contains ≥ 0.1% (w/w) of particles with an aerodynamic diameter of below 50 µm, it should be classified as Acute Tox. 2; H330: Fatal if inhaled, with an ATE = 0,27 mg/L (dusts or mists).

Comments received during consultation

One Member State Competent Authority (MSCA) agreed with the proposed classification for acute inhalation toxicity and the use of a split-entry as proposed by the DS. One Company-Manufacturer and two Company-Importers agreed with the use of a split entry, and the two entries being Acute Tox. 2; H330 and no classification. However, they disagreed with the cut-off limit proposed by the DS and proposed that NDI with a concentration of particles with aerodynamic diameter of below 50 µm should not be classified if their concentration is < 0.1% w/w while be classified as Acute Tox. 2 if ≥ 0.1% w/w.

In their comment, the lead registrant remarked that the thoracic fraction of the substance is the toxicity determining parameter when a split-entry concept applies to acute inhalation toxicity. They stated that the the-cut off limit proposed by the DS was only based on analogy to previous entries. They assumed that the cut-off of 50 µm proposed by the DS was based on the parameters laid down in the plant protection product (PPP) regulation, and stated that in their opinion, analogy to the PPP tolylfluanid is not applicable to an industrial chemical without known spray applications, such as NDI.

Furthermore, the lead registrant presented calculations with the purpose of transposing the available acute inhalation toxicity data on NDI to the typical particle-size of the substance as produced. In their calculation, they used a concentration of the thoracic fraction of 0.02% w/w which they claim correspond to the NDI as produced. In addition, the calculations aimed to recompute the thoracic fraction percentage which would not to trigger classification considering the respective ATE interval of the individual categories of acute inhalation toxicity. Based on these calculations, they proposed the following cut-off limits for classification:

- C_{th} < 5.4% no classification for acute toxicity via the inhalation route.
- C_{th} ≥ 5.4% classified as Acute Tox. 2; H330.

The DS replied by noting that the aim is to classify all possible NDI materials, not just one specific material. Furthermore, they mentioned that, while ECHA's CLP guidance refers to the split-entry concept, it does not provide a workable definition of the thoracic fraction. Moreover, the upper limit of 50 µm used was not derived from the Plant Protection Product Regulation, but from the table 1 in norm EN481. According to this table, 50 µm marks the lowest particle size without contribution to the thoracic fraction (vs. 0.1% of the particles at 40 µm, 1.0% at 30 µm, 3.0% at 25 µm etc.). The DS additionally noted that EN481 also describes the thoracic fraction as a cumulative (log)normal distribution with a median of 11.64 µm and a geometric standard deviation of 1.5. Consequently, the 50 µm limit chosen in previous cases where the split-entry concept was applied might be considered as quite conservative. The DS also stated that the use of 10 µm as the upper limit of the thoracic fraction is not acceptable to as 55.5% of the particles with a diameter of 11 µm, and still 9.1% of the particles with 20 µm diameter, contribute to the thoracic fraction (EN481, table 1). In the Currenta study (2019), submitted during the consultation, almost 74% of the test material had a particle size of 10-50 µm. The DS noted that the proposal from the manufacturer to define classification borders based on the percentage of the thoracic fraction rather than a specific particle size cut-off would bear a considerable risk of under classification if the 10 µm limit was used. Therefore, the DS would rather prefer the classification borders would be defined based on an upper limit particle size. If the percentage of thoracic fraction would be used, then a clear definition would be needed to allow for a correct and unambiguous determination of that fraction.

A Company-Importer first expressed their support for the lead-registrant's comment and argumentation. In addition, they, along with a second Company-Importer, suggested to use already existing values for the definition of the diameter of inhalable dust, in order to have a harmonisation of different legal regulations. They presented as reference the ADR 2019 (chapter 2.2.61.1.3), which describes the principle requirement for the testing of a substance for acute

toxicity by inhalation. This is defined by min 10% w/w of inhalable dust with an aerodynamic radius of < 10 µm. Therefore, they suggested to define the particle size accordingly by < 10 µm instead of < 50 µm as proposed by the DS.

The DS restated their opinion, in particular that an upper limit of 10 µm does not appear sufficiently conservative based on norm EN481.

Assessment and comparison with the classification criteria

There are three studies available to assess NDI's acute inhalation toxicity. Of these, only one can be used directly for classification. This key study was performed according to OECD TG 403 and under GLP in Wistar rats (5 M + 5 F), using 1 x 4h nose-only exposure (Bayer, 1995a). The DS assessed the reliability of this study as 2, due to only the summary being available in the REACH registration dossier. In this study, the LC_{50} value was 0.27 mg/L. As shown in the table below, the LC_{50} value meets the criteria for classification as Acute Tox. 2.

Table: *Comparison of the LC_{50} value for NDI with the classification criteria for dusts and mists according to Table 3.1.1 of the CLP regulation (originally Table 11 in the CLH proposal)*

CLP Acute Toxicity Category	Relevant ATE for dusts/mists (mg/L)	LC_{50}-value calculated for NDI (mg/L)	Resulting classification	Reference
Category 1	≤ 0.05	0.27	**Acute Tox. 2**	(Bayer, 1995a)
Category 2	> 0.05 - ≤ 0.5			
Category 3	> 0.5 - ≤ 1.0			
Category 4	> 1.0 - ≤ 5.0			

The two other GLP studies available cannot be used directly for classification. Bayer (2003) was reported by the lead registrant as a non-guideline study, and the MMAD of the test material was outside the range recommended by OECD TG 403. While the study design of the third study (Bayer, 1995b) was otherwise similar to OECD TG 403, it deviated on the exposure time, 1h instead of 4h, and in the MMAD of the test material which was outside the recommended range. LC_{50} values were not derived in these two studies. In Bayer (2003), where rats were exposed to NDI for 1 x 4h, larger particles (~7-9 µm, GSD ~2.5 µm) tested at dose levels of ~140-150 and ~240-245 mg/m^3 did not cause mortality while smaller particles (~4-5.5 µm, GSD ~2 µm) tested at corresponding dose levels did (see table "Summary by the DS of the animal studies for acute inhalation LC_{50} determination…" above). In Bayer (1995b), 1 x 1h exposure was not lethal at 2075 mg/m^3, when the MMAD was 8.1 µm (GSD 1.7 µm) and, caused 10% mortality at a substantially lower dose level of 1285 mg/m^3 when the particle MMAD was 4.6 µm (GSD 1.6 µm).

RAC agrees with the DS that both studies (Bayer, 2003 and 1995b) show that the particle size of NDI has an impact on its acute toxicity via the inhalation route.

NDI is a solid substance with a very low vapour pressure. Considering the results of the three inhalation toxicity studies, and section 3.1.2.3.2 (p. 242) of the CLP guidance cited under the sub-heading *"Split-entry concept"*, RAC agrees with the DS that a split-entry is applicable.

However, the available data on NDI do not allow determination of a "safe" NDI particle size warranting no classification, which could be used as the cut-off limit for the split entry. The largest particle size tested was 10.1 µm MMAD (GSD 2.8 µm) at one dose level of 1050 mg/m^3 (1.05 mg/L). This was the highest dose tested in the non-guideline study using a 1 x 4h nose-only exposure (Bayer, 2003), and it was 100% lethal. Although not directly applicable to classification purposes, this result would indicate at least a category 3 classification for the acute inhalation toxicity of this particle size.

Therefore, RAC agrees with the DS that 10 µm, as proposed in the consultation, is clearly not an acceptable cut-off limit for the split entry. On the other hand, the cut-off particle size of 50 µm proposed by the DS is a conservative value, aimed at ensuring that all of the particles are above the thoracic fraction.

There is no clear definition available for the particle size of the thoracic fraction, which is a spectrum below 50 µm. As mentioned also by the DS in their response to a consultation comment, the norm EN481 describes the thoracic fraction as a cumulative (log)normal distribution with a median of 11.64 µm and a GSD of 1.5. Furthermore, in the norm EN481, 50 µm marks the lowest particle size without contribution (whereas, 0.1% of the particles at 40 µm, 1.0% at 30 µm, 3.0% at 25 µm etc. contribute to the thoracic fraction). Similarly, according to the Particle Size-Selective Sampling Criteria for Airborne Particulate Matter by the American Conference of Governmental Industrial Hygienists (ACGIH®), thoracic particulate matter is composed by 50% of particles with 10 µm aerodynamic diameter and 2% of particles with 25 µm aerodynamic diameter.

As a practical solution, RAC agrees with the DS to set the cut-off limit to particles just above the thoracic fraction and that it is preferable to clearly define a specific particle size cut-off, rather than a percentage of the thoracic fraction. Especially, as there is no clear-cut definition for the thoracic fraction available. The same cut-off of particle size 50 µm has previously been used for the split entries of tolylfluanid (index numbers 613-116-00-7/613-116-01-4) and several per(oxo)borates (index numbers 005-017-00-7/005-017-01-4, 005-018-00-2/005-018-01-X, and 005-019-00-8/005-019-01-5). Consistency between the split-entries is considered by RAC as appropriate, when there is no specific data or other reason to justify deviating from the previous entries.

Concerning the proposed ATE of 0.27 mg/L (dusts or mists), RAC notes that there is a discrepancy between the LC_{50} value of 0.27 mg/L calculated in (Bayer, 1995a) and the acute inhalation toxicity data. Already at the dose level of 0.238 mg/L 60% of the animals died suggesting an actual LC_{50} < 0.24 mg/L. According to the available information, the LC_{50} was calculated according to the method of Rosiello *et al.* (1972) as modified by Pauluhn (1983), based on the maximum-likelihood method of Bliss (1938). It was stated that "*The interpolated concentration at 50% lethality in this case was designated at approximate* LC_{50}". RAC notes that considering the data (0-0-0-60-60-80-80% mortality, at 0, 0.096, 0.189, 0.238, 0.314, 0.384 or 0.541 mg/L), different curve-fitting equations might yield different LC_{50} value. However, considering that both the calculated 0.27 mg/L and data-based < 0.24 mg/L would result to the same category, RAC supports the ATE value proposed by the DS.

In conclusion, RAC agrees with the DS's proposal that the following split-entry classification is warranted for NDI:

- 1,5-naphthylene diisocyanate **[containing < 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]: no classification**

- 1,5-naphthylene diisocyanate **[containing ⩾ 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]: Acute Tox. 2; H330. Inhalation: ATE = 0.27 mg/L (dusts or mists).**

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

No information on the skin sensitising potential of NDI in humans is available.
One modified LLNA (Integrated Model for the Differentiation of Skin reaction, LLNA/IMDS; similar to OECD TG 429) is presented in the CLH report (Bayer, 2006). The DS considered it reliable with restrictions (reliability 2) since only the study summary was available and, there are deficiencies in reporting, e.g. no information on pre-screen testing for irritancy and systemic toxicity, no experimental details regarding the measurement of proliferation. In this GLP study, NDI (purity 99.8%) was applied at concentrations of 2%, 10% or 50% in acetone/olive oil to female NMRI mice, 6 per group, to the dorsum of both ears for three consecutive days. Appropriate positive control was used (hexylcinnamic aldehyde), which showed a clear sensitising potential. Stimulation indices (SI) of both the cell count in draining lymph nodes and draining lymph nodes weights were significantly higher than in the vehicle control group, and well above 1.4 (a cut-off value for positive response for NMRI mouse strain; Ehling *et al.*, 2005b, see table below).
The "positive level" of ear swelling, defined at about 10% of the control values, was exceeded in all dose groups, which indicates an acute irritating response. The DS, however, pointed out that this irritating property was combined with a strong skin sensitising potential of the test compound. The body weights of the animals were not affected by any treatment.

Table: *Summary of the LLNA/IMDS results (means of 6 animals per group) (Table 10 from the CLH Report)*

Parameter investigated	Vehicle control	Dose groups		
		2%	10%	50%
Stimulation index (weight of draining lymph nodes)	1.00	3.51*	3.79*	3.47*
Stimulation index (cell count in draining lymph nodes)	1.00	4.06*	4.15*	4.42*
Ear swelling in 0.01 mm on day 4 (index)	17.50 (1.00)	20.58* (1.18)	23.42* (1.34)	23.17 (1.32)
Ear weight in mg/8 mm diameter punch on day 4 (index)	11.03 (1.00)	14.29* (1.30)	16.41* (1,49)	17.97* (1.63)

* Statistically significant increase ($p \leq 0.05$)

The DS provided justification for the validity of the assay performed (primarily good inter-laboratory comparability of results described by Ehling *et al.,* 2005a and 2005b; very good agreement with standard LLNA found by Basketter *et al.*, 2011), and concluded that the LLNA/IMDS has been shown to reproduce the results from the standard LLNA very well.

According to ECHA Guidance (Table 3.6), EC3 values in the range > 0.2 - ≤ 2 indicate strong skin sensitising potential. Since in the Bayer's study (2006), NDI concentration of 2% already caused SI values > 4, the DS considered that the EC1.4 (i.e. the effective concentration causing a 1.4-fold increase in lymphocyte count) must be well below 2%. This indicates that that NDI is a strong skin sensitiser, even taking into account some uncertainty about the equivalence of the EC1.4 in the LLNA/IMDS and the EC3 in the standard test. The DS therefore concluded that the criteria for classification as Skin Sens. 1A are fulfilled, according to the Table 3.4.3 of the CLP Regulation.

A specific concentration limit (SCL) has not been proposed because 2% was the lowest NDI concentration tested, and for an extreme sensitiser (which would warrant an SCL of 0.001%), EC3 ≤ 0.2% should be ascertained.

Comments received during consultation

Two MSCAs and one from Industry representative agreed with the DS's proposal.

Assessment and comparison with the classification criteria

RAC agrees with the DS that the only available assay (Bayer, 2006), a GLP study performed as a modified LLNA/IMDS assay, is reliable enough to provide a basis for classification on skin sensitisation.

This study is a LLNA/IMDS assay modified in a way to measure cell count and weights of draining lymph nodes in order to avoid radioactive labelling. Aim of IMDS assay is to discriminate sensitising from irritative potential of a test item by comparing the specific immune reaction in the draining lymph nodes (lymph nodes cell counts and lymph nodes weights) with the unspecific acute inflammatory skin reaction (ear swelling and weight of circular biopsies of the ears, Ehling *et al.*, 2005a). Validity of the LLNA/IMDS has been assessed, and a good inter-laboratory comparability was shown by Ehling *et al.* (2005a, 2005b), as well as very good agreement with standard LLNA (Basketter *et al.*, 2011). WHO also recognised this modification as "evaluated thoroughly in the context of interlaboratory trials" (WHO, 2008).

RAC acknowledges the study's limitations stated above but agrees with the DS that they do not have a major impact on the study's reliability. Namely, the study summary provides enough information for hazard assessment. Further, although there is no information on methodological details regarding cell proliferation measurement, the performing laboratory (Bayer HealthCare AG, Department of Toxicology, Wuppertal, Germany) is an experienced facility and has been involved in above mentioned inter-laboratory validation shortly before performing this assay (Bayer, 2006). Regarding the lack of pre-screen test for irritancy and systemic toxicity, an assessment of irritative potential of NDI was incorporated into IMDS assay, and the animals' body weights were not affected by the treatment.

The study results showed a marked increase in SIs with a dose response for cell count in draining lymph nodes (see table above). In agreement with the DS, RAC considers that these results cannot be explained only by irritative reaction. A clear increase in cell count SI (> 4) was observed already at 2% NDI concentration at which 18% increase in ear thickness was noted. According to ECHA Guidance, an excessive local skin irritation is indicated by an increase in ear thickness of ≥ 25%.

The 2nd ATP[1] and ECHA Guidance indicate that Skin Sens. 1A is applicable when EC3 value is ≤ 2. This value applies to standard LLNA. In case of modified LLNA, a value of 1.4 has been proposed as a cut-off for NMRI mouse strain used in the assay (Ehling *et al.*, 2005b). RAC agrees with the DS that, since in the Bayer study (2006) 2% concentration of NDI already caused SI values of > 4, it could be assumed that the EC1.4 must be well below 2%. RAC therefore supports the DS's proposal to classify NDI as **Skin Sens. 1A; H334**, **with no SCL**.

[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

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 NDI:

"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

World Health Organization (2008) Harmonization Project Document No. 5. Skin Sensitization in Chemical Risk Assessment

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).