Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

trinickel disulfide; nickel subsulfide; [1] heazlewoodite [2]

EC Number: 234-829-6 [1] – [2]
CAS Number: 12035-72-2 [1] 12035-71-1 [2]

CLH-O-0000001412-86-272/F

Adopted

15 March 2019

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

15 March 2019

CLH-O-0000001412-86-272/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: **trinickel disulfide; nickel subsulfide; [1] heazlewoodite [2]**

EC Number: **234-829-6 [1] – [2]**

CAS Number: **12035-72-2 [1] 12035-71-1 [2]**

The proposal was submitted by **Johnson Matthey Chemicals GmbH** and received by RAC on **1 June 2018.**

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

PROCESS FOR ADOPTION OF THE OPINION

Johnson Matthey Chemicals GmbH 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 **18 July 2018**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **18 September 2018**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Betty Hakkert**

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 **15 March 2019** by **consensus**.

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

	Index No	International Chemical Identification	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	028-007-00-4	trinickel disulfide; nickel subsulfide; [1] heazlewoodite [2]	234-829-6 [1] – [2]	12035-72-2 [1] 12035-71-1 [2]	Carc. 1A Muta. 2 STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H372** H317 H400 H410	GHS08 GHS07 GHS09 Dgr	H350i H341 H372** H317 H410			
Dossier submitter's proposal	028-007-00-4	trinickel disulfide; nickel subsulfide; [1] heazlewoodite [2]	234-829-6 [1] – [2]	12035-72-2 [1] 12035-71-1 [2]	**Add** Acute Tox. 4	**Add** H332		**Add** H332			
RAC opinion	028-007-00-4	trinickel disulfide; nickel subsulfide; [1] heazlewoodite [2]	234-829-6 [1] – [2]	12035-72-2 [1] 12035-71-1 [2]	**Add** Acute Tox. 3	**Add** H331	**Modify** GHS06	**Add** H331		**Add** inhalation: ATE = 0.92 mg/L (dust/mist)	
Resulting Annex VI entry if agreed by COM	028-007-00-4	trinickel disulfide; nickel subsulfide; [1] heazlewoodite [2]	234-829-6 [1] – [2]	12035-72-2 [1] 12035-71-1 [2]	Carc. 1A Muta. 2 Acute Tox. 3 STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H331 H372** H317 H400 H410	GHS08 GHS06 GHS09 Dgr	H350i H341 H331 H372** H317 H410		inhalation: ATE = 0.92 mg/L (dust/mist)	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

This proposal was limited to acute inhalation exposure.

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

The dossier submitter (DS) provided a recent acute inhalation study in rats (according to OECD TG 403 and GLP), two single dose intratracheal studies in rats and two intratracheal studies in mice. In the acute inhalation study, LC_{50} (4 h) values of 0.92 mg/L air (female), 1.35 mg/L air (male) and 1.14 mg/L air (average of males and females) were determined for the dust. LD_{50} values of 4 mg/kg bw (male) (fine) and 50 mg/kg bw (male) (coarse) were derived in one intratracheal study in mice indicating that the particle size affected the acute inhalation toxicity. The other intratracheal studies were performed at lower dose levels and did not induce mortality. The DS used the average LC_{50} value for males and females of 1.14 mg/L air when concluding on the proposed classification, resulting in Acute Tox. 4; H332. No ATE value was proposed.

Comments received during public consultation

Comments were provided by two MSCAs. Both MSCAs suggested deriving an ATE value for acute inhalation toxicity in addition to the classification. Both MSCAs also suggested classification as Acute Tox. 3; H331 based on the LC_{50} value of 0.92 mg/L in female rats as females may be more sensitive. One MSCA proposed an ATE value of 0.5 mg/L based on the converted acute toxicity estimate for the acute inhalation toxicity of dusts according to table 3.1.2 of CLP, Annex I. In addition, one MSCA suggested to take into account the available repeated dose inhalation studies in rats and mice which indicate that mice are more sensitive and could thus also be more sensitive in an acute inhalation study.

The DS responded to the comments, not agreeing to use the most sensitive sex and provided additional information to justify that there is no sex difference in acute inhalation toxicity. The DS did also not agree that the available repeated dose studies showed that mice are more sensitive than rats and provided some additional long-term repeated dose data with rats and mice.

Assessment and comparison with the classification criteria

RAC considered the acute inhalation study provided in rats as key for classification because the intratracheal installation studies in rats and mice were not predictive of the acute inhalation effects due to differences in dose rate and site of deposition within the lung.

Groups of 5 rats per dose and sex were exposed nose-only to trinickel disulfide at concentrations of 0.206, 1.02, and 5.15 mg/L for 4 hours in an acute inhalation test according to OECD TG 403 and GLP (EPSL, 2010). The MMAD of the particles were within the recommended range of 1-4 um. However, no information on the geometric standard deviation was provided. LC_{50} values of 1.35 mg/L for male rats, 0.92 mg/L female rats and 1.14 mg/L for male and female rats were determined based on the mortality incidence (see table below). Mortality at 1.02 mg/L occurred between day 4 and 7 and at 5.15 mg/L between day 2 and 5.

***Table**. Mortality incidences after acute inhalation exposure to trinickel disulfide in rats (EPSL, 2010)*

Exposure Levels (mg/L)	Males	Females	Total
0.206	0/5	0/5	0/10
1.02	1/5	3/5	4/10
5.15	5/5	5/5	10/10

As the LC_{50} values were close borderline between category 3 and 4, application of the LC_{50} value for females would result in a different classification than if the LC_{50} values for males or for the combination of male and female rats were used. The difference could be either due to a difference in sensitivity between males and females or due to a chance finding as the LC_{50} values were in the same range. In line with the suggestions from the DS and the commenting MSCAs, the available short term repeated inhalation studies were assessed for potential difference in sensitivity between male and female rats. The repeated dose rat studies (Benson *et al*., 1987, Benson *et al*., 1995; Dunnick *et al*., 1988) indicated that differences in mortality are small and they did not indicate that female rats are more sensitive than male rats. On the contrary, males seemed to be more sensitive than females (Benson *et al*., 1987; Dunnick *et al*., 1988).

The available single intratracheal instillation studies in rats provided no information on effects per sex. Long term repeated dose inhalation studies (90-d and chronic) were not assessed as the mortality in such studies may be affected by differences in other parameters, such as accumulation of the substance or of effects, that cannot be extrapolated to mortality after acute exposure.

RAC agreed with the commenting MSCA that where adequate data show that other species are more sensitive the classification should be based on the most sensitive species. Therefore, an assessment of the difference in mortality between rats and mice in short term repeated dose inhalation studies was performed. As for the rat studies, long term repeated dose inhalation studies (90-d and chronic) were not assessed as the mortality in such studies may be affected by differences in other parameters, such as accumulation of the substance or of effects, that cannot be extrapolated to mortality after acute exposure. Also, the available single dose intratracheal instillation studies in rats and male mice were not used because difference in dosing (often low with no mortalities) and because the exposure conditions were either lacking or not comparable (particle size, dose and vehicle volume). Both available 12-d studies (Benson *et al*., 1987; Dunnick *et al*., 1988) showed that mice are more sensitive than rats. The two 12-d studies showed that rats and mice survived after repeated exposure to 0.005 mg/L, whereas mice showed 100% mortality at 0.010 mg/L where rats showed only limited mortality. Based on this, it can be concluded that mice were more sensitive than rats after short term exposure.

According to the CLP guidance (3.1.3.3.5 c. 'Evidence from other toxicity tests'), early effects from repeated dose testing can be used to estimate the acute toxicity when no acute data exists. In the present case, high quality acute toxicity data were available and there was thus no reason to base the LC_{50} on short term repeated dose toxicity studies. The lowest LC_{50} value of 0.92 mg/L was found in females and was below the cut off value of 1 mg/L for category 3. The LC_{50} value for males was just above the cut off value for category 3. In view of these borderline results, RAC looked at other available information. There were no robust acute data that could be used as supportive evidence for differences in sensitivity between sexes and/or species. The short term repeated dose studies in rats did not indicate a difference in sensitivity between sexes. On the other hand, the short term repeated dose studies in mice did indicate that mice were more sensitive than rats after short term repeated exposure, which could be indicative for a lower LC_{50} value than the LC_{50} value for rats. RAC however noted that repeated dose studies are in general

only used when no acute data exist (CLP guidance 3.1.3.3.5) and also that the mortalities in these repeated dose studies occurred after 5-10 days of exposure, and that the outcome pointed in different directions as regards sensitivity of species and sexes. Furthermore, the CLP guidance states that classification should be based on the lowest ATE available (3.1.2.3.2). Taking this into account, the classification for acute inhalation toxicity was based on the lowest LC_{50} value of 0.92 mg/L observed in female rats in a robust inhalation toxicity study.

RAC concluded that **classification for acute toxicity via the inhalation as Acute Tox. 3; H331 with an ATE of 0.92 mg/L was warranted.**

Additional references

Benson JM, Cheng YS, Eidson AF, Hahn FF, Henderson RF, and Pickrell JA. (1995). Pulmonary toxicity of nickel subsulfide in F344/N rats exposed for 1-22 days. Toxicology; 103:9-22.

Benson JM, Carpenter RL, Hahn FF, Haley PJ, Hanson RL, Hobbs CH, Pickrell JA, and Dunnick JK. (1987). Comparative inhalation toxicity of nickel subsulphide to F344/N rats and B6C3F1 mice exposed for 12 days. Fundamental and Applied Toxicology; 9:251-265.

Dunnick JK, Benson JM, Hobbs CH, Hahn FF, Cheng YS, and Eidson AF. (1988). Comparative toxicity of nickel oxide, nickel sulfate hexahydrate, and nickel subsulphide after 12 days of inhalation exposure to F344 Rats And B6C3F1 mice. Toxicology; 50:145-156.

NTP (National Toxicology Program). (1996). The toxicology and carcinogenesis studies of nickel subsulfide (CAS no 12035-72-2) in F344/N rats and B6C3F1 mice (inhalation studies). NTP Technical Report No 453. NIH Publication No 96-3369. National Institutes of Health, Springfield (VA). Washington DC.

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).