Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

nickel bis(sulfamidate); nickel sulfamate

EC Number: 237-396-1
CAS Number: 13770-89-3

CLH-O-0000001412-86-185/F

Adopted

22 September 2017

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CLH-O-0000001412-86-185/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: **nickel bis(sulfamidate); nickel sulphamate**

EC Number: **237-396-1**

CAS Number: **13770-89-3**

The proposal was submitted by **Umicore NV/SA** and received by RAC on **9 November 2016.**

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

PROCESS FOR ADOPTION OF THE OPINION

Umicore NV/SA 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 **21 November 2016**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **16 January 2017**.

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 **22 September 2017** 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, ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	028-018-00-4	nickel bis(sulfamidate); nickel sulfamate	237-396-1	13770-89-3	Carc. 1A Muta. 2 Repr. 1B STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D*** H372** H334 H317 H400 H410	GHS08 GHS09 Dgr	H350i H341 H360D*** H372** H334 H317 H410		STOT RE 1; H372: C ≥ 1 % STOT RE 2; H373: 0,1 % ≤ C < 1 % Skin Sens. 1; H317: C ≥ 0,01 % M=1	H
Dossier submitter's proposal	028-018-00-4	nickel bis(sulfamidate); nickel sulfamate	237-396-1	13770-89-3	**Add** Acute Tox. 4 Acute Tox. 4	**Add** H302 H332	**Add** GHS07	**Add** H302 H332		**Retain** STOT RE 1; H372: C ≥ 1 % STOT RE 2; H373: 0,1 % ≤ C < 1 % Skin Sens. 1; H317: C ≥ 0,01 % M=1	**Retain** H
RAC opinion	028-018-00-4	nickel bis(sulfamidate); nickel sulfamate	237-396-1	13770-89-3	**Add** Acute Tox. 4	**Add** H302	**Add** GHS07	**Add** H302		**Add** oral: ATE = 853 mg/kg bw (anhydrate) oral: ATE = 1098 mg/kg bw (tetrahydrate)	**Retain** H
Resulting Annex VI entry if agreed by COM	028-018-00-4	nickel bis(sulfamidate); nickel sulfamate	237-396-1	13770-89-3	Carc. 1A Muta. 2 Repr. 1B Acute Tox. 4 STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D*** H302 H372** H334 H317 H400 H410	GHS08 GHS07 GHS09 Dgr	H350i H341 H360D*** H302 H372** H334 H317 H410		oral: ATE = 853 mg/kg bw (anhydrate) oral: ATE = 1098 mg/kg bw (tetrahydrate) STOT RE 1; H372: C ≥ 1 % STOT RE 2; H373: 0,1 % ≤ C < 1 % Skin Sens. 1; H317: C ≥ 0,01 % M=1	H

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

The harmonised classification of nickel (bis)sulfamidate specifies CAS 13770-89-3 and EINECS 237-396-1 as numerical identifiers. As described in chapter 1.1.1.3 of Annex VI of CLP, the EINECS number includes both anhydrous and hydrated forms of a substance and the CAS number included relates to the anhydrous form only. The EINECS number describes the substance more accurately than the CAS number. Therefore, both forms are included in the revised Annex VI entry. In addition, the acute oral toxicity estimates (ATEs) of both forms differ due to the difference in molecular weight. The revised entry containing both forms in Annex VI shouldstate the different ATEs.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Acute oral toxicity

Two acute toxicity studies by the oral route are available, but only one of them was considered to be reliable, and was hence used for justifying the proposed classification. The latter study (EPSL, 2008; Henderson *et al*., 2012b) was performed according to OECD TG 425 (acute oral toxicity: Up and Down procedure), in female Sprague Dawley rats, with single doses of 175, 550 and 2000 mg/kg bw nickel sulfamate tetrahydrate via gavage. The LD_{50} value was estimated to be 1098 mg/kg bw. This LD_{50} value places the substance in the same acute toxicity category as other water soluble nickel compounds (Acute Tox. 4; H302; LD_{50} values between 300 and 2000 mg/kg bw).

The result of the acute toxicity study is consistent with the similar solubility (i.e., bioaccessibility of Ni ion) of the nickel compounds observed in gastric and intestinal fluids (Henderson *et al*., 2012a). Taken together, the dossier submitter (DS) concluded that nickel sulfamate should be classified as Acute Tox. 4; H302.

Acute inhalation toxicity

Data from sulfate hexahydrate (nickel sulfate) was used by the DS for the assessment of acute inhalation toxicity because data from the source substance are not available. The read-across was based on a "bioelution concept" which enables grouping of target nickel substances for classification purposes according to bioaccessibility in interstitial and/or lysosomal fluid.

According to the DS, the first group of nickel substances are those that would be read-across from sulfate hexahydrate. This group applies to highly water-soluble Ni. Data demonstrate that all Ni soluble substances tested have similar bioaccessibility (at 24 and 72 hours of testing) in interstitial fluid to the source substance, sulfate hexahydrate (nickel sulfate). Therefore, this read-across assessment concludes that e.g. Ni sulfamate should be read-across from sulfate hexahydrate for the assessment of acute inhalation toxicity.

In an OECD TG 403 study (acute inhalation toxicity; EPSL, 2009b), Sprague Dawley rats (5 male and female rats/group) were exposed to 0.063, 0.53, 2.12, and 5.08 mg/L of sulfate hexahydrate. An LC_{50} value of 2.48 mg/L air was estimated and the DS proposed to classify the substance in Category 4 (Acute Tox. 4; H332; LC_{50} values between 1 and 5 mg/L).

Acute dermal toxicity

This hazard class was not evaluated by the DS.

Comments received during public consultation

One MSCA did not support the proposed classification, and provided several points of criticism, the main one being that the proposal is based on the bioelution concept, for which there is currently no formal agreement on how to apply this concept by regulatory authorities. The same MSCA also criticised the use of nickel sulfamate tetrahydrate (CAS no 124594-15-6) instead of nickel bis(sulfamidate) (CAS no 13770-89-3) for the acute oral toxicity.

Two MSCAs agreed to the proposal for both acute oral and inhalation toxicity.

Assessment and comparison with the classification criteria

Acute oral toxicity

Nickel bis(sulfamidate) has not been previously classified for acute oral toxicity. A recently completed OECD guideline compliant study reported an oral LD_{50} of 1098 mg/kg nickel sulfamate tetrahydrate (CAS no 13770-89-3) in female rats. The newly reported LD_{50} value meets the criteria for classification as Acute Tox 4; H302 according to CLP criteria.

The current entry in Annex VI of CLP covers both the anhydrate and the tetrahydrate of nickel (bis)sulfamidate. While the classification of the tetrahydrate can obviously be based directly on the result of the provided acute oral study with the tetrahydrate, the classification of the anhydrate form requires extrapolation of the results obtained with the tetrahydrate. Extrapolation is acceptable because the acute oral study was performed with nickel sulfamate mixed with water and it was stated that the concentration of the test substance in water was limited to 60% because of the too high viscosity of a more concentrated solution. This suggests that at least a substantial part and possibly all of the substance was dissolved. The water solubility of both nickel sulfamates are in the same range (background document table 8: 49.9 – 60%). This shows that a similar acute oral toxicity test can be performed with the anhydrate dissolved in water. Therefore the result of the study with the tetrahydrate is considered relevant for the anhydrate after correction for the difference in molecular weight. The estimated ATE of nickel sulfamate is 250.9 g/mol (molecular weight nickel sulfamate) / 322.9 g/mol (molecular weight nickel sulfamate tetrahydrate) * 1098 mg/kg bw (LD_{50} nickel sulfamate tetrahydrate) = 853 mg/kg bw. This LD_{50} results in classification in category 4 (300 – 2000 mg/kg bw).

In line with the DS, RAC agrees with the proposed classification of nickel sulfamate as **Acute Tox. 4; H302** but with an **ATE of 853 mg/kg bw for the anhydrate** and an **ATE of 1098 mg/kg bw for the tetrahydrate.**

Acute inhalation toxicity

No data on acute inhalation toxicity exists of nickel bis(sulfamidate) (both anhydrate and hydrate) only of nickel sulfate hexahydrate (nickel sulfate). The DS proposed a read-across approach from nickel sulfate hexahydrate (target substance) based on *in vitro* bioaccessibility data in synthetic lung fluids from various nickel compounds and *in vivo* verification data for three nickel compounds. Information on the bioaccessibility of nickel bis(sulfamidate) tetrahydrate was provided but not

for the anhydrate form. However, the nickel content differs (23.4% versus 18.2%) and therefore also the nickel release is expected to be different. The proposed classification of nickel bis(sulfamidate) as Acute Tox. 4; H332 is based on a recently conducted OECD TG 403 study where rats were exposed to nickel sulfate hexahydrate. No animals died at concentrations of 0.063 and 0.53 mg/L nickel sulfate. Immediately after exposure to 2.12 mg/L, one male appeared hypoactive and exhibited abnormal respiration. This male was found dead on the same day after the exposure. At the highest dose level of 5.08 mg/L rats exhibited clinical signs including abnormal respiration, hypoactivity, abnormal posture, and/or anogenital staining. All males and females died at this dose level, some already during the exposure period. Necropsy of the rats revealed discoloration of the lungs, liver and intestines. The LC_{50} (females and males) was 2.48 mg/L, hence classification as Acute Tox. 4 (H332) is warranted (CLP Guidance: $1 < LC_{50} \leq 5$ mg/L => Acute Tox 4 (H332)).

RAC noted that the outcome of the bioaccessibility-based read-across assessment of the DS suggests that the acute inhalation toxicity of nickel bis(sulfamidate) tetrahydrate could be read-across from nickel sulfate hexahydrate and therefore should be classified as Acute Tox 4; H332. It is noted however, that no justification is provided for the read-across for the anhydrate.

The proposed read-across approach by the DS is based on the assumption that the toxicity of nickel and nickel compounds is caused by nickel 2+ ions (Ni^{2+}) released from the substance and interacting at the target site. For acute toxicity after inhalation exposure, it is suggested that the respiratory tract is the target site. As no *in vivo* information is available on the presence of Ni^{2+} in the respiratory tract after exposure to the source and the target substances, the DS compared the bioaccessibility data after 24-72 hour bioelution in interstitial fluid. Three groups are defined with bioaccessability of 7-11%, approximately 1% and less than 1% for classification in category 4, category 4 and no classification, respectively.

RAC notes that the DS applied read-across for the classification of one substance to another substance. However, read-across is a method to be used to interpolate or extrapolate a test result from the source to the target substance. For acute inhalation toxicity, an estimate should be made of the LC_{50}, or LC_{50} range, of the target substance based on the available information on the source substance(s) and the target substance. This means that direct read-across of a classification from the source substances to the target substance can not be applied.

Further, the DS's assumption that the acute inhalation toxicity of nickel and nickel compounds is determined by the local availability of Ni^{2+} in the respiratory tract is not substantiated by the available information. In contrast, the provided acute inhalation study with nickel sulfate hexahydrate (nickel sulfate) shows discoloration of the intestines besides discoloration of the lungs and liver. This shows that a substantial part of the inhaled nickel sulfate hexahydrate (nickel sulfate) is transported upwards by the respiratory tract, is swallowed and enters the intestinal tract. Although it is known that undissolved inhaled particles can induce local toxicity this is considered less likely in the case of highly soluble compounds. Further, the available data show an increase in acute toxicity with solubility. Overall, RAC concluded that the available data are inadequate to fully justify the theoretical assumption that Ni^{2+} ions determine the acute inhalation toxicity of nickel and nickel compounds. However, for soluble nickel compounds, this is considered likely.

RAC stresses that there is still much debate on the applicability of the bioelution concept. Although it seems straighforward in the calculation of the external exposure in well-defined cases, and it is also used on a case-by-case basis for reading across, there is a lot of debate on whether this concept can be used for the purpose of classification and labelling. So far, there are no internationally agreed guidelines for conducting bioelution techniques/studies and no data have demonstrated a systematic relationship between bioelution and systemic availability. Major concerns that are encountered in the bioelution study (KMHC, 2010) are:

- In the bioelution study (KMHC, 2010), there is a lack of information on the particle size of the tested nickel compounds. In the case of inhalation, if verification of read-across for acute effects is conducted using toxicokinetic studies, the sameness of the samples used in both studies is critical: for example the size of the particles in the samples in both studies should be the same. Indeed, the particle size of the aerosol (mass median aerodynamic diameter, MMAD and geometric standard deviation, GSD), together with particle density and breathing parameters will determine the deposited dose in different regions of the respiratory tract. Undissolved particles deposited in the upper airways and tracheobronchial region of the lung will be removed by the mucociliary escalator, swallowed and partly or entirely absorbed via the gastrointestinal tract. Undissolved particles in the alveolar region may also be transported by macrophages to the lymph nodes and the airway lumen. As a result, the absorption mechanisms of different nickel substances will vary. Different particle size aerosols of even the same substance are expected to have different deposition and removal rates in various regions of the respiratory tract.
- In addition, the particle size of the nickel compounds used in the bioelution tests should be comparable and preferably the same as in the inhalation test. A difference in particle size results in a difference in surface area and potentially in a difference in dissolution rate. It is noted that no information is provided on the particle size in the bioelution tests with the nickel compounds.
- In the study report it is indicated that each extraction experiment (at 2, 5, 24 and 72 hours) was performed using 1 concentration of 0.1 gram nickel sample in 50 ml of fluid. This is a limitation of the study since the concentration can influence the rate of ion dissolution from the particles. It is not clear whether the tested concentration is biologically realistic or relevant. In addition, some samples completely dissolved in the artificial fluids within the duration of the study indicating that a higher dissolved concentration would have been possible. These limitations are considered relevant for the *in vivo* validation of the *in vitro* bioelution tests.

RAC notes that the abovementioned information is lacking in the background document, which hampers a scientific justification and assessment of the read-across using the bioelution concept as proposed by the DS.

Incorporation of bioaccessibility data into any type of read-across assessment first requires an evaluation of its correlation with *in vivo* verification data (see table below). For the inhalation route this has been done by looking at the correlation between the LC_{50} (mg compounds/L or mg Ni/L after a 4 hour exposure) and the bioaccessibility in interstitial or lysosomal lung fluid after 5, 24, or 72 hours (% Ni release/g sample or % Ni release of available Ni) for the four compounds (Ni sulfate hexahydrate, Ni subsulfide, and green Ni oxide, black Ni oxide). These analyses, however, did not yield very meaningful relationships due to the few data points available and the fact that for black and green Ni oxide samples the true LC_{50} values are not known (LC_{50} > 5-8 mg Ni oxide/L; > 4-6 mg Ni/L). Further, the difference in time to mortality for the sulfate and the subsulfide indicates that different parameters may be relevant for these substances. The best results were obtained with the dissolution in interstitial fluid. Based on these (*in vivo* correlation) data, it is not possible to assess the most appropriate predictor of acute toxicity effects. Therefore, the *in vivo* verification does not show that the proposed read-across approach is valid. However, for these good water soluble nickel substances with comparable nickel fraction, it could be assumed that the acute inhalation toxicity is comparable unless affected by the counter-ion.

Table. Bioelution, water solubility and LC_{50} values of several nickel compounds.

Sample	Cas No.	Ni Content (%)	Water solubility (mg/L)	Interstitial Bioaccessibility (% Ni/sample) 24-72 hrs	Lysosomal Bioaccessibility (% Ni/sample) 24-72 hrs	Acute Toxicity inhalation (LC_{50}; mg substance/L)
Water-soluble nickel compounds						
Ni Sulfate Hexahydrate	10101-97-0	22	625000	10.7-12.80	20.35-21.35	2.48 (0.55)
Nickel Sulfamate hexahydrate	**124594-15-6**	**18**	**49900 – 60000 (pH=1.3)**	**8.25 – 8.60**	**18.30 – 18.30**	**Not determined**
Nickel Sulfamate	**13770-89-3**	**23.4**	**Not determined**	**Not determined**	**Not determined**	**Not determined**
Sulfidic Nickel Compounds						
Ni subsulfide	12035-72-2	61 (70)	16 (144 h)	2.65-3.60	20.7-26.20	1.14 (0.80)
Oxidic nickel compounds						
Ni oxide green	1313-99-1	77 (81)	0.035	0.08 - 0.10	0.44 - 0.82	>5.08 (>4.1)
Ni oxide black	1313-99-1	75	2.26	0.42 - 0.56	10.60 - 24.50	>5.15 (>3.9)
Other nickel compounds						
Ni hydroxy carbonate	12122-15-5	49 (49)	33	0.52 – 1.65	47.20 – 47.20	>2,09 (F); 0.24 (M)

No information was provided by the DS on the difference in toxicity between the sulfate and the sulfamate forms. In addition, the pH of concentrated solutions of nickel sulfamate was very low indicating a probable influence of irritation or corrosivity on the mechanism for local lung toxicity. Therefore, the absence of an influence of the counter-ion on the toxicity is not shown.

RAC acknowledges that read-across supported by bioavailability, bioaccessibility and bioelution information can be useful for classification of metal salts and this has been applied for nickel compounds under DSD. However, the application of read-across should be sufficiently justified as required under CLP. Although the proposed read-across approach for acute inhalation toxicity for nickel compounds is not sufficiently justified, for highly soluble nickel compounds with comparable nickel fraction, read-across might be acceptable if it is shown that there is no difference in counter-ion toxicity. However, in the current case information on the difference in counter-ion toxicity is lacking. Therefore, RAC concludes that there is insufficient information available to support the proposed grouping approach using read-across as well as the proposed classification. Therefore **no classification is concluded for acute inhalation toxicity based on the absence of relevant data**.

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).