Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

nickel (II) sulfide; [1]
nickel sulfide; [2]
millerite [3]

EC Number: 240-841-2 [1] 234-349-7 [2] -[3]
CAS Number: 16812-54-7 [1] 11113-75-0 [2] 1314-04-1 [3]

CLH-O-0000001412-86-170/F

Adopted
22 September 2017

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON NICKEL (II) SULFIDE; [1] NICKEL SULFIDE; [2] MILLERITE [3]

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public 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 public 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 public 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.

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Substance name: nickel (II) sulfide; [1] nickel sulfide; [2] millerite [3]
EC number: 240-841-2, 234-349-7
CAS number: 16812-54-7, 11113-75-0, 1314-04-1
Dossier submitter: Terrafame Oy

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2016	Germany		MemberState	1
Comment received				
DE-MSCA supports the proposal. Nevertheless, we have some general comments: PHYS CHEM (1) In section 6, table 8 of the CLH report the following value for the relative density is given: "5.66 Exp3 at 24°C". According to IUCLID section 4.4 the relative density is 5.66 at 24.0 ± 0.5°C. Please amend the value in the CLH report accordingly. (2) In section 6, table 8 of the CLH report the water solubility is given without mentioning the corresponding pH value. Please add the pH value (as given in IUCLID section 4.8). ACUTE TOXICITY With respect to classification for acute toxicity there are major concerns. Although it is of importance that any false perception should be avoided that nickel sulphide might not be of concern for acute inhalation toxicity, the argumentation provided by the dossier submitter for classification is based on the bioelution concept which is currently a framework mainly intended by industry to be used for relief from classification proposals. However, there is no agreed understanding by regulatory bodies whether and how to use bioelution techniques for regulatory purposes on human health endpoints. As there are up to now no internationally agreed guidelines for the conduction of bioelution techniques and no data to show a systematic relationship between bioelution and systemic availability, it is considered premature to use this concept for classification and labelling as this could create a precedent case. It is of note that the concept of bioelution has been brought up in the context of CARACAL (see also the DE comment (20151105_DE_comment-bioelution-mixture-classification-19caracal.docx) to CA_90_2015 discussed at CARACAL 19) and that only recently ECHA had				

been asked by the Commission to establish an expert group to discuss the regulatory use and applicability of the bioelution method. This expert group will work in parallel with activities at the Joint Research Center (JRC) which has agreed to support the assessment and validation of the in vitro method proposed by the metal industry.

Especially with respect to local and inhalation toxicity the German CA has already stated within discussions in the context of CARACAL that bioelution/bioaccessibility information is not sufficient to address these aspects of toxicity as particle induced effects might also contribute.

Therefore, in this particular case a clear hypothesis/proof should be given whether and to which extent particle-driven effects contribute to acute inhalation toxicity and the argument that the metal ion would be the factor governing acute inhalation toxicity should be substantiated.

With regards to the data presented in Table 14 it is noteworthy to see that the difference of LC50-value appears to be minor for the Ni Sulphate Hexahydrate (being bioaccessible at high percentages) and Ni Oxide Green (with a low rate of bioaccessibility in the test fluids). To our view the soluble nickel compounds may be grouped for classification on acute toxicity based on the water solubility alone (which may also the reason for similar values in the bioaccessibility tests). The non-coherence of bioaccessibility and LC50-values is obvious for Ni subsulphide, low bioaccessibility should not induce such a low LC50-value.

It is of note that section 9.2.7. (In vivo verification: acute toxicity studies) uses mainly speculative arguments instead of sound data.

It is further of note that several uncertainties such as those listed in section 9.2.10 (Uncertainties in read-across for acute inhalation toxicity) are considered by BfR as sound arguments to conclude that it is currently premature to use bioelution for classification purposes.
It is further of note, that there are currently no validated or commonly agreed protocols for bioelution studies considering the different uptake routes.

Dossier Submitter's Response

PHYS CHEM

The dossier submitter appreciates Germany's astute observations on these values. As we cannot submit a revised CLH report, we confirm here that the correct values are:

1. The relative density is 5.66 at 24.0 ± 0.5°C.
2. The water solubility is 8.80 x 10^{-2} g/l at 20.0 ± 0.5°C at pH 6.1 – 6.6

ACUTE TOXICITY

Agreement with the CLH proposal

The dossier submitter notes that the German CA supports the CLH proposal for nickel sulphide.

Other matters raised by the German CA

The dossier submitter appreciates Germany's concerns based on a perception that the read-across of an acute toxicity classification for inhalation is exclusively based on the use of bioaccessibility data. We note that Germany does not challenge the proposal on the basis of

these considerations. Nevertheless we would like to provide some further clarifications regarding our approach in response to these comments. We note that we did not base the read-across only on bioaccessibility data; rather, we used relative bioaccessibility data in lung fluids in a weight of evidence-approach that also included: a) *in vivo* validation of bioaccessibility in interstitial lung fluid as predictor of acute inhalation toxicity, b) validation of relative Ni(II) bioaccessibility in interstitial lung fluid as predictor of *in vivo* bioavailability by considering information on particle clearance and relative absorption c) *in vitro* data on particle uptake and toxicity of nickel sulphide compared to nickel subsulphide, and d) consideration of relative toxicity of counter ion (sulphide) derived from nickel sulphide and nickel subsulphide.

As indicated in section 9.2.1 of the Ni sulphide CLH report, the approach is consistent with ECHA's Guidance On Information Requirements And Chemical Safety Assessment, Chapter R.6: QSARs and grouping of chemicals (ECHA, 2008) and in the Application of the CLP Criteria Guidance to Regulation, Section 1.4.3: Read Across (ECHA, 2015; EC, 2009b). Section R.6.2.5.6 (ECHA, 2008), states:

> "*The concept of chemical categories has traditionally been widely used for hazard assessment for certain endpoints and risk assessment of inorganic substances. The approaches have generally been based on the occurrence of a common metal ion or anion and the use of read-across to fill data gaps […] it is the bioavailability of the metal ion (or a redox form of this ion) at target sites that in most cases determines the occurrence and severity of the effects to be assessed for the read-across of metal substances. Supporting information to assess the bioavailability of the metal ion at the target site can include information on a number of different factors (e.g. physico-chemical properties such as water solubility, degree of dissociation of the metal–containing compound, particle size and structure, in vitro solubility, in vivo data on systemic effects, toxicokinetics)".*

Germany states that "*… the bioelution concept which is currently a framework mainly intended by industry to be used for relief from classification proposals*." The submitter does not agree with this observation since the proposal under consideration is exactly the opposite; we are using bioaccessibility information to add a classification for acute inhalation toxicity when one does not currently exist. In relation to the use of bioelution test data in the classification of alloys, the consideration of bioaccessibility data could lead to less or more restrictive classifications, depending on the alloy.

Germany states that "*As there are up to now no internationally agreed guidelines for the conduction of bioelution techniques and no data to show a systematic relationship between bioelution and systemic availability, it is considered premature to use this concept for classification and labelling as this could create a precedent case."* We would like to kindly remind Germany that there are 150+ nickel compounds that carry harmonized classifications in the CLP. These classifications were assigned in 2006 using a read across approach that a) was *only* based on water solubility and minimal phys.-chem. data, b) was applied to all routes of exposure and most endpoints, and c) included ~4 reference nickel compounds. We think these classifications already constitute a "precedent" for considering bioaccessibility data in the read-across for classification of substances. Yet, contrary to the water-solubility-based approach applied to the classification of those nickel compounds, in the CLH report for nickel sulphide bioaccessibility data relevant to each route of exposure was used, with in vivo validation and other relevant information, and considered the data in a weight of evidence approach. The available data has been presented in a transparent way

and the uncertainties associated with the approach have been outlined. These uncertainties in no way invalidate the approach taken but clearly describe the limitations of the method. Our overall approach could be considered a refinement/improvement over previous precedents of water solubility-based read across approaches.

The submitter agrees with Germany that "*Especially with respect to local and inhalation toxicity … bioelution/bioaccessibility information is not sufficient to address these aspects of toxicity as particle induced effects might also contribute*." There is a discussion in the nickel sulphide CLH report on the possible contribution of particle effects to acute inhalation toxicity compared to its contribution to chronic toxicity after repeated exposure (sections 9.2.5. and 9.2.6). We look forward to the discussions of the ECHA expert bioelution group on this topic.

With regard to the data in Table 14, the submitter considers that a difference in LC_{50} of > 7-fold between Ni sulphate hexahydrate (0.55 mg Ni/L) and Ni oxide (> 4 mg Ni/L) is not "*minor*." Because nickel oxide demonstrated no toxicity whatsoever at the highest concentration tested (4 mg Ni/L) it is likely that the difference in LC50 could be 10-fold or more. The difference in bioaccessibility from Ni sulphate hexahydrate (10%) and Ni oxide (~0.2%) would suggest that the difference should be ~50-fold. This is not inconsistent with the in vivo findings.

Once again we thank the German CA for their comments and supporting the CLH proposal for nickel sulphide. As noted, we look forward to further discussions of the ECHA expert bioleution group on the issues Germany has raised here.

RAC's response

RAC understands and shares some of the concerns expressed by the German CA, however RAC is of the opinion that under certain circumstances read across could be used. In this case, in line with the comments given by the Geman CA RAC considers the arguments for the read across of the acute toxicity via inhalatory route as inadequate as explained in the opinion document.

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2016	Belgium		MemberState	2

Comment received

BE CA thanks Finland for submitting this proposal for Harmonized Classification and Labelling. We note that the dossier submitter proposed read-across approach from nickel subsulphide based on bioaccessibility data in synthetic lung fluids from various compounds and in vivo verification data for 3 source nickel compounds. Submitted CLH dossier is built on the following general reasoning:
- for Ni-containing substances adverse effects in the respiratory tract are dependent upon of the metal ion bioavailability at the target sites;
- there are indications that solubility in the respiratory tract may be primary factor for lung toxicity including dissociation in extracellular (e.g., interstitial and alveolar) and/or intracellular (e.g., lysosomal) fluids for particles easily taken up by the cells;
- release of Ni (II) ion in relevant lung fluids can provide information on the mechanism of action and ultimately on the potential to cause toxicity;
- solubility in biological fluids varies depending upon the chemical form of nickel => nickel subsulphide and nickel sulphide are both water-insoluble, but partial solubility in some biological fluids has been observed;
- investigation of bioaccessibility via inhalation route of exposure was performed on both

source and target nickel substances (bioelution testing) which resulted in distinction of 2 main groups: substances releasing approximately >1% Ni/g sample (i.e. nickel subsulphide) and those releasing approx. <1% Ni/g sample (nickel oxides);
- from in vivo verification of inhalation toxicokinetic studies, a following trend of inhalation absorption was found: Ni sulphate > Ni subsulphide (approx.. 4-fold lower) > nickel oxide (100-fold lower), which is consistent with the relative inhalation absorption data observed in vivo;
- the interstitial release and acute toxicity data allowed distinction in 2 groups:
A) the nickel oxides: low interstitial bioaccessibility (< approximately 1% Ni/g sample or 1% of available Ni at 24 hours) and low acute toxicity (LC50 values >5-8 mg substance/L or > 4-6 mg Ni/L),
B) water soluble compounds (Ni sulphate) and water insoluble sulphidic compounds (Ni subsulphide) characterized by interstitial bioaccessibility higher than 1% Ni/g sample or >1 % of available Ni for 24 hours and LC50 values <3 mg substance/L (< 1.0 mg Ni/L).
Hence, basing on the fact that:
- the interstitial release for Ni sulphide is around 1% Ni/g sample;
- both nickel sulphide and nickel subsulphide share the same counter ion (sulfur) and are known to have similar properties;
- in vitro studies indicated similar toxicities and cellular uptakes of nickel sulphide and nickel subsulphide;
- in vivo verification: repeated exposure toxicity studies: bioaccessibility in lysosomal fluid (15-30% Ni /g sample)
it has been concluded that the read-across from nickel subsulphide to nickel sulphide for acute toxicity via inhalation route and repeated dose toxicity via inhalation route is plausible. This conclusion is also supported by BE CA.

Dossier Submitter's Response

The dossier submitter thanks Belgium for detailing the reasoning of the read-across approach from nickel subsulphide to nickel sulphide based on a weight of evidence approach that includes bioaccessibility data in synthetic lung fluids from various compounds and in vivo verification data for 3 source nickel compounds. We note that Belgium indicates this read across approach is plausible, and supports the CLH proposal.

RAC's response

We thank Belgium CA for the comments. As explained in the opinion document, RAC has reservations about the read across proposal for the inhalation route.

Date	Country	Organisation	Type of Organisation	Comment number
30.09.2016	France		MemberState	3

Comment received

We agree with the proposed harmonized classification for Acute tox 4 and STOT RE 1.

Dossier Submitter's Response

The dossier submitter thanks the French CA for their support of the harmonized CLH proposal for nickel sulphide.

RAC's response

We thank French CA for the comments. As explained in the opinion document, RAC has reservations about the read across proposal for the inhalation route and on STOT RE 1.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
30.09.2016	Finland		MemberState	4
Comment received				
The proposed classification of nickel sulphide as Acute Tox. 4; H332 is based on a new study OECD 403 where rats were exposed to nickel subsulphide. It was noted that nickel subsulphide doesn't have a harmonised classification and labelling for acute inhalation toxicity. Nonetheless, read across is used as a basis of the proposed classification and labelling for nickel sulphide. LC50 value of 1.14 mg/L was reported from the rat study and it meets the criteria for acute inhalation toxicity category 4. The FI CA can support the proposed harmonised classification and labelling of nickel sulphide as Acute Tox. 4; H332.				
Dossier Submitter's Response				
The dossier submitter thanks the Finnish CA for their support of the harmonized CLH proposal for nickel sulphide.				
RAC's response				
See response to the German CA and Belgium CA, comments 3 and 4.				

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2016	Belgium		MemberState	5
Comment received				
As BE CA agrees with the read-across approach proposed by the dossier submitter, the classification for Acute Toxicity Category 4 (H332) by using the new data for nickel subsulphide (study performed according to OECD TG 403) is also supported. In this new study an average LC50 (females and males) of 1.14 mg/L was obtained, hence classification as Acute Tox. 4 (H332) is warranted (CLP Guidance: 1< LC50≤5 mg/L => Acute Tox 4 (H332)).				
Dossier Submitter's Response				
The dossier submitter thanks Belgium for agreeing with the read-across approach from nickel subsulphide to nickel sulphide based on a weight of evidence approach including bioaccessibility data in synthetic lung fluids and for their support of the CLH proposal.				
RAC's response				
See response to the German CA and Belgium CA, comments 3 and 4.				

Date	Country	Organisation	Type of Organisation	Comment number
30.09.2016	France		MemberState	6
Comment received				
Since nickel subsulphide is not currently classified for acute toxicity by inhalation, an update of its classification is needed in regards to the study presented in this CLH report. The submission of a CLH report for updating its harmonized classification would be welcome.				

Dossier Submitter's Response
The dossier submitter notes that the Nickel REACH Consortia have indeed coordinated the submission of CLH dossiers for Ni sulphide, subsulphide and sulphamate at the same time. We express the hope that the work done on this CLH dossier for nickel sulphide will ease the review of the other two CLH dossiers for nickel subsulphide and sulphamate. Fance has previously indicated their support of the harmonized CLH proposal for nickel sulphide in comment 3. Thus we are wondering if the above comment 6 was directed instead towards the CLH proposal for nickel subsulphide for Acute Toxicity Category 4 based on new data for nickel subsulphide (as read-across is not mentioned).
RAC's response
See response to the German CA and Belgium CA, comments 3 and 4.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
30.09.2016	Finland		MemberState	7
Comment received				
The proposed addition of the target organ "lungs" and the route of exposure "inhalation" to the STOT RE endpoint are justified based on the justification presented in the CLH report. Thus, the FI CA agrees with the proposed classification and labelling of nickel sulphide as STOT RE 1; H372 (lungs/ inhalation).				
Dossier Submitter's Response				
The dossier submitter thanks the Finnish CA for their agreement with the proposed classification and labelling of nickel sulphide as STOT RE 1; H372 (lungs/ inhalation).				
RAC's response				
Article 37(2) of the CLP Regulation states the following: *A manufacturer, importer or downstream user of a substance may submit to the Agency a proposal for harmonised classification and labelling of that substance and, where appropriate, specific concentration limits or M-factors, provided that there is no entry in Part 3 of Annex* *VI for such a substance in relation to the hazard class or differentiation covered by that proposal.* Consequently, the DS's proposal to revise the hazard class STOT RE 1 in the current Annex VI entry by adding the target organ (lungs) and the route of exposure (inhalation) could not be evaluated by RAC.				

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2016	Belgium		MemberState	8
Comment received				
BE CA agrees with the dossier submitter that subchronic (13-week) inhalation studies with respirable size nickel subsulphide in rats and mice have provided clear indications that the lungs are the target organs for toxicity:				

☐ Benson et al., 1987: 12 days exposure to nickel subsulphide resulted in significant toxicity at exposure ≥5 mg nickel subsulphide /m3 in both rats and mice: labored respiration, emaciation, dehydration, decreased weight gain, altered organ weights, and mortality in some cases. Moreover, necrotizing pneumonia, emphysema, or fibrosis in exposed rats were also observed;
☐ Benson et al., 1995: time course evaluation of exposure to lower doses (0.6 or 2.5 mg nickel subsulphide/m3 for up to 22 days) resulting in the following exposure-related observations: decrease in body weight, increased lung weight, morphological changes (e.g., nasal lesions, degeneration of olfactory epithelium), and a number of biochemical effects associated primarily with inflammation (e.g., increased alveolar macrophages, hyperplasia of bronchiolar epithelial cells, presence of inflammatory cells in bronchial lumen, LDH activity);
☐ Dunnick et al., 1989: following 13 weeks of exposure to nickel subsulphide (0.15 to 2.5 mg/m3) in both rats and mice no exposure-related mortality was observed, but changes in bodyweight and lung weights were significantly impacted. Additional toxicities included inflammation in the nasal cavity, bronchial lymph nodes and the lung, alveolar macrophage hyperplasia, chronic active inflammation, and olfactory epithelial atrophy;
☐ Benson et al., 1989: study measuring biochemical responses in bronchoalveolar lavage fluid (BALF) recovered from lungs of exposed animals in both rats and mice exposed to nickel subsulphide for 13 weeks: significant and dose-dependent effects in a number of biochemical and cytological parameters were found (e.g., levels of lactate dehydrogenase, β-glucuronidase, percentage of neutrophils and macrophages in lavage fluid) as well as tissue damage (e. g chronic inflammation, macrophage proliferation) were observed;
☐ Dunnick et al., 1995: chronic exposure (exposure duration: 2 years) to concentrations up to 1 mg nickel subsulphide/m3 was not associated with increased mortality or adverse changes in body weight, but time- and dose-dependent increases in lung weights were observed due to inflammation seen in histopathological analyses (alveolar/bronchiolar hyperplasia, inflammation, fibrosis, and lymphoid hyperplasia of the lung-associated lymph nodes). The most critical effects were pulmonary fibrosis, chronic inflammation, and proteinosis.

As indicated by the dossier submitter the inflammatory effects were detected at exposure levels of 0.14 mg nickel subsulfide/m3 or 0.1 mg Ni/m3, hence the criterion for classification as STOT RE1 is fulfilled, and consequently proposed classification as STOT RE 1 H372** (target organ/route of exposure: lungs/inhalation) is supported by BE CA.

Dossier Submitter's Response

The dossier submitter thanks the Belgian CA for their careful review of the data that indicated that the lungs are the target organs for repeated dose toxicity of nickel sulphide and note that they support the proposed classification and labelling of nickel sulphide as STOT RE 1; H372 (lungs/ inhalation).

RAC's response

See response to comment 7.