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 bis(sulfamidate); nickel sulfamate

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

CLH-O-0000001412-86-185/F

Adopted
22 September 2017

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON NICKEL BIS(SULFAMIDATE)|NICKEL SULFAMATE

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.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: nickel bis(sulfamidate)|nickel sulfamate
EC number: 237-396-1
CAS number: 13770-89-3
Dossier submitter: Umicore NV/SA

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
16.01.2017	Germany		MemberState	1
Comment received				
The German CA does not support the proposed classification of nickel bis(sulphamidate) on the basis of the presented data. 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. Additionally the German CA strongly recommends the setting of harmonized ATEs whenever a substance is classified as acute toxic to facilitate the consistent classification of mixtures.				
Dossier Submitter's Response				
The dossier submitter appreciates Germany's comments but notes that the proposal for acute toxicity classification (oral and inhalation) relied on both 1) the results of a newly available OECD 425 study of acute oral toxicity of nickel bis(sulphamidate) (more commonly known as nickel sulphamate) and 2) read across from nickel sulphate for acute inhalation toxicity. Bioaccessibility data was only used as the basis for read-across from nickel sulphate to nickel sulphamate for the acute toxicity classification for inhalation. We disagree with several statements made by Germany which may have been the result of some misunderstandings regarding the identification of the substance; this is explained further in the response to Germany's specific comments on the acute toxicity endpoint below.				

Germany states that "*… the bioelution concept which is currently a framework mainly intended by industry to be used for relief from classification proposals*." We do not agree with this observation since the proposal under consideration is exactly the opposite; we are using bioaccessibility information, in a weight of evidence approach, to add a classification for acute inhalation toxicity when one does not currently exist. Thus, the consideration of bioaccessibility data can lead to less or more restrictive classifications, depending on the properties of the substance. The acute systemic toxicity (i.e., mortality) of metals and their inorganic substances is primarily associated with the bioavailable metal ions. Determining bioaccessibility of metal ions under surrogate physiological conditions is therefore more relevant to classification than previous read-across paradigms based on water solubility alone.

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 draw attention to the fact that there are 130+ 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." Yet, contrary to the simplistic approach applied to the classification of those nickel compounds, in the CLH report for nickel sulphamate we have relied on data for acute oral toxicity of sulphamate which supports the proposed classification for acute inhalation toxicity derived from the bioaccessibility-based read across. Bioaccessibility data relevant to the inhalation route of exposure was used with *in vivo* validation and other relevant information, and considered the data in a weight of evidence approach for the proposed classification for acute inhalation toxicity. We have presented all the available data in a transparent way and have outlined the uncertainties associated with our approach. These uncertainties in no way invalidate what we have done but clearly describe the limitations of the method. Our overall approach could be considered a refinement/improvement over the previous precedent of applying only water solubility-based read across.

RAC's response

Although the RAC has sympathy for the comments made by German CA, RAC is of the opinion that under certain circumstances read across could be used. In line with the comments given by the Geman CA the arguments for the inhalatory route are inadequate as explained in the opinion document.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
04.01.2017	France		MemberState	2
Comment received				
We agree with the classification proposal for both acute toxicity by oral and inhalation route.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON NICKEL BIS(SULFAMIDATE)|NICKEL SULFAMATE

Dossier Submitter's Response
The dossier submitter thanks the French CA for their support of the harmonized CLH proposal for the substance.
RAC's response
We thank the French CA for the comments. RAC agrees with the comments on the acute oral route about the proposed classification of nickel sulphamate as Acute Tox. 4; H302 but with an ATE of 853 mg/kg bw for the anhydrate and of 1098 mg/kg bw for the tetrahydrate. As explained in the opinion document, RAC has reservations with the substantiation for the inhalation route.

Date	Country	Organisation	Type of Organisation	Comment number
16.01.2017	Germany		MemberState	3
Comment received				
With respect to classification for acute oral toxicity (pages 14, 15, 29, and 30 of the CLH dossier) there are major concerns, as no justification is provided why the registrant did not use the substance of concern, nickel bis(sulphamidate), in the presented acute toxicity study (OECD TG 425 - Acute Oral Toxicity: Up-and-Down Procedure). Instead nickel sulphamate tetrahydrate (CAS no.: 124594-15-6) was used and it was stated that this substance "is equivalent to the substance identified in the CLH dossier". However, there is neither any information presented in the CLH dossier regarding the physicochemical properties of nickel sulphamate tetrahydrate (e.g. water solubility), nor is official data available regarding those properties of nickel sulphamate tetrahydrate to be able to directly compare the two substances and assess the potential of nickel sulphamate tetrahydrate to serve as source substance for nickel bis(sulphamidate) in a read-across approach. Without presenting a valid justification for the read-across or submitting further results of studies employing the substance of concern, an indisputable classification of nickel bis(sulphamidate) is not feasible. Hence, this information needs to be added to the CLH dossier to be able to classify nickel bis(sulphamidate) appropriately. With respect to classification for acute inhalation toxicity (pages 16 – 27, and 30 – 32 of the CLH dossier) there are also major concerns. Although it is of importance that any false perception that nickel sulphamate 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 DE-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 16 it is noteworthy to see that the difference of LC50-values 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 be 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 9.1.7. (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 9.1.9 (Uncertainties in read-across for acute inhalation toxicity) are considered by the DE-CA 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 uptakes routes.

Dossier Submitter's Response

The dossier submitter appreciates Germany's comments and provides the following clarifications. Nickel bis(sulphamidate) and nickel sulphamate are synonyms that refer to the same compound and therefore have the same CAS and EC numerical identifiers as well as the same structural formula. Furthermore, *hydrated and anhydrous forms of compounds shall be regarded as the same substance for the purpose of a registration*, according to the Guidance for identification and naming of substances under REACH and CLP (ECHA, 2016). Consequently, nickel sulphamate tetrahydrate (CAS no.: 124594-15-6) is covered under the same registration and EC entry as nickel bis(sulphamidate), following the "One Substance, One Registration (OSOR) principle" and ECHA's advice to include the anhydrous form as primary reference substance for technical reasons. However, it should be noted that the anhydrous form of the substance is only possible to be obtained under very specific conditions, according to *Gmelin Handbook of Inorganic Chemistry - Nickel: Teil B — Lieferung 2. Verbindungen bis Nickel-Polonium* (*R.J. Meyer*, 1966), and it is currently neither imported nor manufactured in the EU. It is therefore not reasonably foreseen that the substance will transform into the anhydrous form at any point during professional and non-professional uses, as this can only happen under very particular conditions.

Furthermore, we highlight that in accordance with Article 5(1) of the CLP Regulation, information used for hazard classification "shall relate to the forms or physical states in which the substance is placed on the market and in which it can reasonably be expected to be used". Similarly, in accordance with Article 6(8) of CLP Regulation, tests "shall be carried out on the substance or on the mixture in the form(s) or physical state(s) in which the substance or mixture is placed on the market and in which it can reasonably be expected to be used.Therefore, OECD TG 425 - Acute Oral Toxicity: Up-and-Down Procedure was performed with the form of the substance under consideration for classification: nickel sulphamate tetrahydrate.

The dossier submitter appreciates Germany's concerns about the exclusive use of bioaccessibility data as the basis for read-across of an acute toxicity classification for inhalation. 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* data from acute inhalation studies with reference substances, b) *in vivo* information on lung clearance and relative absorption of nickel from various nickel compounds, and c) consideration of relative toxicity of the counter-ions, sulphamate and sulphate, derived from nickel sulphamate and nickel sulphate, respectively.

As indicated in section 9.1.1 of the Ni sulphamate CLH report, our 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) mentions *in vitro* solubility (bioelution) when it 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*." We do not agree with this observation since the proposal under consideration is exactly the opposite; we are using bioaccessibility information, in a weight of evidence approach, to add a classification for acute inhalation toxicity when one does not currently exist. Thus, the consideration of bioaccessibility data can lead to less or more restrictive classifications, depending on the properties of the substance. The acute systemic toxicity (i.e., mortality) of metals and their inorganic substances is primarily associated with the bioavailable metal ions. Determining bioaccessibility of metal ions under surrogate physiological conditions is therefore more relevant to classification than previous read-across paradigms based on water solubility alone.

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 draw attention to the fact that there are 130+ 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." Yet, contrary to the simplistic approach applied to the classification of those nickel compounds, in the CLH report for nickel sulphamate we have used bioaccessibility data relevant to each route of exposure, with in vivo validation and other relevant information, and considered the data in a weight of evidence approach. We have presented all the available data in a transparent way and have outlined the uncertainties associated with our approach. These uncertainties in no way invalidate what we have done 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 and thus a reduction of uncertainties as compared to a purely water solubility-based approach. The bioelution protocols used, although not yet internationally harmonised, have performed well in a round-robin study that included Ni substances (Henderson *et al*., 2014). Bioaccessibility considerations have also been used by the metals industry for grouping and read-across as discussed at an expert workshop held in Helsinki in 2012 and in the OECD Guidance on Grouping Chemicals (2014).[1]

We agree 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 sulphamate CLH report on the possible contribution of particle effects to acute inhalation toxicity of various nickel compounds compared to its contribution to chronic toxicity after repeated exposure (sections 9.1.5. and 9.1.6). Importantly, it should be noted that in the specific case of acute (mortality) effects by nickel sulphamate, this compound is highly soluble in water and synthetic lung fluids; thus, no particles would be expected to remain as such in the lungs, and particle effects will be negligible for acute effects.

While we agree that in the particular case of Ni sulphamate and Ni sulphate, water solubility and synthetic lung fluid solubility are equivalent, this is not the case for other less-soluble Ni compounds. With regard to the data in Table 14, we consider that a difference in LC_{50} of > 7-fold between Ni sulphate hexahydrate (0.55 mg Ni/L) and green or black Ni oxide (> 4 mg Ni/L) is not "*minor*." Because nickel oxides demonstrated no toxicity whatsoever at the highest concentration tested (4 mg Ni/L) their LC50 is higher than 4 mg Ni/L. Thus, it is likely that the difference in LC50 could easily be 10-fold or higher. The difference in interstitial fluid bioaccessibility from Ni sulphate hexahydrate (11%) and Ni oxides (average 0.3%) was <50-fold. This is not inconsistent with the *in vivo* findings.

Once again we thank the German CA for their comments and look forward to further discussions of the ECHA expert bioleution group on the issues Germany has raised here.

RAC's response

As indicated in the opinion document RAC agrees with the comments on the acute oral route about the proposed classification of nickel sulphamate as Acute Tox. 4; H302 but with an ATE of 853 mg/kg bw for the anhydrate and of 1098 mg/kg bw for the tetrahydrate. As regards to the inhalation route RAC agrees with the comments made by the German CA and as a consequence no classification is proposed due to absence of data.

[1] Henderson RG, Verougstraete V, Anderson K, Arbildua JJ, Brock TO, Brouwers T, Cappellini D, Delbeke K, Herting G, Hixon G, Odnevall Wallinder I, Rodriguez PH, Van Assche F, Wilrich P, Oller AR. Inter-laboratory validation of bioaccessibility testing for metals. Regul Toxicol Pharmacol. 2014 Oct;70(1):170-81.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON NICKEL BIS(SULFAMIDATE)|NICKEL SULFAMATE

Date	Country	Organisation	Type of Organisation	Comment number
13.01.2017	Finland		MemberState	4
Comment received				
The proposed classification of nickel bis(sulphamidate) as Acute Tox. 4; H332 is based on read across from nickel sulphate hexahydrate. Nickel sulphate hexahydrate and nickel bis(sulphamidate) belong to water-soluble nickel compounds and the justification for the read across is well presented in the CLH report. Acute inhalation toxicity study in rats conducted with nickel sulphate hexahydrate resulted in LC50 value of 2.48 mg/L, which meets the criteria Acute Tox. 4; H332. Acute oral toxicity study in rats conducted with nickel bis(sulphamidate) resulted in LD50 value of 1098 mg/kg bw. The result meets the criteria for Acute Tox. 4; H302. The FI CA supports the proposed harmonised classification and labelling of nickel bis(sulphamidate) as Acute Tox. 4; H332 and H302.				
Dossier Submitter's Response				
The dossier submitter thanks the Finnish CA for their support of the harmonized CLH proposal for the substance.				
RAC's response				
See responses to the German CA and French CA				