Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Pyridine-2-thiol 1-oxide, sodium salt

EC Number: 223-296-5
CAS Number: 3811-73-2

CLH-O-0000006914-67-01/F

Adopted

8 October 2020

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PYRIDINE-2-THIOL 1-OXIDE, SODIUM SALT; PYRITHIONE SODIUM; SODIUM PYRITHIONE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during 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 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 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: pyridine-2-thiol 1-oxide, sodium salt; pyrithione sodium; sodium pyrithione
EC number: 223-296-5; 240-062-8
CAS number: 3811-73-2; 15922-78-8
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2019	Germany	German Paint and Printing Ink Association (VdL)	Industry or trade association	1
Comment received				
Sodium pyrithione (SPT - CAS No 3811-73-2) is a biocidal active substance, which is of high importance for the paint and coatings industry in Germany. We are aware that the public consultation on the proposed classification should only consider scientific arguments on inherent properties and we refer to the comments submitted by the suppliers. Nevertheless, in the following we would like to highlight the importance of SPT for our industry. Over 70% of the production of paints and printing inks in Germany is water-based. Most of these products need preservatives to prevent microbial growth. We estimate that alone in the German market for paints and printing inks a business volume of around 2.6 billion € is relying on in-can preservatives. However, we fear that in the future less and less suitable active substances will be available. One reason is the coupling between the CLH process and the biocidal products regulation (BPR), for instance the exclusion criteria. With several of the isothiazolinones being classified as skin sensitizers with very low specific concentration limits, the formaldehyde releasers being under pressure due to the classification of formaldehyde and the proposed classification for Zinc Pyrithione, SPT is one of the very few remaining highly effective active biocidal substances. To ensure effective preservation of water-based paints and coatings in the future and safe, high quality products it is essential to ensure SPT will remain available to the industry. Furthermore, as SPT is non-volatile, its use in indoor applications is particularly favorable. With almost all available actives for in-can preservation under scrutiny in the review process, future availability of water-based dispersion paints and coatings is becoming				

increasingly uncertain.

We remain available to provide further information.

The German paint and printing ink association (VdL) represents over 180 – mostly mid-sized – manufacturers of paints, coatings and printing inks. The VdL stands for nearly 90 percent of this industry in Germany. In 2018 the German manufacturers of paints, coatings and printing inks realized sales of ca. 8 billion euros and employed ca. 25,000 staff.

Dossier Submitter's Response

Thank you for your comments highlighting the importance of sodium pyrithione for your industry while acknowledging that these are not relevant to the current CLH process.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2019	Germany		MemberState	2

Comment received

Substance ID:
In section 1.1 of the CLH report the second CAS number is not correct (15933-78-8 ☐ 15922-78-8).

Classification and labelling elements:
Table 2.1 (p.6):
H372:
1. We doubt that the specification with "mortality" is correct.
2. Please add the affected organ (neuromuscular system) also in the column of the labelling elements.
Acute tox. inhalation:
ATE value should read as follows: ATE= 0,5 mg/l (dusts or mists)

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE-MSCA_Comments_CLH-Pyridine-2-thiol_1-oxide,_sodium_salt_Attach.docx

Dossier Submitter's Response

Thank you for your comment.

Substance ID:
Thank you for spotting the typo. The second CAS no. in the Table 1.1 of the CLH report should be 15922-78-8.

Classification and labelling elements (Table 2.1 of the CLH report):
1. The hazard statement H372 allows for stating affected organs, however, the DS considers that it is important to communicate the hazard that the substance causes also mortality through repeated exposure.
2. Mortality and neuromuscular system should also be in the labelling column.
Acute tox. inhalation:
Alternatively, it can also read as: ATE = 0.5 mg/L (dusts/mists)

RAC's response
Agree with the DS, however the decicison will be taken in plenar regarding indication mortality to be included in the STOT RE assessment.

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2019	United Kingdom	Lonza Cologne GmbH, Janssen PMP (a division of Janssen Pharmaceutica NV) and Thor GmbH, industrial manufacturers of NaPT	Company-Manufacturer	3

Comment received

The Dossier Submitter (DS) has, in general, used three sources of information to make their proposal: two biocide submission dossiers (for which they have the full studies to review) and a REACH dossier (where they are relying only on summary data and have not got the full studies to evaluate). It was observed that, particularly for the environmental studies, the DS has downgraded the Klimisch score (often to a 3) on studies where the full reports are available but has not changed the Klimisch scores for those studies where they are only relying on IUCLID summaries (still accepting the score of 1).
In most cases it was not open and transparent why this downgrading was done as the reasons stated are not sufficient to justify a devaluation of a study (i.e. Klimisch score 3). Two examples are provided:
1) Photo-oxidation in air. The CLH report comments that (p 173) "The reliability for this study is only considered to be 3 (Klimisch score) as the results are based on calculations instead of data." (Page 173). However, according to the IUCLID drop down menu, results derived from a valid QSAR model and falling into its applicability domain with adequate and reliable documentation and justification should be assigned to a reliability of 1 - 2. Please note that the use of a calculation model does not justify a reliability of 3 if no deficiencies were identified.
2) Toxicity to sewage treatment plant microorganisms. The CLH report comments that (p 179) "However, DS has given the studies a reliability of 3 (due to that the test substance was not measured and missing information on storage of stock solution), which means it is difficult to draw any conclusions only based on these studies." According to the guideline OECD 209 it is not a requirement to measure the test substance concentration. Thus, it is not justified to attribute Klimisch score of 3 to this study. Additionally, missing information on stock solution is also not sufficient to downgrade the studies which fulfil all validity criteria according to the guideline.

In addition to the downgrading of the studies, it is also not an open and transparent process when the data considered as integral to the proposal are not available to the DS. We would hope that RAC and the appointed Rapporteur would be able to see the currently unavailable studies to ensure a fair and consistent review of the data.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment NaPT CLH comment on effects upon reproduction_ final.pdf

Dossier Submitter's Response
Thank you for your comments. The DS would like to point out and clarify that most studies in the Reach registration dossier concerning the aquatic compartment and NaPT were already available to the DS through the active substance dossier evaluated under BPD 98/8/EC and (EU) BPR 528/2012. Evaluations of those studies were based on full study reports. For the two cases where the DS did not have access to the full study reports this fact is explicitly mentioned in the CLH-report. The RIs that are reported in the CLH-report without brackets are based on full study reports and set by the DS. The RIs whithin brackets are set by the Reach registrant. 1) Photo-oxidation in air: We agree that the reliability of the study can be considered to be higher than 3. The Atkinson estimation model has been used, which is an acceptable model for estimating a chemical's gas-phase reaction rate. It is described in the OECD Environmental Monograph No 61 (and is also used by the EPA in the EPI suite program in the model AOPWIN). However, we modelled sodium pyrithione's affinity to aerosols (particles in air) using EPIWEB 4.1. There, the Mackay and Junge-Pankow models in the AEROWIN program (v. 1.00) predicted that 10.2–20.1% of the sodium pyrithione would be bound to aerosols. The AOP Program warns that the sorbed fraction may be resistant to atmospheric oxidation. Hence, a lower photo-oxidation rate may be expected in natural air. For completeness the study should also preferably include speciation of sodium pyrithione in air and photo oxidation of other pyrithione species such as hydrogen pyrithione. Furthermore, the compound has non-volatile properties and the majority of sodium pyrithione present in the environment is not expected to be found in the air compartment (but can reach the air via e.g. soil dust, or dust from very finely fragmented building material such as gypsum boards or dried paints). The reliability for the study per se can in spite of this be set to 2 as the study is performed in accordance with an accepted guideline, but there are some reservations concerning speciation of pyrithione in air and adsorption to aerosols that can prevent photo oxidation. The scope of reliability aside, the relevance of the obtained result is questionable. 2) Toxicity to sewage treatment plant microorganisms: Yes, it is true that the OECD test guideline 209 does not ask for measured test concentrations per default for all situations, however it does open for the fact that for some purposes measured concentration of the test substance might be needed. The study is performed/submitted as an ecotoxicity study in order to come to a reliable conclusion regarding an ecotoxicity endpoint for regulatory purposes. In the introduction to the OECD 209 guideline it is stated that the purpose of the guideline is to provide a rapid screening method/range-finding test. For this purpose the same accuracy is not necessarily needed as it is for a reliable conclusion on a NOEC/EC50.

RAC's response
Noted and taking into consideration. However, all submitted studies have been taken into account for the assessment of NaPT.

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2019	Germany	Thor GmbH	Company-Manufacturer	4
Comment received				
Ready Biodegradability (p 174) The Dossier Submitter (DS) comments that "[...] this was seen in spite of the fact that the sewage inoculum came from a treatment plant, which predominantly treats domestic waste, and therefore could be expected to be adapted to pyrithione background.". However, we disagree with the comment of the DS, noting that it is actually stated in the guideline OECD 301 that the inoculum should be taken from a sewage treatment plant that predominantly treats domestic sewage (cf. § 9; 17). Therefore, the requirements of the OECD guideline 301 in regards to the source of activated sludge were fully met.				
Dossier Submitter's Response				
Thank you for your comment. To clarify: The text quoted is simply a discussion regarding the results. It is not a discussion regarding whether it is correct that the inoculum comes from a treatment plant or not. The full text in the relevant paragraph is as follows (with an added period after the word "observed" in order to hopefully make it a bit easier to read): "Sodium pyrithione was also tested as an aqueous liquid solution (Doc III A7.1.1.2.1/01, 1998). The results showed 2% degradation after 8 days, 60 % degradation after 18 days, 70 % after 43 days. A lag period of circa 6 days was observed. This was seen in spite of the fact that the sewage inoculum came from a treatment plant, which predominantly treats domestic waste, and therefore could be expected to be adapted to pyrithione background. However, in the test for inhibitory properties, sodium pyrithione was non-inhibitory as defined by the guideline (OECD 31 B, §25). A degradation plateau was attained at approximately Day 28. These results indicate that sodium pyrithione is readily biodegradable." *I.e.* what we mean is that we did not expect to see the lag phase.				
RAC's response				
Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2019	Germany		MemberState	5
Comment received				
A study with less than 50% survival in low, medium and high dose groups in both males and females (combined chronic toxicity/carcinogenicity study, 104 weeks, oral gavage, rats) limits the power and reliability. This should be acknowledged. Nevertheless, the proposal for non-classification is supported.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE-MSCA_Comments_CLH-Pyridine-2-thiol_1-oxide,_sodium_salt_Attach.docx
Dossier Submitter's Response
Thank you for your comment. Indeed the DS has acknowledged this in the summary table of carcinogenicity studies (Table A.75) and under Section A3.9.1 of the CLH report.
RAC's response
Noted.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2019	United Kingdom	Lonza Cologne GmbH, Janssen PMP (a division of Janssen Pharmaceutica NV) and Thor GmbH, industrial manufacturers of NaPT	Company-Manufacturer	6

Comment received

A.3.10. Reproductive toxicity
A.3.10.1. Sexual function and fertility
No comment.
A.3.10.2. Developmental toxicity
Section A.3.10.2. gives a thorough overview of relevant studies on the developmental toxicity endpoint. We agree with the conclusion that classification of sodium pyrithione for this endpoint is not supported by the available data. There are, however, some points to address for the two PNDT studies in rats.
For the oral PNDT study, table A.82 and A.83(a)(iii) state that the incidences of incomplete ossification of 6th sternebrae and metatarsals was increased in the high dose group (positive for dose-response). The study report did not present statistical analyses of these endpoints, but simply noted (section 5.11) that "The only sign of toxicological relevance was the increased incidence of incomplete ossification of 6th sternebrae…and metatarsal(s) observed in high-dose foetuses compared to controls". However, the incidences of these two endpoints were not found to be statistically significantly different from the control group ($p>0.05$) in a subsequent analysis (see attachment). The only foetal endpoints that were statistically significantly changed in the high-dose group were litter and foetal weight, incidence of small foetuses, and incidence of foetuses with absent ossification of the metacarpal(s).
Analysis of covariance has been applied to the foetal weight data, with adjusted maternal body weight gain (weight gain throughout gestation adjusted for the weight of the gravid uterus) and live foetuses per litter as dependent covariates. This analysis showed no significant treatment-related effects compared to control, while the influence of adjusted maternal body weight gain in the model was significant ($p<0.05$). Similarly, nested logistic regression of small foetuses and missing ossification of metacarpals with adjusted maternal weight gain as dependent covariate showed no significant treatment-related effects compared to control, but a significant influence of adjusted body weight gain ($p<0.05$).
These analyses further support the conclusion that reduced foetal weight, small foetuses, and absent ossification were secondary to maternal toxicity.

With regards to the dermal PNDT study, and as noted in the CLH proposal, all effects in the offspring were only observed in the high-dose group (7 mg/kg bw/day). This dose level also induced maternal toxicity (5/25 maternal mortalities) that clearly exceeds the general 10% mortality limit recognised in the current OECD TG 414 and CLP Regulation (3.7.2.4.4): "Maternal mortality greater than 10 % is considered excessive and the data for that dose level shall not normally be considered for further evaluation." Indeed, the study report acknowledges, "This dosage level is considered excessively high for a teratology study." If the high-dose group is excluded from the assessment, there were no identified effects upon the progeny. The assessment of this study would be strengthened by reference to the accepted limit of mortality as given in the CLP Regulation. A.3.10.3. Effects on or via lactation No comment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment NaPT CLH comment on effects upon reproduction_ final.pdf
Dossier Submitter's Response
Thank you for the comment including the attachment. Your subsequent statistical analyses of the oral PNDT study in rats (Doc IIIA A6.8.1/04) are noted.
RAC's response
Noted. The additional information on statistical evaluation of oral PNDT in rats are referred to in the RAC evaluation.

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2019	Germany	German Paint and Printing Ink Association (VdL)	Industry or trade association	7
Comment received				
Our toxicological experts have reviewed the data and we agree with the dossier submitter that the substance specific data leads to the conclusion that no classification for adverse effects on sexual function and fertility, on development or via lactation for sodium pyrithione is applicable according to the CLP criteria.				
Dossier Submitter's Response				
Noted. Thank you for your comment.				
RAC's response				
Noted				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2019	Finland		MemberState	8
Comment received				
Hazard class Acute Tox. 4, H302: Harmful if swallowed The LD50 values of the available four acute oral toxicity studies on sodium pyrithione in rats are 1208 mg/kg, 1100 mg/kg, 300-816 mg/kg and 200-2000 mg/kg. There were no				

deaths at 300 mg/kg in the third study, and no deaths at 200 mg/kg in the fourth study. The observed toxic effects were systemic and non-specific. Category 4 for acute oral toxicity under CLP regulation is assigned for substances with LD50 value > 300 and ≤ 2000 mg/kg. FI CA supports the proposed classification of Acute Tox. 4; H302 for sodium pyrithione. Hazard class Acute Tox. 4, H312: Harmful if in contact with skin Acute dermal toxicity of sodium pyrithione has been investigated in two rat and one rabbit studies. The LD50 values are > 2000 mg/kg in both of the rat studies and 1800 mg/kg in the rabbit study. The observed toxic effects were systemic and non-specific. Category 4 for acute dermal toxicity under CLP regulation is assigned for substances with LD50 value > 1000 and ≤ 2000 mg/kg. Because the lowest LD50 value, 1800 mg/kg, is derived from a reliable study, classification is justified. FI CA supports the proposed classification of Acute Tox. 4; H312 for sodium pyrithione. Hazard class Acute Tox. 3, H331: Toxic if inhaled There are two acute inhalation toxicity studies available on sodium pyrithione. The LC50 value in the first rat study (supporting, with whole-body exposure) is 1.08 mg/l, and in the second rat study (key) it is 0.5-1 mg/l. Category 3 for acute inhalation toxicity under CLP regulation is assigned for substances with LC50 value > 0.5 and ≤ 1.0 mg/l for dusts and mists. The observed toxic effects were systemic and not indicative of toxicity to any specific organ. Therefore, FI CA supports the proposed classification of Acute Tox. 4; H331 for sodium pyrithione.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2019	Germany		MemberState	9
Comment received				
Classification for skin irritation (Category 2) for sodium pyrithione and the corresponding hazard statement is H315: Causes skin irritation is supported. ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE-MSCA_Comments_CLH-Pyridine-2-thiol_1-oxide,_sodium_salt_Attach.docx				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2019	Finland		MemberState	10
Comment received				
The skin irritation potential of sodium pyrithione has been investigated in four rabbit studies and one in vitro study. In the first in vivo study severe erythema and eschar formation were observed in 2 of 3 tested animals, with mean scores of 0, 3.3 and 2.3 at 24, 48 and 72 hours, respectively. Edema was observed in all three animals, with mean scores of 0, 4.0 and 1.0 at the same timepoints. All findings were reversible within 14 days. In the other three rabbit studies absent to well-defined erythema and very slight to slight edema were observed, with mean scores of < 2.3 at all timepoints. All findings were reversible. Sodium pyrithione was found to be non-irritant in the in vitro study on Episkin™ model. Based on the results of the first in vivo study, FI CA supports the classification of sodium pyrithione as Skin Irrit. 2, H315.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2019	Germany		MemberState	11
Comment received				
Classification for eye irritation (Category 2) for sodium pyrithione and hazard statement H319: Causes serious eye irritation is supported. ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE-MSCA_Comments_CLH-Pyridine-2-thiol_1-oxide,_sodium_salt_Attach.docx				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2019	Finland		MemberState	12
Comment received				
The eye irritation potential of sodium pyrithione has been investigated in five rabbit studies, one monkey study and one in vitro study. Main observed effect was conjunctival irritation, which was present in all in vivo studies (with a mean score of ≥ 2 for conjunctival redness in 4 of 6 rabbits in one reliable study). Iritis was observed in two and corneal opacity in one of the six in vivo studies. All ocular effects were reversible. Treatment-related mortality was observed in three of five rabbit studies. FI CA supports the classification of sodium pyrithione as Eye Irrit. 2, H319 with a supplemental labelling phrase EUH070 ´Toxic by eye contact´.				
Dossier Submitter's Response				
Thank you for your support.				

RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2019	Germany	German Paint and Printing Ink Association (VdL)	Industry or trade association	13
Comment received				
Many paint companies have set up hotlines for allergy sufferers. This is where allergy sufferers can get suitable information and advice. Moreover, via these hotlines the companies also obtain information about prevalent allergies. We are not aware of a single consumer in Germany that has become sensitized due to the use of SPT in paints. Furthermore, since SPT is non-volatile no emissions to indoor air occur, which is beneficial in any case any consumer should be sensitized.				
Dossier Submitter's Response				
Noted. Thank you for the information.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2019	Germany		MemberState	14
Comment received				
For Sodium pyrithione there was data of two LNNAs submitted. 1. Calculated EC3 values should be reported in the table A.47 as requested in the head of the results column. 2. According to the guidance on application of the CLP criteria skin sensitizers shall be classified into subcategories 1A and 1B where data is sufficient (Annex I: 3.4.2.2.1.2.). Considering that the registrant proposed reliability 1 for the LLNA study in the REACH registration dossier, subclassification into 1A should be possible as the EC3 is below 2%. Otherwise reliability should be reduced into 2 due to the technical error during preparation of the single cells suspension. The four human Patch tests reported were conducted at 1% or 0.1% concentration. In Germany the standard skin allergy testing series 37 DKG Industrielle Biozide also uses Natrium-2-pyridinethiol-1-oxid (Natrium-Omadine) at 0.1%. Thus the concentration used in the dossier studies is scientifically justified. Number of published cases is < 100. According to CLP guidance (Tab. 3.2) high frequency in humans could not be assigned, which is one criterion for subcategory 1A. This should be taken into account in a WoE approach when deciding about subclassification. Overall, we support Cat.1. ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE-MSCA_Comments_CLH-Pyridine-2-thiol_1-oxide,_sodium_salt_Attach.docx				
Dossier Submitter's Response				
Thank you for your overall support for classification as Skin Sens. 1.				

1. In the CLH report the calculated EC3 values of 16% (LLNA, BPR Art. 95 dossier) and 1.3% (LLNA, REACH dossier) are reported only under Sections A3.5.1 and A3.5.2 of the CLH report. Indeed these should have been reported also in the Table A.47 of the CLH report.

The DS has in addition noted that in the Table A.47 of the CLH report under the first GPMT (Doc IIIA A6.1.5/01), the total number of animals that died after topical induction should be six (and not four). This is correctly reflected though under Section A3.5.1 of the CLH report.

2. The DS agrees to change the reliability score of the LLNA from the REACH dossier to 2 as the results of the highest test concentration were discarded due to technical error during preparation of the single-cell suspension.

Human patch tests: The DS did consider the human data in a WoE approach under the Section A3.5.2 of the CLH report. The available human data on sodium pyrithione indicates relatively low frequency of occurrence of skin sensitisation at relatively low exposure suggesting Category 1 (according to the sub-categorisation decision table (Table 3.4) of the CLP Guidance, ver. 5).

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2019	United Kingdom	Lonza Cologne GmbH, Janssen PMP (a division of Janssen Pharmaceutica NV) and Thor GmbH, industrial manufacturers of NaPT	Company-Manufacturer	15

Comment received

A3.5 Skin sensitisation
The Sodium Pyrithione manufacturer, Lonza Cologne GmbH, Janssen PMP (a division of Janssen Pharmaceutica NV) and Thor GmbH welcome the opportunity to provide comments on the classification proposal for Sodium Pyrithione (NaPT, CAS 3811-73-2). In providing our comments, we refer to the Regulation (EC) 1272/2008, on classification, labelling and packaging of substances and mixtures (CLP), and the most recent Guidance on the Application of the CLP Criteria Version 5.0 , (CLP Guidance) released by ECHA in July 2017.

GPMT (Doc. IIIA A6.1.5/01)
The first (2002) of the two available guinea pig maximisation tests (GPMTs) with NaPT was conducted as two experiments, each using 10 NaPT-treated animals and 5 for the control group. In the first phase, no animals exhibited a skin reaction, and body weights and survival were unaffected. In the second phase, 2 NaPT-treated animals showed skin reactions of score 2 and 3 (compared to one in the control group with a score of 1), 6 animals died (including two spare animals), the group mean body weight among the survivors was significantly reduced compared to control, and there were clinical signs of reduced well-being.

The net sensitisation rate was 2.5%: 2/16 (test substance group) – 1/10 (negative control group).
The obvious restriction with this study is that the dose applied in the second experiment's induction phase (which was the same as in the first experiment's induction phase) exceeded the requirement of OECD test guideline (TG) 406 that the applied "concentration of test substance used for each induction exposure should be well-tolerated systemically". This deviation from the TG has a clear negative impact on the outcome of the study that is, as correctly stated in the CLH report, that "The test substance is toxic by the epicutaneous exposure" (Table A 47, p. 73).
The study was conducted according to OECD TG 406 and GLP, and has been given a reliability rating of 1. However, the guideline deviation and thus deficiencies noted above suggest a reliability of 2 might be more appropriate.

GPMT (Doc IIIA A6.1.5/02)
The second study (1987) was conducted using 10 NaPT-treated males. There was no control group. At the 24h evaluation, 2/10 animals showed mild erythema (score=1), and 3/10 at 48h.
The unadjusted sensitisation rate is therefore 30%. While this fulfils the criteria for a positive result (≥30%) in the current OECD TG 406, the study report defines the test item as a non-sensitiser, but did not confirm in a follow-up group of animals. Furthermore, since there was no concurrent control group, the net sensitisation rate is unknown, and potentially <30%.
The study was conducted according to GLP and references the original literature of Magnusson & Kligman, but neither follows, nor complies with, the OECD TG 406 which recommends a group size of 20 animals and the inclusion of a control group. The study has been given a reliability rating of 1. However, the deficiencies noted above suggest a reliability of 3, is more appropriate.

LLNA (BPR Art. 95 dossier)
The reporting of the mouse LLNA (5 female CBA/J mice per group) was critically discussed with the conducting laboratory, as we as the study sponsor find the results as reported inconclusive and rather misleading.
Essentially, the 25% dose level of the main study does not meet the assay's criteria for selection of the high dose. As delineated in the OECD TG 429 the highest concentration should not cause systemic toxicity or excessive local skin irritation. Actually, for the same reasons the 30% dose level was rejected in the pre-screen test, e.g. body weight loss (- 2 gram) (systemic toxicity) in combination with ear swelling exceeding 25% (local skin irritation).
The main argument for the exclusion of the high-dose group (25% dose level) from the evaluation is the occurrence of ear thickness increase >25% in that dose group. Generally, the observation of ear thickness >25% on any day of measurement leads to an exclusion of the corresponding dose group. The highest dose selected for the evaluation of the results then needs to be the next lower dose (cf. OECD 429). Nota bene, all animals of the 25% Sodium pyrithione dose group showed visibly enlarged ears, although not all exceeded the 25% threshold of increase in ear thickness (cf. Study report).
In reaction to the occurrence of ear thicknesses >25%, the laboratory simply rejected those animals that fulfilled the exclusion criteria from interpretation, i.e. had an ear thickness >25%. Thus, in the present study, the exclusion of the 2 animals (Nos. 19 and 20) leaves only 3 animals in the high-dose group. This is an additional argument for the exclusion of the 25% NaPT group since the OECD Guideline 429 recommends a minimum of 4 animals per dose group. Even the reduced LLNA uses four animals per dose group but less dose groups. In other words the evaluation of the high-dose group can be seen as deviation from the guideline if the group is not excluded.

Therefore, based on the deficiencies notes above, the complete 25% NaPT group should have been excluded from the interpretation.
The remaining NaPT concentrations, fit for interpretation, were 5, 10 and 15% with Stimulation Index (SI) values of 1.0, 1.8 and 2.5, respectively. It can be concluded that NaPT would not be regarded as a skin sensitiser according to the recommendations made in the test guidelines and thus, the test substance does not have to be classified.

LLNA (REACH dossier)
Another LLNA in Balb/c mice (REACH registration dossier, JS member, Opt-out, 2000) was performed but the study report was not available for evaluation. The study summary accessible via the ECHA REACH registration dossier is lacking in details, specifically on local response to application. Further, in the available study summary it is reported that "due to a technical error the results of the highest concentration (25% w/v) were not representative, and have therefore been discarded". It is not clear on which "technical error" lead to the exclusion of the highest concentration. The study was conducted according to OECD 429 and GLP, and has been given reliability 1. However, this study cannot be considered as reliability 1. Generally, a robust study summary does not suffice to assign reliabilities of 1 or 2, because an expert judgement is simply not possible. Taking into consideration the deficiencies noted above a reliability of 3 is appropriate.

Human data
Taking all available human data into consideration, it becomes evident that 1 out of 396 subjects may have become sensitised towards NaPT. With regards to the frequency this corresponds to 0.25%. According to the CLP Guidance and as the Data Submitter correctly states this "[…] indicates relatively low frequency of skin sensitisation at relatively low exposure […]".Most importantly we note that no case reports of NaPT skin sensitisation are published in open literature. Furthermore, from a manufacturer perspective we are not aware of any worker or consumer who acquired a skin sensitisation from contact with NaPT.

Overall weight of evidence
To summarise, the available GMPT studies do not support the skin sensitisation classification for NaPT, as the first GPMT (Doc. IIIA A6.1.5/01) was negative and the second GPMT (Doc IIIA A6.1.5/02) has to be considered as non-reliable (reliability 3). From 2 LLNA studies, in the first study (BPR Art. 95 dossier) no evidence for skin sensitisation was found at concentrations up to and including 15%. Above this exposure level excessive local and systemic toxicity were observed, so that the higher dose levels were inappropriate for evaluation. The second LLNA (REACH dossier) has to be considered non-reliable (reliability 3) as, due to the limited information available, no expert judgement is possible.
In sum, the available animal data show that no potency in animals can be presumed. All available human diagnostic patch test data assessed in industry workers with occupational dermatitis show an incidence of 1/396 for skin sensitisation against NaPT. Additionally, there are no other well documented episodes of allergic contact dermatitis with NaPT from industry workers, professional consumers or the general public.
In conclusion, the overall weight of evidence around the skin sensitisation hazard shows that NaPT is not sensitising via the dermal route.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment NaPT CLH comment on effects upon reproduction_ final.pdf

Dossier Submitter's Response

Thank you for the comment.

The DS notes that during the submission of the two GPMTs (Doc. IIIA A6.1.5/01 and Doc IIIA A6.1.5/02) under the biocides legislation, you, as an applicant, had assigned a reliability score of 1 for these two studies.

However, owing to the systemic toxicity (incl. mortality, decreased body weight) observed in the first GPMT (Doc. IIIA A6.1.5/01) the DS agrees with your above comment that a reliability score of 2 might be more appropriate.

Regarding the second GPMT (Doc IIIA A6.1.5/02), due to the deficiencies (except the group size) noted above by you the DS considers a reliability score of 2 as more appropriate. For the GPMT, the OECD 406 allows a minimum of 10 animals in the treatment group if it is possible to conclude that the test substance is a sensitiser.

LLNA (BPR Art. 95 dossier): The calculated EC3 value including the 25% test concentration group (with 3 animals) is 16%. Even if this group is excluded, the EC3 value calculated by extrapolation of 10% and 15% groups would be 18.5%. Both the calculated EC3 values (16% and 18.5%) are well below the 30% dose level that was rejected in the pre-screen test. Therefore, the DS considers that this LLNA is positive and the calculated EC3 value of 16% as appropriate.

LLNA (REACH dossier): The study summary is indeed lacking in details, nevertheless, the study was GLP compliant and a deviation was reported (that due to a technical error during single-cell suspension preparation the 25% concentration group was discarded). The DS proposes to change the reliability score to 2 instead (also in agreement with the comment number 14 above).

In conclusion, in a WoE approach including the available human data (indicating relatively low frequency of occurrence of skin sensitisation at relatively low exposure) and considering the above changes in the reliability scores of the animal studies from 1 to 2, the DS still considers its proposal in the CLH report to classify sodium pyrithione as Skin Sens. Category 1 as appropriate.

RAC's response

RAC agrees with the comment that there are some deviations in conduct and or reporting of all the animal studies. For the LLNA test from the REACH dossier RAC notes that a Klimish score of 3 would be warranted, as the study is only available as a summary. However, since all available should be included in classification, RAC supports the reliability factor of 2 attributed by the DS. RAC supports the downgrade to a reliability 2 by the DS for all four animal studies. The comment also included reference to negative allergic data from humans in addition to the 4 articles identified by the DS. However, as no concrete reference supporting this statement was provided, RAC supports the evaluation of the human data by the DS.

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2019	Finland		MemberState	16

Comment received

There are two GPMT studies, two LLNA studies and four human patch test reports available on sodium pyrithione. 12.5% of the animals were sensitised in the first GPMT study 12 and 48 hours after the challenge, and 6 of 10 animals died. In the second GPMT

study, mild erythema was observed in 20% of the animals at 24.5 hours and in 30% of the animals at 48 hours at 5% intradermal induction dose. In the first LLNA study, the EC3 value was 16%. Only two concentrations were used in the second LLNA study, the EC3 value of which was 1.3%. In humans, sodium pyrithione was found to be negative in three patch test reports on metallurgical industry workers with occupational dermatitis at concentrations of 0.1 and 1%. The substance was positive in one female worker at 0.3%, but negative in 10 adult volunteers at the same concentration. FI CA considers that even though the available human data are predominantly negative, the results from reliable animal studies support classification of sodium pyrithione in Category 1. The data are not sufficient for subcategorisation, because although only two concentrations were used in the second LLNA study, category 1A cannot be reliably excluded. FI CA supports the classification of sodium pyrithione as Skin Sens. 1, H317.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2019	Germany		MemberState	17
Comment received				
Classification as STOT RE 1; H372 (mortality, neuromuscular system) based on the effects mortality, hind limb weakness/paralysis, skeletal muscle effects and reduced body weight gain observed in rat studies is supported. ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE-MSCA_Comments_CLH-Pyridine-2-thiol_1-oxide,_sodium_salt_Attach.docx				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2019	United Kingdom	Lonza Cologne GmbH, Janssen PMP (a division of Janssen Pharmaceutica NV) and Thor GmbH, industrial manufacturers of NaPT	Company-Manufacturer	18
Comment received				
A3.7 Proposed STOT-RE Classification by the Dossier Submitter (Sweden) The Dossier submitter of the CLH document on sodium pyrithione proposes STOT RE Cat				

1 classification based on:
- Neurotoxicity and mortalities in rats at 2 and 8 mg/kg bw/day after oral exposure for 90 days.
- Neurotoxicity and mortality in rats at 15 and 50 mg/kg bw/day after dermal exposure for 90 days.
- Neurotoxicity in rats at 0.0081 mg/L after inhalation exposure for 90 days.

According to the dossier submitter, classification as STOT RE 1; H372 (mortality, neuromuscular system) is proposed for sodium pyrithione according to the CLP criteria. It is proposed not to specify the route of exposure as mortality was observed by two routes (oral and dermal) and effects on neuromuscular system were observed by three routes (oral, dermal and inhalation).
Classification in STOT RE 1 (hazard statement H372 – Causes damage to organs through prolonged or repeated exposure) is proposed for sodium pyrithione.

(1.1) Response to the Proposed Classification by Dossier Submitter
Lonza Cologne GmbH, Janssen PMP (a division of Janssen Pharmaceutica NV) and Thor GmbH, industrial manufacturers of NaPT challenge this proposal for the reasons outlined below.

(2.1) Pyrithione Exposure: Hind limb Weakness
Repeated exposures of rats to sodium pyrithione, regardless of the route of administration, has resulted in the observation of decreases in weight gain and skeletal muscle atrophy—characterised by generalised muscle weakness and generally referred to as hind limb weakness—that has been shown to be fully, and completely, reversible following cessation of treatment. The finding of hind limb weakness has only been observed in rats and occasionally in rabbits, but has never been observed in mice following repeated administration, that includes an 18-month dermal carcinogenicity study.
In addition, no observation of skeletal muscle atrophy (hind limb weakness) has been observed in non-human primates following 28-days, 90-days, or up to one year of repeated oral administration of zinc-, sodium-, or copper pyrithione. A clear NOAEL for the pyrithiones from two 28-day primate studies is 11 mg/kg/day 1, 2 (Lonza, 1992, 1994) with no signs of neurological deficit even at the highest doses that were evaluated, 22 mg/kg/day for ZnPT and 44 mg/kg/day for CuPT. Moreover, when corrected for duration of study, these doses are 15–30 times greater than the corresponding NOAEL for rodents in 90-day studies (0.5 mg/kg/day), indicating rodent-specific sensitivity (cf. 2.1.1). These data bring into question the likelihood that pyrithione exposure produces neurotoxicity in humans.
The dossier submitter has assigned the 52-week long-term oral toxicity study of sodium pyrithione in Cynomolgus monkeys a reliability rating of 3, based on minor documented deviations which do not detract from the integrity of the study. Two of the noted deviations—inadvertent dosing of control group animals on one day, and inadvertent administration of incorrect vehicle volume to control group animals on one day—do not weaken the importance and relevance of a study in which doses were administered daily over a one-year period. It was the opinion of the study director that these events did not affect the quality or integrity of the study. The dossier submitter also states that "emesis shortly after dosing makes it difficult to estimate the actual dose the animals were exposed to." Although emesis was noted in most low-dose group animals and all animals from the mid- and high-dose groups, review of the data in Table 2 of the study report shows that this was not a consistent finding throughout the course of the study. Consequently, the study is reliable (a reliability of 2 should be assigned); a clear NOAEL can be established, and neuromuscular effects were not observed at any dose level. Furthermore, in the 28-days studies on ZnPT and CuPT, in which the test items were

administered in gelatin capsules rather than by gastric intubation, there were no reports either of emesis or of neuromuscular involvement at doses up to 22 mg/kg/day for ZnPT and 44 mg/kg/day for CuPT.
It is considered by Lonza Cologne GmbH, Janssen PMP (a division of Janssen Pharmaceutica NV) and Thor GmbH, industrial manufacturers of NaPT that, for the purposes of classification and labelling, primates are the more appropriate surrogate for humans and data on primates should be used to derive the classification if the data already exist. The Companies would, therefore, welcome the opportunity to discuss this at the RAC meeting and to hear the views of the experts at RAC as we consider it pivotal that all available data on monkeys are taken into account when classifying a relatively data rich substance like sodium pyrithione.
In support of Category 1 for STOT RE, dossier submitter refers to a PDNT study in rabbits via the dermal route (Doc IIIA A6.8.1/06), in which body weight gain was reduced at an applied dose of 5 mg/kg/day. There were no reports of mortality or neuromuscular deficit in this study, so its inclusion in support of classification is unwarranted. Dossier submitter also refers to a two-generation reproduction toxicity study in rats (Doc IIIA A6.8.2/02) in which no mortalities or clinical signs of neuromuscular deficit were reported, and in which "histopathological examinations … did not include previously identified target organs: skeletal muscle, sciatic nerve and spinal cord."
(2.1.1) Comparative sensitivity of rat and primate
The available data clearly show that rodents respond to treatment with sodium pyrithione with a characteristic neuromuscular weakness. These effects are not seen in primates, even at higher doses.
The dossier submitter notes the published work that demonstrates a 30-fold difference in sensitivity of motor neurons from rats and monkeys to increased intracellular Ca2+ induced by sodium pyrithione, but opines "the RMS considers this data to indicate that there is merely a difference in sensitivity between rodents and primates". Nevertheless, this study explains the differences in species sensitivity towards neuromuscular effects of sodium pyrithione, and why the rat responds while the nonhuman primate is refractory.
(2.1.2) Further considerations and implications for classification
The Companies consider that an allometric scaling factor is appropriate to account for the differences in toxicity between rat and primate, since the thresholds for classification for STOT RE given in Annex 1: 3.9.2.9.6 and 3.9.2.9.7 are based, specifically, on data from the rat.
In the available primate studies on pyrithiones, neurotoxic effects are not observed at the highest dose rate tested, 44 mg/kg bw/day2 for CuPT administered over 28 days (Lonza, 1994). Nor were such effects noted in the one-year study of sodium pyrithione (Lonza, 1992)
REACH guidance on information requirements and chemical safety assessment chapter R.8 indicates that the allometric scaling factor from rat to primate should be set at 2. A duration factor of 3 also applies to scaling a 28-day study to 90 days. Together, these adjustments mean that the guidance values for a 28-day oral primate study should be 15 mg/kg/day for Category 1 and 150 mg/kg/day for Category 2.
Similarly, in a 1-yr oral study in primates, the guidance values should be 2.5 mg/kg/day for Category 1 and 25 mg/kg/day for Category 2.
Consequently, it is proposed that a STOT-RE based on neurotoxicity and, therefore, the central nervous system as the target organ is not warranted.

(2.2) Pyrithione exposure: Mortality
As stated above by the Companies, for the purposes of classification and labelling, primates are the more appropriate surrogate for humans and, therefore, data on primates should be used to derive the classification if the data already exist.
No substance related mortalities have been observed in primates treated with pyrithiones

by the oral route at much higher dose levels in comparison to the rat (25 mg/kg bw/day in a 1-year study)1, 2, 3, 4. Therefore, mortality is not considered to be an appropriate endpoint for the determination of a STOT-RE by this route of administration.
No substance related deaths were observed in the repeat dermal study in the rat and therefore there is no direct evidence from the available studies on sodium pyrithione to indicate the need to classify sodium pyrithione on this basis.
No mortality was observed in the repeat dose (90d) inhalation study in rats.
(2.3) Lonza Cologne GmbH, Janssen PMP (a division of Janssen Pharmaceutica NV) and Thor GmbH, industrial manufacturers of NaPT Proposed STOT-RE Classification
It is proposed by the Companies that a STOT-RE 1 classification is not warranted for sodium pyrithione.
(2.4) References
1. Lonza (1992), A Repeated Dose Toxicity Study of Zinc Omadine Powder to Cynomolgus Monkeys for 28 Days Followed by a 2-Week Recovery Period.
2. Lonza (1992), A Repeated Dose Toxicity Study of Copper Pyrithione Administered Orally to Cynomolgus Monkeys for 28 Days and Followed by a 14-Day Recovery Period.
3. Lonza (1973), Oral Administration of Zinc Omadine (WIN 9546) to Rhesus Monkeys for Three Months.
4. Lonza (1989), A One Year Oral Toxicity Study in Cynomolgus Monkeys with Sodium Omadine.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment NaPT CLH comment on effects upon reproduction_ final.pdf

Dossier Submitter's Response

Thank you for the comment.

(2.1) Pyrithione Exposure: Hind limb Weakness and (2.1.1) Comparative sensitivity of rat and primate:

According to Annex I Section 3.9.1.1 of the CLP Regulation, both reversible and irreversible significant health effects are considered for STOT RE classification.

You propose that the hind limb weakness effects of sodium pyrithione are due to rodent-specific sensitivity and these effects were not observed in monkeys and "*[the] data bring into question the likelihood that pyrithione exposure produces neurotoxicity in humans*".

The DS reiterates that due to the deficiencies mentioned in the CLH report, the 28-day range-finding study (Doc IIIA A6.4.1/03) and the one-year study (Doc IIIA A6.4.1/04) in Cynomolgus monkeys with sodium pyrithione are not reliable (score 3). Moreover, there is no scientific data presented by you to support that the hind limb effects observed in rodents with sodium pyrithione are not relevant to humans.

Thank you for rightly pointing out that there were no reports of mortality or neuromusclar effects in the PNDT study in rabbits via the dermal route (Doc IIIA A6.8.1/06) and it does not support the proposed classification in Category 1. Via the dermal route, mortality (Doc IIIA A6.8.1/05) and neuromuscular effects (Doc IIIA A6.4.2/02 and Doc IIIA A6.8.1/05) supporting classification in Category 1 were observed only in rats. Under Section A3.7.4.2 of the CLH report the correct sentence would be: "Mortality and effects on neuromuscular system warranting STOT RE Category 1 were ~~also~~ observed in study(ies) on rats ~~and rabbits~~ also via dermal route."

(2.1.2) Further considerations and implications for classification:

The use of allometric factors is not considered for classification purposes since it is focused on hazard identification.

(2.2) Pyrithione exposure: Mortality:

For classification, generally the studies giving the most severe classification are used in a weight of evidence evaluation. The STOT RE Category 1 classification based on mortalities observed in reliable studies in rats via the oral and dermal routes cannot be overridden by no mortalities being observed in unreliable studies in monkeys via the oral route or in a reliable study in rats via the inhalation route.

RAC's response

Noted. This information is taken into consideration and is included in the opinion.

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2019	Finland		MemberState	19

Comment received

Long-term toxic effects of sodium pyrithione have been investigated in five subchronic and three chronic toxicity studies. Main effects observed in rats after oral administration were skeletal muscle effects, hind limb paralysis/weakness, sciatic nerve degeneration and mortality. Histopathological findings, although lacking from several studies, support the observed neuromuscular toxicity (with changes in skeletal muscle and spinal cord). Because the adverse effects on neuromuscular system occurred via oral, dermal and inhalation routes and mortality via oral and dermal routes, FI CA agrees that the route of exposure cannot be specified. FI CA supports the proposed classification of STOT RE 1; H372 (neuromuscular system) for sodium pyrithione.

Dossier Submitter's Response

Thank you for your support.

RAC's response

Noted.

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2019	Germany		MemberState	20

Comment received

Please see attachment.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE-MSCA_Comments_CLH-Pyridine-2-thiol_1-oxide,_sodium_salt_Attach.docx

Dossier Submitter's Response

Thank you for your comment. The DS agrees that we have interpreted the results from the Grewer-Oven incorrectly and that the conclusion would be that further testing according to UN Test N.4 would be necessary to conclude on the classification for self-heating substances. However, we are unsure about changing it to "data lacking" as data were available and since this conclusion would have implied that it should not have been open for public consultation. We are happy that it was open for public consultation as

these valid comments means that we now can request further data in the biocidal process.
RAC's response
Noted.

PUBLIC ATTACHMENTS
1. DE-MSCA_Comments_CLH-Pyridine-2-thiol_1-oxide,_sodium_salt_Attach.docx [Please refer to comment No. 2, 5, 9, 11, 14, 17, 20]
2. NaPT CLH comment on effects upon reproduction_ final.pdf [Please refer to comment No. 3, 6, 15, 18]