Committee for Risk Assessment

RAC

Annex 4

Records

of the targeted public consultation on aquatic hazard following Industry submission of additional experimental aquatic toxicity studies

pyrithione zinc; (T-4)-bis[1-(hydroxy-.kappa.O) pyridine-2(1H)-thionato-.kappa.S]zinc

EC Number: 236-671-3
CAS Number: 13463-41-7

CLH-O-0000001412-86-239/F

Adopted

14 September 2018

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

A proposal for Harmonised Classification and Labelling (CLH) for pyrithione zinc; (T-4)-bis[1-(hydroxy-.kappa.O)pyridine-2(1H)-thionato-.kappa.S]zinc was submitted by the Swedish competent authority and was subject to a public consultation from 23 May until 7 July 2017. The comments received by that date are compiled in Annex 2 to the opinion.

During its June meeting, following industry's submission of two additional aquatic studies the Committee for Risk Assessment (RAC) asked for comments on these two studies. Targeted public consultation on the newly submitted information was launched on 18 July 2018 and lasted until 1 August 2018.

Comments provided during the targeted public consultation are made available in this table as submitted by the webform. Please note that the comments displayed below may have been accompanied by attachments which are not published in this table.

Please note that in addition, another targeted public consultation on toxicity to reproduction was launched on 7 March and lasted until 21 March 2017. The comments received by that date are compiled in Annex 3 to the opinion.

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

Last data extracted on 2 August 2018

Substance name: pyrithione zinc; (T-4)-bis[1-(hydroxy-.kappa.O)pyridine-2(1H)-thionato-.kappa.S]zinc
EC number: 236-671-3
CAS number: 13463-41-7
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2018	Germany		Individual	1
Comment received				
With the proposed classification of Reprotox Cat 1B, zinc pyrithione would fall under the exclusion criteria listed in Article 5 of the BPR and would likely be restricted for biocidal use in most applications. In addition, the proposed environmental classification (M factors for Aquatic impact) would also affect the current PT 6 applications for ZnPT in e.g. Paints, coatings, adhesives and glues Zinc pyrithione is a key biocide for such applications and for polymer dispersions, especially in combination with isothiazolinones. Why would it make sense to classify ZnP as reprotoxic and hence severely limit the use as a PT6 preservative to a few ppm, while a content of up to 2% is considered safe in cosmetics and hair shampoos?				

It would be very odd and impossible to explain to an average consumer, that I can put 2% of ZnPT on my skin in one case, but in the other case, a few ppm, coming into contact with skin by coincidence in the case of paint/adhesives, would be classified as hazardous. We finally need in Europe a more risk based approach to classify chemicals, and not a pure hazard based approach! The current uncoordinated approach to evaluate PT6 biocides is on the best way to make it impossible to preserve waterborne formulations sufficiently, because one biocidal active substance after the other is virtually taken out of the market (like e.g. the forthcoming 15 pm limit for MIT, Methylisothiazolinone).
RAC's response
RAC notes this comment but unfortunately this targeted public consultation is only concerned with effects on the aquatic environment.

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2018	Spain	European Polymer Dispersion and Latex Association (EPDLA)	Industry or trade association	2
Comment received				
The members of EPDLA welcome the opportunity to comment on the proposed harmonised classification and labelling of zinc pyrithione (ZnPT – CAS 13463-41-7). Please find EPDLA comments in the file attached to this public consultation. We kindly ask to consider these for future discussions on the proposed harmonised classification and labelling of zinc pyrithione. In this respect, we urge to follow a more risk based approach to evaluate substances, particularly preservatives, rather than to focus on a pure hazard based approach. ECHA note – An attachment was submitted with the comment above. Refer to public attachment EPDLA-Comments on CLH of zinc pyrithione-FINAL 07.18.pdf				
RAC's response				
Noted. Please be aware that the process is confined to the assessment of hazard.				

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
01.08.2018	Germany	German Paint and Printing Ink Association (VdL)	Industry or trade association	3
Comment received				
As we already stressed in the original public consultation, zinc pyrithione (ZnPT – CAS No 13463-41-7) is a biocide active, which is of high importance for the paint and coatings industry in Germany. We would like to highlight the severe impact, which the supposed classification (especially the question of reproductive toxicity) would have on our industry and especially the deco paint sector.				

ZnPT is one of the key actives for dry-film preservation (PT 7). Dry-film preservation is most important for organic resin-based coatings and prevents the growth of microorganisms like algae and fungi on coated surfaces, such as the facades of buildings.

Apart from its use in PT 7, ZnPT is also increasingly employed as an in-can preservative. 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. With the isothiazolinones being subject to severe restrictions and the formaldehyde releasers being under pressure due the classification of formaldehyde, ZnPT is one of the very last remaining alternatives. This situation has been severely tightened by the decision of the REACH Committee to adopt the ATP, which also includes the harmonized classification of MIT (CAS No 2682-20-4). It is feared that the specific concentration limit for skin sensitization of MIT of 15 ppm will lead to a de facto ban of this substance for consumer products under biocides legislation. If this happens, our industry will have to rely on the availability of ZnPT and a few other substances to ensure the future of water-based dispersion paints.

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 2016 the German manufacturers of paints, coatings and printing inks realized sales of ca. 8 billion euros and employed ca. 25,000 staff.

RAC's response

Noted.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
01.08.2018	Germany	German Paint and Printing Ink Association (VdL)	Industry or trade association	4

Comment received

The currently proposed acute and chronic environmental classification for zinc pyrithione (ZnPT) is based on a study by Ward and Boeri (2004) in Skeletonema costatum. As was raised by the ZnPT Consortium during the earlier Public Consultation, the Ward and Boeri study has some fundamental flaws and, so, should not be considered suitable for classification purposes. The reliability of the study is compromised by, amongst other things, the presence of copper contamination in the culture medium and inappropriate use of photolysis data to estimate TWA exposure.

The two new studies in S. costatum with ZnPT (in addition to another earlier study submitted by the consortium) remove the original flaws and improve on the marine algae study. Therefore, the Ward and Boeri study should be excluded from further consideration and endpoints from the remaining three reliable studies should be used for the classification of ZnPT.

For the derivation of the correct M-factors on the basis of these studies we refer to the work of the ZnPT industry consortium.

RAC's response
Agreed. The proposed classification is based on the two new studies in S. costatum with the lowest effect concentrations for ErC50 and ErC10 (72 hour) supplied by Goudie (2018). Based on an acute toxicity of zinc pyrithione with a 72 h ErC50 = 0.00088 mg/L (0.88 µg/L), zinc pyrithione may be classified as Aquatic Acute 1, with an M factor 1000 (0.0001 < ErC50 ≤ 0. 001 mg/L). The lowest chronic 72 h ErC10 value is 0.00068 mg/L which falls in the [0.0001 < ErC10 ≤ 0.001 mg/L] range giving a chronic M-factor of 10 for a rapidly degradable substance while maintaining the Aquatic Chronic 1 classification.

Date	Country	Organisation	Type of Organisation	Comment number
01.08.2018	Netherlands		MemberState	5

Comment received
NL CA appreciates the submission of two new studies with the marine diatom Skeletonema costatum. In the classification proposal, the NOEC from a study with S. costatum yielded the lowest NOEC on which chronic classification was based. It appears that the two new studies are identical both in study design and the chosen test concentrations. The NL CA wonders why this is the case, especially when considering that in both studies at the lowest two test concentrations actual test concentrations fell below LOQ already early during testing, which leads to less accurate geometric mean test concentrations. In the reports LOQ was taken in those cases, but half the LOQ would be more appropriate when calculating geometric mean test concentrations. Also, exposure duration was 120 hours, while 72 hours is common according to OECD TG 201. The new studies report higher NOECs and EC10 values compared to the S. costatum study that is currently used in the classification proposal. Furthermore, while in the previous study a decrease in inhibition was observed after 48 hours, this does not appear to be the case for the new studies, with longer exposure duration leading to lower effect concentrations. Therefore, it is necessary to determine if the new studies are sufficiently similar to the already available study for direct comparison, and if so which exposure duration is considered most relevant.
RAC's response
The new studies presented to RAC confirm that *Skeletonema costatum* may be considered the most sensitive species to zinc pyrithione. A comparison of the key design features of the four *S. costatum* studies, including the culturing conditions, availability of analytical data and incorporation of exposure concentrations into the reported results is available in the opinion document. The two new studies (Goudie, 2018; Hoover, 2018) were designed primarily according to US guidelines (OSCPP 540.5400) but are also consistent with OECD 201 test guidelines. The two new studies are identical both in study design and the chosen test concentrations and sponsored by the same industry partner and performed by the same testing laboratory. They were conducted by different study directors and run at different times using different batches to guarantee independence of results. The studies were conducted using study conditions appropriate for S. costatum, included daily analytical determinations, and produced robust statistical results with low variability, suggesting optimal algal growth conditions. They are acceptable to RAC. The point about taking half the LOQ in preference to the LOQ as being more acceptable is agreed but we have what we have and the studies are finalised. The two new studies address deficiencies in the older studies so a direct comparison is inappropriate. RAC considers the two new studies to be sufficient in themselves to determine classification for aquatic toxicity. The 72 hour exposure is considered to be most compliant with OECD 201 and effect concentrations from this time point are used to propose classification:

- Aquatic Acute 1, with an M factor 1000
- Aquatic Chronic 1, with an M factor 10 (rapidly degradable)

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2018	United Kingdom		MemberState	6

Comment received

COMMENTS – JULY 2018
Based on the two expert reviews(1, 2) of the Boeri 2004 study with S. costatum, it appears that study endpoints are not reliable for classification based on study limitations principally due to lack of analytical support, uncertainty regarding actual exposure concentrations and potential copper contamination in test media.

Based on the two expert reviews of the Rebstock 2010(1, 2) study with S. costatum, there are significant study limitations with regard to study validity criteria at varying acute/chronic endpoints. It is currently unclear if there are definitive reliable acute and chronic endpoints from the study.

The two new algal growth inhibition studies with S. costatum dated July 2018 and referenced as #86821 and #86820 are acceptable and meet all study validity criteria. The endpoints from these studies are based on mean measured concentrations with reliable endpoints in the following acute and chronic classification ranges:
acute classification range 0.0001-0.001 mg/l
chronic classification range 0.0001-0.001 mg/l

Overall, based on the #86821 and #86820 studies, the following environmental classification would be appropriate:
Aquatic Acute 1 (M-factor 1000), Aquatic Chronic 1 (M-factor 100 for NRD substance)

Cited references:
1. De Schamphelaere, Karel (2018) Comparative evaluation of two toxicity studies of zinc-pyrithione to Skeletonema costatum for classification purposes. Ghent University.

2. Arts, Gertie (2018) Summary and evaluation of two algal inhibition studies investigating the toxicity of zinc pyrithione to the marine diatom Skeletonema costatum. Wageningen Environmental Research Team.

RAC's response

Agreed except that the substance is considered rapidly degradable and thus the chronic M factor should be 10.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2018	Netherlands		MemberState	7

Comment received

In the study report the registrant reported that the validations criteria will be reached (exponential grow in controls ≥16x (was 47 & ; 25x, resp.); coefficient of variation of average specific growth rates during the whole test period in replicate control cultures <10% (was 7 and 5%, resp.) but there is no determination available of the mean coefficient of variation for section-by-section specific growth rates in controls lower is

35%. Furthermore the EC10 and EC50 values should be determined according OECD TG 201 method.

RAC's response

Agreed.

Goudie (2018):
The mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for the 72 hour test) in both controls did not exceed 10%, being 4-5%, 6-9% and 4-7% for each respective interval. This meets the validity criteria in OECD 201 (CV should not exceed 35% for a 72 hour test).

Table: Goudie (2018) Summary of the effect concentrations (i.e., ErC) based on growth rate. Results are based on geometric mean measured concentrations (µg a.i./L).

EC type	48-hour	72-hour	96-hour
ErC10	1.35	**0.68**	0.518
ErC50	1.68	**0.88**	0.645
NOEC	0.34	**0.26**	0.22

Hoover (2018):
The mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for the 72 hour test) in both controls did not exceed 12%, being 7%, 8-12% and 2-9% for each respective interval. This meets the validity criteria in OECD 201 (CV should not exceed 35% for a 72 hour test).

Table: Hoover (2018) Summary of the effect concentrations (i.e., ErC) based on growth rate. Results are based on geometric mean measured concentrations (µg a.i./L).

EC type	48-hour	72-hour	96-hour
ErC10	0.991	0.778	0.686
ErC50	1.23	0.969	0.854
NOEC	0.54	0.42	0.33

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2018	Belgium	The ZnPT Industry CLH Consortium	Industry or trade association	8

Comment received

These comments are being submitted on behalf of Lonza, Janssen and Procter & Gamble, manufacturers of Zinc Pyrithione (ZnPT) and of downstream products made with ZnPT, respectively.

A full detailed review is submitted as a supportive document in the "Public Attachment" including consideration of the relevant guidance, the adequacy of all four studies for classification purposes, an overview of independent evaluations of the Ward and Boeri and Rebstock studies, and conclusions on the classification. It is, therefore, very important that the attachments are reviewed, as they contain all the details including key information in graphs and tables that could not be published through the webform.

The proposed acute and chronic environmental classification for zinc pyrithione (ZnPT) is based on the Ward and Boeri (2004) study in Skeletonema costatum, which is currently considered the key study for the aquatic classification of ZnPT. As was raised during the Public Consultation and in comments on the RAC Opinion (ODD), the Consortium considers the Ward and Boeri (2004) study to be fundamentally flawed and, thus, not adequate for classification purposes. The reliability of the study is compromised by:
- the presence of copper contamination in culture and test medium at 5 times above the reliable NOEC in the copper REACH dossier for S. costatum; this alone renders the study unreliable;
- the use of photolysis data to estimate the TWA exposure in an algal study is inappropriate because the experimental conditions in photolysis studies and algal toxicity studies are different and not comparable;
- the lack of intermediate and final analytical determinations makes any estimated TWA effect concentrations highly uncertain;
- the statistical analysis in the Ward and Boeri study is not reproducible;
- the high variability in growth and growth rate between control replicates are indicative of questionable study quality and reliability; and,
- the 24h light regime is not appropriate for a light-sensitive compound nor recommended for the test species S. costatum.

An additional study on S. costatum with ZnPT (Rebstock, 2010) had been submitted, previously, for evaluation and had been considered reliable (RI=2) in the BPR PT21 evaluation of CuPT, but was not included in the CLH report on ZnPT. To confirm the reliability of the Rebstock study and to further address any uncertainties about the relative reliability of both studies, the Consortium conducted two additional studies in S. costatum with ZnPT. The two new studies (report numbers 86820 and 86821) were conducted by different study directors and run at different times using different batches of ZnPT.

The Rebstock study and the two new studies were designed, technically, to remove the original flaws and improve on the Ward and Boeri study. ZnPT, due to rapid photolysis, is exceptionally difficult to test in algal toxicity studies, which are conducted under static conditions with light exposure. The Rebstock, 86820 and 86821 studies were conducted using study conditions appropriate for S. costatum, included daily analytical determinations, and produced robust statistical results with low variability, suggesting optimal algal growth conditions. All three studies are valid, reliable, and give results that are remarkably similar, indicating that the results are reproducible. Therefore, the Ward and Boeri study should be excluded from further consideration in the classification process and the endpoints from the remaining three reliable studies should be used for the classification of ZnPT.

Because of the rapid degradation of ZnPT in the test system, the 48 h results from the S. costatum studies with ZnPT are most appropriate for classification, as this timepoint best balances the statistical considerations for growth rate with the decreasing certainty in the results as ZnPT degrades. Especially for an acute evaluation of a rapidly degrading (photolytically unstable) substance, results based on peak exposures make the most

sense, scientifically. Considering the weight of the evidence provided by the three reliable studies on S. costatum, the appropriate aquatic classification for this rapidly degradable substance, ZnPT, should be as follows:

Aquatic Acute 1 with an M-factor of 100 (0.001 mg/L < ErC50 <= 0.01 mg/L)

Aquatic Chronic 1 with an M-factor of 10 (0.0001 mg/L < ErC10 <= 0.001 mg/L)

ECHA note – An attachment was submitted with the comment above. Refer to public attachment ZnPT CLH Aquatic public consultation final 31072018.pdf

RAC's response

Agreed. Ward & Boeri (2004) is no longer considered.
The revised classification proposal is based on the two new studies.
RAC considers the 72 hour results sufficient and in line with OECD 201 and that the substance is rapidly degradable..

RAC proposes:

Aquatic Acute 1 with an M-factor of 1000 (0.0001 mg/L < ErC50 <= 0.001 mg/L)

Aquatic Chronic 1 with an M-factor of 10 (0.0001 mg/L < ErC10 <= 0.001 mg/L)

Date	Country	Organisation	Type of Organisation	Comment number
25.07.2018	Finland		MemberState	9

Comment received

FI CA has evaluated the relevancy and the quality of two static growth inhibition tests with marine diatom, Skeletonema costatum in targeted public consultation of pyrithione zinc. Both studies are considered reliable without restrictions with Klimisch score 1. The cell density in the control was greater than 16 times initially inoculated at 72 hours and the guideline criteria was met with the coefficients of variation for cell density in both studies. The other validity criteria according to guidelines OECD 201 and U.S. EPA OCSPP 850.4500 were also met sufficiently. FI CA considers these studies valid for the classification purposes.

The most relevant chronic toxicity endpoints are 96 and 120 h EC10 values for growth rate inhibition of Skeletonema costatum. The 96 h EC10 values of 0.000518 and 0.000686 mg/L and the 120 h EC10 values of 0.00043 and 0.000618 mg/L based on geometric mean measured concentrations are obtained, respectively.

For acute aquatic hazard classification 72 or 96h EC50 values are preferred for algal species. For Skeletonema costatum 72 h EC50 values of 0.000881 and 0.000969 and 96 h EC50 values of 0.000645 and 0.000854 mg/L based on geometric mean measured concentrations for growth rate inhibition are obtained, respectively.

Solely based on these studies M-factor of 1000 for classification Aquatic Acute 1 and M-factor of 100 for classification Aquatic Chronic 1 (not rapidly degradable substance) could be warranted for pyrithione zinc. This would result in different M-factor for chronic toxicity

than currently proposed (M-factor=10). However, FI CA has not evaluated previous CLH-dossiers in this targeted public consultation of pyrithione zinc.
RAC's response
Agreed except that RAC proposes classification based on the 72 hour EC10 values from the new studies for aquatic chronic 1 classification with an M factor of 10.

PUBLIC ATTACHMENTS

1. ZnPT CLH Aquatic public consultation final 31072018.pdf [Please refer to comment No. 98]
2. EPDLA-Comments on CLH of zinc pyrithione-FINAL 07.18.pdf [Please refer to comment No. 2, 99]