**Committee for Risk Assessment**

**RAC**

Annex 3

**Records**

of the targeted public consultation on human health following Industry submission of additional information regarding toxicity to reproduction

# 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.

Due to the submission by Industry of additional information regarding toxicity to reproduction, a targeted public consultation on the newly submitted information was launched on 7 March and lasted until 21 March 2017.

Comments provided during 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 aquatic hazard was launched on 18 July 2018 and lasted until 1 August 2018. The comments received by that date are compiled in Annex 4 to the opinion.

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

**Last data extracted on 22.03.2018**

**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 |
|---|---|---|---|---|
| 20.03.2018 | United Kingdom | British Coatings Federation | Industry or trade association | 1 |
| Comment received | | | | |
| We would like to thank the authorities for providing us with a further opportunity to comment on the proposed harmonized classification of Zinc Pyrithione (ZnPT). We would like to take this opportunity to bring to the attention of the authorities the significant impact that such a classification could ultimately have on the paints, coatings and printing inks industries, through the link between the harmonized classification process (CLH) and the Biocidal Products Regulation (EU) 528/2012 (BPR).<br>ZnPT is a key biocide used in inks, paints, and coatings for decorative, industrial and marine applications, primarily providing dry-film (Product Type 7) protection against fungal growth on e.g. the façades of buildings. It is also an extremely useful co-biocide for in-can preservation (PT6, especially in combination with isothiazolinones) and for use in antifouling paints (PT21). If the proposed classification of Reprotoxin cat. 1B for ZnPT was approved by the authorities then this important substance would fall into the scope of Article 5 of the BPR (i.e. meet the exclusion criteria), which would lead to restrictions and the requirement for it to be removed from use in key sectors of our industry. In addition, the proposed environmental classification (M factors for Aquatic impact) will also affect the current applications for ZnPT in our industry. | | | | |

We fully support the detailed arguments defending a less severe classification for ZnPT, that have been presented in the past and during the previous consultation (May-July 2017) by the manufacturers and key stakeholders, especially those presented by the ZnPT CLH Defence Consortium. The Additional Information Report provided on this substance in December 2017 is particularly welcome, as this provides a detailed evaluation of the findings from the study 'Prenatal Developmental Toxicity Study of Zinc Pyrithione in Rabbits by Oral Gavage', presented by Thor GmbH. Specifically, we understand that this additional information changes the perspective on evaluating the findings to this study, and reinforces the statement that the developmental effects are only observed in the presence of severe maternal toxicity.
We would like to ask the authorities to ensure that comprehensive in-depth discussions take place within the appropriate ECHA committees on the following key points:
i) The developmental effects are only observed in the presence of severe maternal toxicity;
ii) These effects are a non-specific secondary consequence (ZnPT mode of action);
iii) ZnPT does not have an intrinsic property to produce adverse reprotoxic effects;
iv) It is essential that a balanced, weight of evidence approach is followed;
v) ZnPT, and other pyrithiones, have already been assessed by several global regulatory authorities, who have looked at the same data and came to significantly different conclusions to those proffered in the CLH dossier.
This includes the use of ZnPT in cosmetics applications, where the Scientific Committee for Consumer Safety (SCCS) concluded from their risk assessment for shampoos – 'Based on the scientific data provided the SCCS considers that zinc pyrithione, when used in a concentration up to 2.0% as an anti-dandruff agent in rinse-off hair care products, is safe for the consumer' . We understand that the SCCS has recently completed a further review of their risk assessment and have come to the same conclusion as previously, to allow up to 2% of Zinc pyrithione in anti-dandruff shampoos, which again contradicts the original assertions made in the CLH dossier regarding developmental toxicity.

The potential loss of yet another key biocide (to add to our current issues with MIT, propiconazole and formaldehyde-releasers) from our formulating toolbox is of major concern to European manufacturers of paints, coatings and inks. The pyrithione family of biocides are, like the isothiazolinones, an essential technology for our sector, to ensure the safe and sufficient preservation of our waterbased products. They are also essential for the efficient control of marine organism growth on the hulls of ships and yachts. Once again, we would like to re-emphasize our European industry message that the loss of active substances due to either exclusion (due to an unfavourable harmonized classification) or due to unsuccessful authorization under the BPR is leading us towards a very uncertain future with regard to product preservation. Please refer to the numerous papers (references below and copies available) that have been published by ourselves and partner trade associations over the past three years on this subject.
It is essential for the well-being of the general public, the protection of the environment, and the health of the coatings and inks industry that we are able to continue to fulfil our duty to our customers, to be able to provide coatings and inks that are sufficiently protected and perform efficiently and effectively.
BCF Regulatory Affairs Department, 20th March 2018

References:
'Scientific Committee on Consumer Safety Opinion on Zinc pyrithione COLIPA n° P81', SCCS/1512/13, June 2013
'The need for a holistic approach on in-can preservatives - Views from downstream user sectors' - CEPE/AISE/FEICA/EPDLA paper, April 2014, for the CA meeting in May 2014, CA-May14-Doc. 4.4
'The need for a holistic approach on in-can preservatives' – CEPE/AISE/FEICA/EPDLA

paper, October 2014, for the CA meeting in November 2014, CA-Nov14-Doc.4.6
'The need for a holistic approach on dry-film preservatives' – CEPE paper, May 2016
'Comments on the proposed harmonised classification and labelling of MIT by the Risk Assessment Committee' – EPDLA paper, July 2016
'The need for a holistic approach on in-can preservatives' – CEPE/AISE/FEICA/EPDLA new revised paper for meeting with EU Commission (DG GROW), September 2016
'MIT use in decorative paints and adhesives' – BCF-BASA paper, March 2017
'A holistic approach to the evaluation of in-can preservatives' – Joint European Downstream Association paper presented at the CA meeting in March 2017 (CEPE, FEICA, AISE, EPDLA, EFCC, EBPF, FECC, EDANA)
'Innovation in the biocides industry - general considerations relevant for preservatives' – EBPF, March 2017
'CEPE is calling for the REACH Committee to reconsider the proposal from the RAC to set an SCL for MIT of 15ppm, thus ensuring that this is fully justifiable and correct as the induction limit for this important biocide.' CEPE, April 2017

RAC's response

The CLH process does not concern socioeconomic aspects. Support for other commenting parties is noted and addressed under these comments. RAC always endeavours to enable comprehensive in-depth discussions about all aspects regarding hazard identification of each substance under evaluation.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 21.03.2018 | Belgium | EPDLA –European Polymer Dispersion and Latex Association | Industry or trade association | 2 |

Comment received

As zinc pyrithione is under review for approval as an in-can preservative (product-type 6) under the Biocides Regulation and may be used as a co-biocide for such purpose in polymer dispersions, the classification of Reprotoxic Category 1B proposed by the dossier submitter would likely lead to a restriction for such biocidal use. Therefore, the members of EPDLA –European Polymer Dispersion and Latex Association - request specific consideration of the amended study report with respect to the classification for developmental toxicity. As mentioned in the EPDLA comments submitted during the first public consultation, we call for a holistic view on in-can preservatives as the number of available ones is being reduced one by one via the technical and regulatory requirements of the BPR and the CLP.

RAC's response

The CLH process does not concern socioeconomic aspects.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 19.03.2018 | Belgium | CEPE | Industry or trade association | 3 |

Comment received

With reference to the document dated 21 June 2017 that we submitted during the first public consultation, we would like to reiterate that this substance is important for our Industry and therefore that careful attention should be given to the new toxicological

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| information that has been submitted. The very limited number of available biocide substances needed to protect our products is a reality that has not been taken into account in the current sequential review of biocide substances under the BPR. We are pleading for a holistic approach to the problem. |
| RAC's response |
| The CLH process does not concern socioeconomic aspects. Please see response to comments in the previous consultation. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 19.03.2018 | Germany | German Paint and Printing Ink Association (VdL) | Industry or trade association | 4 |
| 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.<br><br>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.<br><br>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.<br><br>We remain available to provide further information.<br><br>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 | | | | |
| As noted already in previous comments, the CLH process does not concern socioeconomic aspects. Please see response to comments in the previous consultation. | | | | |

**TOXICITY TO REPRODUCTION**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|

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|---|---|---|---|---|
| 21.03.2018 | Netherlands | | MemberState | 5 |
| Comment received | | | | |

Reproductive toxicity

Overall, the evaluation of the amended study report concerning one of the rabbit developmental toxicity studies does not change the opinion of The Netherlands concerning classification of zinc pyrithione for Reproductive toxicity, and we still agree with the proposed classification of zinc pyrithione for reproductive toxicity for effects on development (Repro. 1B; H360D, May damage the unborn child).

It is stated that the low body weight gain between days 7-20 pc in six dams (46, 49, 54, 55, 58, and 62) in the mid dose group is attributable to maternal toxicity, and the cause of the high number of resorptions in these six animals.

However, there were also three dams with equally low body weight gains (48, 50, 59) and no or only one resorption (see table).
Moreover, if the body weight would have been reduced at this dose by high toxicity of zinc pyrithione, you would expect that dams with a high number of resorptions would have a low corrected body weight gain. In fact, the data show the opposite: the dams with the lowest corrected body weight gain in the mid dose group (between day 7-29 pc), had the largest litters (8-10 pups) and no or only one resorption.
Also if all dose groups are considered, the corrected body weight gain became higher (less negative) with higher doses, at which litters were smaller due to high early resorptions. This goes against the hypothesis that the low body weight gain is caused by zinc pyrithione toxicity. If fact, the data suggests that the body weight gain of the dams is linked to the number of viable pups. The number of viable pups decreases in a dose-dependent manner, which leads to a lower total body weight gain, but a higher corrected body weight gain.

Animal Absolute body weight gain (day 7-20 pc) Corrected bw gain (day 7-29 pc) Number of viable pups Number of resorptions
46 -101 216.5 0 2
48 6 -290.7 10 0
49 157 -106.8 5 2
50 100 -299.4 9 0
54 47 -20.6 2 7
55 51 -187.2 8 0
58 112 35.9 3 4
59 79 -20.8 3 1
62 -14 -24.3 1 9

As a last remark on body weight, it should be noted that the differences in body weight gain were relatively small when compared with the total weight of the animals. This is reflected in the relative corrected weight gain, which was on average -3.0%, -2.8%, -2.2%, and 0.1% in control, low, mid, and high dose groups respectively.

Regarding the incidence of omphalocele, it is stated that the incidence in the mid and high dose group is related to maternal stress, because this malformation also occurred in historical control studies. As it is not clear what the incidence was of omphalocele within the historical studies meant (years 2006 to 2017), it is not possible to assess the validity of this argument. The remark that omphalocele was equally distributed among the dose groups indicates that these were not actually control data.
The historical control data included in the report (2008-2012) at least suggest omphalocele is very rare (1 out of 2205 pups in 15 studies). For this reason, we remain of

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| the opinion that the occurrence of omphalocele in the mid and high dose groups is substance related. |
| RAC's response |
| Noted and agreed. The issue of maternal toxicity is a complex one. The argument that excessive maternal toxicity in a few does in the mid-dose group as evidenced by reductions in body weight gain should be interpreted to mean that these should not be evaluated along with the rest of the group is erroneous by the ZnPT Industry CLH Consortium. The corrected maternal weight gain was in the same range as the controls in the worse effected does. The maternal toxicity (decrease in weight gain) in these 6 does was due to the high incidence of resorptions in this group (similar as in the high-dose group).<br><br>The historical control data supplied with each independent rabbit study (1993 and 2015) indicates omphalocele (protrusion of several loops of intestine through a defect in the abdominal wall at the umbilicus) is a rare malformation.<br><br>*HCD supplied with Rabbit 1993 study:*<br>Omphalocele incidence → 3 foetuses in 3 litters out of: 56 studies (1985 – 1990); 5872 foetuses in 806 litters.<br><br>HCD supplied with Rabbit 2015 study:<br>Omphalocele incidence → 1 foetus in 1 litters out of: 15 studies (2008 – 2012); 2205 foetuses in 279 litters (very similar relative incidence to earlier studies) |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 21.03.2018 | Germany | | MemberState | 6 |
| Comment received | | | | |
| The classification of zinc pyrithrione proposed by the DS as Repr. 1B (hazard statement H360D – May damage the unborn child) is still supported. Based on the documents "Additional information report for zinc pyrithrione" and "Prenatal developmental toxicity study of zinc pyrithrione in rabbits by oral gavage – Amendment No. 1" of 30 November 2017 the following comments should be taken into account:<br><br>1. Evidence is missing on how maternal stress leads to the occurrence of omphalocele in two fetuses at 1.5 and two fetuses at 4 mg/kg bw/d, i.e. by proposing a putative mode of action, which shows that the observed malformations are not the result of a direct teratogenic effect of the test substance. The incidences of omphalocele in the developmental toxicity study in rabbits are clearly above the HCD (1 fetus in 1 litter, Addendum B). Maternal stress is mainly substantiated by 1 abortion (out of 22 dams) in group 3 and 4 (1.5 and 4 mg/kg bw/d), red/orange urine (due to early resorptions) in 1 dam of group 3 and 10 animals of group 4, reduced bw, bw gain and food consumption in dams of group 4, respectively.<br><br>2. The number of total incidences per fetus/litter of skeletal, visceral and external malformations (and variations) per dose group is not provided. Some skeletal malformations clearly exceed the HCD at least in the highest dose group of 4 mg/kg bw/d, i.e. fused sternebrae, rib and vertebral anomalies. As mentioned in the report a relation to treatment could not be excluded for these findings.<br><br>3. The absolute incidences and group allocation of cleft palate and carpal/tarsal flexure is | | | | |

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| not provided, since they were not considered treatment-related by the authors. |
| RAC's response |
| Noted. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 20.03.2018 | Sweden | | MemberState | 7 |
| Comment received | | | | |
| We note that the amendment to the final study report is made based on the 'existing data' and not any 'new primary data'. Detailed evaluation of the maternal body weight individual data, particularly referring to the six animals in the mid-dose group with "excessive" maternal toxicity and references to some historical control data to imply that omphalocele is common, sporadic and spontaneous in nature were already provided by the Industry in the developmental toxicity review paper (dated June 2016, referred to in the CLH report by the dossier submitter). Such comments were repeated by the Industry also during the earlier public consultation of the CLH report. The dossier submitter had already responded to those comments in the RCOM (see response to comment number 56 in the RCOM). We note that the original study report (from March 2015) was amended (in November 2017) only after the public consultation. | | | | |
| RAC's response | | | | |
| Noted. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 20.03.2018 | Germany | | Individual | 8 |
| Comment received | | | | |
| Critical Review of Reproductive Toxicity data of Zinc pyrithione (ZPT)<br><br>As a reproductive toxicologist I read the Additional information report with detailed information regarding the amendment of the Thor study reports for Zinc Pyrithione (EC Number: 236-671-3, CAS Number: 13463-41-7). I come to the conclusion to en-dorse this report which adds significant information to the already available data of this compound relevant for the CLH classification of the given compound for the endpoint development. I furthermore conclude that, in the light of these new data, any classification higher than cat. 2 is not warranted.<br>This amendment can be summarized as follows:<br>The evaluation of maternal and fetal findings (including fetal morphological examinations) were amended based on a detailed evaluation of the maternal body weight individual data and additional information on the historic control data from the study laboratory on the occurrence of omphalocele as non-specific response to maternal stress.<br>This impacts the original perspective provided in the CLH report that was subject to the previous public consultation and is the basis for this new and targeted public consultation.<br><br>The amendment mainly focuses on three points, namely<br><br>1. Correct interpretation of body weight data in the medium dose group as an expression of maternal toxicity<br>2. Clear link between maternal toxicity data in individual animals and the in-crease in postimplantation loss in the medium dose group.<br>3. Improved interpretation of omphalocele in the high dose group as a conse-quence of maternal stress. | | | | |

The amendment now correctly assesses the fact that in the mid dose group there were six does that showed more signs of maternal toxicity than others, mainly ex-pressed as decreased body weight gain at the beginning of treatment. This is now correctly interpreted as maternal toxicity rather than an indirect consequence of em-bryofetal toxicity since the weight of the uterine contents at this period of pregnancy is negligible. It was also shown that the most affected litters in terms of postimplan-tation loss originated from exactly these six does, i.e. based on individual animal data it could be shown that postimplantation loss mainly occurred in the pres-ence, and most likely as a consequence, of maternal toxicity during the days relevant to induce these embryofetal effects.
The data now submitted with this additional information report clearly support this assessment of the very complex situation. All in all, the authors now correctly set a NOAEL of 0.5 mg/kg both for maternal and developmental toxicity.

In a detailed manuscript now accepted for publication in the journal "Reproductive Toxicology", comprehensive data are provided to support the hypothesis that om-phalocele in rabbits can be induced by maternal food restriction and it also oc-curs spontaneously and is not an uncommon finding in rabbits.

Summary and conclusions

Based on the now amended data and applying weight of evidence in interpreting them, it can be concluded that

Increase in postimplantation loss occurs only in the presence, and most likely as a consequence of maternal toxicity

Slight increase in omphalocele occurs only in doses causing maternal tox-icity, they are common findings and can also be caused by maternal food re-striction

In summary, the now presented data strongly support the conclusion that ZPT does not have "an intrinsic property to produce an adverse effect on reproduction".

Consequently, any classification higher than cat. 2 is not warranted in the light of these supportive data.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment ZPT Buschmann.pdf

RAC's response

RAC notes the support to the revised study report. The points raised are discussed in detail in the opinion document. There is no new added data. RAC notes comment 7 above and the DS's response outlined under comment 56 in the first and original RCOM document.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 20.03.2018 | Sweden | | Individual | 9 |

Comment received

I'm a former Professor in Toxicology who has long experience (> 35 years) in assessing the impact of maternal toxicity in embryofetal devel-opment studies of chemicals and

drugs (both as regulator and working in industry). I've also participated in arranging international workshops at SOT, American -and European Teratology Societies on the complex issue of Maternal Toxicity. I have previously commented to ECHA what regards, the proposed classification and labelling of Zinc Pyrithione (ZnPT) as reproductive toxicant Cat 1B; this is not warranted. The main reasons for me to not support Cat 1B, were based on findings in studies in the rat (both in vivo and vitro data) including
- ZnPT does not have an intrinsic property to produce adverse effects on development -developmental effects of ZnPT in rats were only observed in the pres-ence of excessive signs of maternal toxicity, including se-vere decrements in maternal body weights at a dose of 15 mg/kg- follow-ing 11 days dosing. The 15mg/kg dose was three times higher than the lethal dose (5mg/kg); a dose which caused death general toxicity toxicity after 17-18 days of dosing in the rat.
-the proposal to classify in Cat 1 B is against the CLP rules for "classification as a reproductive toxicant is intended to be used for substances which have an intrinsic, specific property to produce an adverse effect on reproduction and substances shall not be classified if such an effect is produced solely as a non-specific secondary consequence of other toxic effects".
The new additional information report on findings in the rabbit further support my previous view, Cat 1B is not warranted. The presented data further support the relation between "non-specific secondary consequence of other toxic effects" and developmental toxicity. The new data from the rabbit study clearly show the observed incidences of early resorptions in the mid dose group (1,5 mg/kg) only occurred in a six animals with marked maternal toxicity (manifested as marked decreases in body weigt gain). The other rabbits in the mid dose had normal body weight gain and no increase in early resorptions. These data also show that the NOAEL is 0,5 mg/kg and not 1,5 mg/kg in rabbits.Furthermore, the new data show strong evidence on that the observed cases of omphalocele is related to maternal stress. The new additional data show that omphalocele is one of the most common malformations in rabbits (in 16 out of 40 studies), equally distributed among dose groups, including controls. It is generally accepted in the field of teratology that common fetal defects (also occur-ring in high incidences in controls) can be increased as a non-specific response to maternal stress.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Rabbit ZnPT ECHA comments.docx

RAC's response

RAC notes the support to the revised study report. The points raised are discussed in detail in the opinion document. There is no new added data. RAC notes comment 7 above and the DS's response outlined under comment 56 in the first and original RCOM document.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 20.03.2018 | Germany | | Individual | 10 |

Comment received

I am a toxicologist with 35 years of professional experience and more than 300 publications in high impact journals. I have also been member of a number of advisory boards to regulatory agencies.

Classification of zinc pyrithione (CAS # 13463-41-7, ZPT) as a category 1B reproductive toxicant regarding effects on development has been proposed based on unspecific high-dose effects of ZPT on fetal development in the presence of excessive maternal toxicity. The report of one of the key studies in the developmental toxicity database for ZPT has

been amended and ECHA has requested comments on the new information presented in the amended report.
The amended report now clearly shows a pronounced reduction in body weight gain as a consequence of maternal toxicity in six does and a clear correlation between maternal toxicity and post-implantation loss in these does in the mid-dose in the rabbit developmental toxicity study. This observation further supports the conclusion that all developmental effects of ZPT in this rabbit developmental toxicity study occur only after administration of excessive doses inducing severe maternal toxicity. In the "additional information report", the study director acknowledges that the reported external malformations/variations observed (omphalocele) were not related to ZPT treatment and that "no treatment-related malformations and variations were noted up to 4 mg/kg" doses of ZPT. Omphalocele occurs spontaneously in rabbits and can be caused by maternal food restriction. As already described in my comments submitted in response to the consultation of the CLH report on ZPT, I agree with this conclusion.
Identical conclusions are also applicable to the other developmental toxicity studies with ZPT that reported effects on fetal development. These studies also applied excessive doses of ZPT that induced severe maternal toxicity expressed as a pronounced reduction of maternal weight gain. Therefore, the developmental effects have to be considered as non-specific consequences of the excessive doses. The excessive dosing confounds interpretation of the study results. Thus, according to CLP-guidance, the observation on developmental effects after these excessive doses should not be used to conclude on classification and labeling of ZPT.
Other comments submitted during the consultation on the CLH-report on ZPT remain valid. These were:
-Integration of all available data using weight-of-evidence as required in the CLP directive and recommended in the scientific literature (Beyer et al., 2010) was not performed
-specificity of the adverse effects to the embryo is not assessed
-key information (expert review on consequences of massive reductions in maternal body weight for study evaluation, results of food restriction studies) was not correctly interpreted

RAC's response

RAC notes the support to the revised study report. The points raised are discussed in detail in the opinion document. There is no new added data. RAC notes comment 7 above and the DS's response outlined under comment 56 in the first and original RCOM document.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 20.03.2018 | United Kingdom | | Individual | 11 |

Comment received

COMMENTS ON THE ADDITIONAL INFORMATION FOR THE REPORT ON ZINC PYRITHIONE - BY PROFESSOR JIM BRIDGES

Basis for these comments

I am commenting, as an independent expert, on the additional Information report which relates to the 'Prenatal Developmental Toxicity Study in Rabbits by Oral Gavage' (Thor 2015 report- amendment) along with the full report on zinc pyrithione which were provide to me. I received no instructions on the nature of my comments, nor did I request them. I have examined the full report in the following respects:
• its usefulness to the weighing of the overall evidence

• background incidence of the observed effects (including information on historic controls)
• reproducibility of all effects noted and their dose response relationship and whether the findings support the previous conclusion (i.e. that the adverse effects associated with foetal development are linked to maternal toxicity).
• comparison of my conclusions from this with those set out in the additional information report.

1. Its usefulness to the overall weighing of the overall evidence

The following criteria have been applied in assessing the quality and relevance of this developmental study and, in particular, the amendments (see Dekant and Bridges 2016):

Quality aspects

i) The rationale for provision of the additional information is clear and justified.

ii) Overall experimental design. Complies with appropriate OECD guideline methodology. Four groups each of 22 animals were established (group 1 - control, group 2 - dose 0.5mg/kg/d, group 3 - 1.5mg/kg/d and group 4 -dose of 4.0mg/kg/d). Unfortunately, from an effect and cause relationship perspective, this design relies solely on the assessment of measurement of food intake and maternal body weight to identify maternal toxicity.

iii) Chemical characterisation confirmed

iv) Animal husbandry appropriate

v) Measurement methodology well described and reported

vi) All raw data available

vii) Suitable statistical analysis

Relevance aspects

i) Suitability of species and strain selection. Recent evidence has confirmed the important of conducting reproductive studies in rabbits as well as rats. New Zealand white rabbits are widely used as the rabbit species of choice (Theunissen et al 2016). Consequently, the study and its amendments have high general relevance for classification and labelling assignment.

ii) Information is given on both maternal and foetal toxicity

iii) Consistent with other studies previously reported to ECHA on zinc pyrithione.

Conclusions:
This additional information should be given a high rating in terms of the conclusions on the overall weight of evidence.

2. Background incidence of the observed effects (including information on historic controls)

The background incidence of two conditions, highlighted in the additional information report, is of relevance in assessing whether any effects observed are or are not due to the administration of zinc pyrithione:

-Omphalocele, an abdominal wall deficiency, was observed in two foetuses in the 1.5 mg/kg group and two in the 4mg/kg group. Both findings were noted also in historic controls. Omphalocele, and the parallel condition gastroschisis, occur in humans also. For gastroschisis the role of maternal stress appears to be quite well established (Palmer et al 2013). However, for omphalocele the role of maternal stress is less clear. In New Zealand white rabbits, a recent literature review of many developmental studies that were conducted over a 35-year period, has concluded that omphalocele does not appear to be compound or dose related(Daston and Beekhuijzen, 2018). The authors conclude that it may be a spontaneous malformation and/or related to maternal stress.

Conclusions:
Based on the above it appears most unlikely that the omphalocele observed in the Thor 2015 study are compound related.

-Early resorptions

Resorptions, particularly early resorptions, are common in historic controls. This may be attributed to a variety of possible causes including: maternal need to conserve nutrients, stress, infection, and/or other causes of an abnormal maternal environment. In the Thor 2015 study similar numbers of early resorptions were observed in the controls and the 0.5mg/kg group, with 3 addition late resorptions in the control group. In the 1.5 mg/kg and the 4mg/kg groups there was a dose related increase in the early resorptions although the likely reason(s) for this were not discussed in the report or in the additional report summary. This will be discussed in Section 3. It is noted that an increase in foetuses with skeletal malformations was only found in group 4 and this was only from mothers with negative corrected body weight gains.

Conclusions:
The incidence of early resorptions in the control group and in historic controls is an important consideration in the identification of compound related effects.

3. Reproducibility of findings and their interpretation

An important consideration in summarising the findings for this study (as with many others) is the considerable interindividual differences in the findings at each dose level.

Body weight changes and resorptions

The average maternal body weights were comparable at the outset for each of the four groups. However, the increase in body weight demonstrated considerable individual differences in each group. In group 3 and again in group 4 about half a dozen mothers showed poorer or no gain in body weight in contrast to other mothers in their group. In general, these mothers also suffered the highest number of early resorptions.

Conclusions:
This correlation indicates that the likely cause of the resorptions is related to poorer nutrient utilisation by the mothers. This is compatible with the previous weight of evidence analysis that adverse effects on the foetus are caused by inhibition of energy

generation in the mothers.

4. Comparison of my conclusions from this with those set out in the additional information report.

My conclusions following an independent, detailed examination of the full report and the amendments made are in full agreement with those presented in the additional information report. I consider that report and amendments provide important additional high quality and relevant findings. They support the already strong weight of evidence that ECHA already has that zinc pyrithione should not be classed as a developmental toxin because the adverse effects on foetal development are due to maternal toxicity.

References


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• Dekant W and Bridges JW (2016) 'A Quantitative weight of evidence methodology for the assessment of reproductive and developmental toxicity and its application for classification and labelling of chemicals' Regul Toxicol Pharmacol 82, 173-185
• Palmer SR, Evans A, Broughton H, Huddart S, Drayton M, Rankin J, Draper ES, Cameron A and Paranjothy S (2013) 'The role of maternal stress in early pregnancy in the aetiology of gastroschisis: an incident case control study' PLoS One ,8(11):e80103
• Theunissen P, Beken S, Beyer B, Breslin W, Cappon G, Chen C, Chmielewski G, De Schaepdrijver L, Enright B, Foreman J, Harrouk W, Hew K, Hoberman A, Hui J, Knudsen T, Laffan S, Markis S, Martin M, Mcnerney M, Siezen C, Stanislaus D, Stewart J, Thompson K, Tornesi B, Van der Laan J, Weinbauer G, Wood S and Piersma A (2016) 'Comparison of rat and rabbit embryo-fetal developmental toxicity data for 379 pharmaceuticals: on the nature and severity of developmental effects' Critical Reviews in Toxicology 46(10): 900-910


Professor Jim Bridges Emeritus Professor of Toxicology and Environmental Health, University of Surrey, UK March 18th 2018

RAC's response

RAC notes the support to the revised study report. RAC agrees that the study is well performed. The points raised on the results are discussed in detail in the opinion document.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 20.03.2018 | Belgium | The ZnPT Industry CLH Consortium | Industry or trade association | 12 |

Comment received

ZNPT INDUSTRY CLH CONSORTIUM COMMENTS ON TARGETED CONSULTATION ON ZINC PYRITHIONE (EC 236-671-3; CAS 13463-41-7) - March 7, 2018-March 21, 2018

These comments are being sent on behalf of the ZnPT Industry CLH Consortium. Please note that due to technical limitations in the webform, figures and tables are provided in Annex 1 attached to these comments. We also include two additional documents in support of our comments on omphalocele (Annex 2) and on the food restriction studies

(Annex 3).

The ZnPT Industry CLH Consortium agrees with the conclusions in the amended study report ("Prenatal developmental toxicity study of zinc pyrithione in rabbits by oral gavage" (Thor, 2015)): that there was significant maternal toxicity in the high dose group (i.e. 4.0 mg/kg/day) and in several does in the mid-dose group (i.e. 1.5 mg/kg/day); the adverse developmental effects were restricted to the litters of those highly affected does, and the effects are secondary to the maternal toxicity. We also provide additional information to support that omphalocele is a common and non-specific finding in New Zealand White rabbits.

Importantly, the study amendment contradicts the following DS statement: "The most compelling evidence that developmental effects occur even in the absence of ("excessive") maternal toxicity for ZnPT comes from the pre-natal developmental toxicity study in rabbits with ZnPT via oral route (Thor GmbH Art. 95 dossier, 2015)" (RCOM pp. 76). There is no clear evidence of an adverse effect on development in the absence of other toxic effects in the Thor 2015 study.

The conclusions in the amended study report are consistent with those of the other rabbit and the rat developmental toxicity tests: ZnPT only induces developmental toxicity at doses that cause excessive maternal toxicity and there is no evidence of developmental toxicity potential for ZnPT in the absence of maternal effects. Embryotoxicity data have shown that ZnPT does not have an intrinsic property to cause developmental effects. All these data, together with the information on mode of action (i.e. secondary to non-specific effect on the maternal organism due to high toxicity of ZnPT), submitted during the initial public consultation by the ZnPT Industry CLH consortium (and summarized below), show that there is no scientific basis for a the proposed Repr. 1B classification by the DS.

1) "Final Report Amendment No. 1" to the "Prenatal developmental toxicity study of zinc pyrithione in rabbits by oral gavage" (Thor, 2015) - New information

We agree with the conclusions made in the amended report by the study director: (i) the effects seen in several animals of the mid dose were indirectly due to maternal toxicity, (ii) the increase in resorption rate was not the reason for the decreased body weight in these animals, and (iii) the observation of omphalocele is not a direct effect of the test item treatment and is regarded as a non-specific response to maternal stress.

The re-analysis of maternal weight data on an individual basis establishes that there were six animals in the mid-dose group (i.e. 1.5 mg kg/day) for which toxicity was severe. The attached figures (See Annex 1 in attachment to these comments) provide a graphical illustration of how these animals differ from controls, as well as others in the same dose group, in the magnitude of effect on body weight gain. Each graph (blue line) in Figure 1 of Annex 1 represents body weight gain in an individual mid-dose animal over the course of the study (Gestation Day, GD 0-29). The black line in each graph is the mean control body weight gain, for comparison. There is marked toxicity, i.e. decrease in body weight gain, in the six most affected animals (bottom six graphs – doe 46, 58, 62, 54, 55 and 49). As noted in the amended report, the average weight gain over the period of embryonic development (GD 7-20) was 42 grams in the 6 affected animals, vs. 143 grams in the concurrent control and 150 grams in the remaining mid-dose does.

As previously shown during the initial public consultation, ZnPT has a very steep dose-response curve for toxicity with a sharp inflection point to the rising phase of the curve,

with six animals exhibiting excessive maternal toxicity. The 1.5 mg/kg/day dose level in this study was at the inflection point, with six animals exhibiting excessive maternal toxicity. All the adverse developmental effects in the 1.5 mg/kg/bw group occurred in the litters of the highly affected animals. The does not suffering excessive toxicity had litters of normal size, weight and morphology. The does in which developmental effects were observed had decreased body weight gains more than 20% for prolonged periods, which is evidence of "excessive" maternal toxicity (Figure 2 of Annex 1). Although the CLP guidance does not provide a bright line for what constitutes an excessive effect on maternal body weight gain, an ILSI-HESI workshop concluded that maternal body weight gain decrements above 20% for prolonged periods should be avoided (Beyer et al., 2001). In a recent decision (Case A023/2015; published in December 2017), the ECHA Board of Appeal referred to the ILSI workshop and to the 20% figure indicated in its conclusions. This is also corroborated by scientific articles (e.g. Wise et al. 2009; Giavini & Menegola, 2012) and OECD Guideline 426 (Developmental Neurotoxicity Study, 2007) which provides a limit of 10% decrement in weight gain above which maternal toxicity would be considered excessive.

The DS remarked that the presence of omphalocele in two fetuses in the mid dose (1.5 mg/kg/day) and high (4.0 mg/kg/day) dose groups was evidence of specific developmental toxicity. However, a retrospective analysis of data from the lab conducting the study indicated that the effect is quite common, occurring in 16 of 40 studies. We have conducted an even more extensive retrospective analysis of the literature, covering almost 5000 litters and 37,000 fetuses and found that omphalocele occurs in 43% of those literature citations, in an apparently non-dose-related manner (i.e., occurred in roughly the same frequency in every dose group) except in two cases. This analysis has been peer-reviewed and accepted for publication in Reproductive Toxicology, the official journal of the European Teratology Society. A copy of the paper is attached. (Annex 2 to these comments)

2) Prenatal developmental toxicity study of zinc pyrithione in rabbits by oral gavage" (ZnPT CAR Doc IIIA A6.8.1/01)
As stated, ZnPT has a very steep dose-response curve for toxicity with a sharp inflection point to the rising phase of the curve. In the Prenatal developmental toxicity study of zinc pyrithione in rabbits by oral gavage (Thor, 2015, Reliability factor 1); the 1.5 mg/kg/day dose level was at the inflection point, with six animals exhibiting excessive maternal toxicity.

The dose-response curve was similarly steep in the 2nd GLP rabbit gavage study on ZnPT (Schardein, 1993; ZnPT CAR Doc IIIA A6.81./01; Reliability factor 2), as well as for the rat gavage studies. The apparent inflection point in the Schardein (1993) rabbit study was also 1.5 mg/kg/day, with a 41% decrement in weight gain over the dosing period, GD 6-19 (Table 1 of Annex 1). Animals in the highest dose level in this study, 3 mg/kg/day, had virtually no weight gain over the dosing period (GD 6-19) (Figure 3 of Annex 1). The magnitude of changes in body weight gain above the inflection point in the dose-response curve is large, often a decrement of 40% or more. In retrospect, dose selection of 1.5 and 3 mg/kg BW in this study by the investigators was too high and there is justification that these dose groups should be completed discounted from any evaluation because of this.

The study report (ZnPT CAR DOCIIIA A6.8 1/01) concluded that "the test article was not deemed to be a teratogenic hazard since the malformations occurred only at doses that produced frank maternal toxicity". This is contrary to the position of the Dossier Submitter. Post-implantation loss and malformations seen in this 2nd Rabbit ZnPT

developmental study were also a secondary effect to excessive maternal toxicity.

Because only a limited number of measurements of maternal toxicity are made in most developmental toxicity studies, it is important to carefully consider the appropriate way to evaluate the data in interpreting developmental toxicity. The most appropriate time to measure maternal weight gain to interpret developmental effects such as structural abnormalities or embryonic deaths (resorptions) is during the embryonic period, as this is when both these adverse events occur during development. The embryonic period in the rabbit spans from gestation day 7, when implantation occurs, to gestation day 19. Therefore, measurement of weight gain over that period (GD 7-19) provides the most relevant information about the status of maternal health during the time that structural abnormalities or embryonic death may occur. Importantly, rabbit fetuses weigh very little during this period (only 4-5 grams at the end of the period) so virtually all the effect on weight is on the maternal side. Particularly for effects that are caused during the embryonic period, like embryonic death or structural abnormalities, maternal weight changes during the embryonic period are far more relevant than measurements taken more than a week later, i.e. entire study period. This would be the equivalent of a doctor measuring a patient's body temperature days after having a life-threatening fever and concluding the patient had never been ill.

In summary, developmental toxicity of ZnPT is only observed at doses that induce severe maternal toxicity. Conversely, at those dose levels in which maternal toxicity is not observed, no developmental effects were observed. Overall, the CLH-proposal has not evaluated whether the developmental effects retained as the basis for the classification proposal were observed in presence or absence of maternal toxicity and particularly, whether the level of maternal intoxication in those studies could be responsible for the observed developmental effects, as required by the CLP.

3) Disagreement with DS submitted interpretation on Food Restriction Studies.
The DS mis-interpreted a literature citation investigating the effects of food restriction (Cappon et al, 2005 and Fleeman et al., 2005; Section 10.10.6; pages 83-84 of CLH report) on development, claiming it provides justification for discounting the effects of maternal toxicity on development (CLH report: section 10.10.6 pages 83 and 84 and RCOM, page 76). The misinterpretation by the Dossier Submitter is confirmed by one of the authors of the Cappon et al. 2005 and Fleeman et al., 2005 studies (in a letter submitted as Annex 3 to these comments ) who states that it is "incorrect to conclude that because of maternal feed restriction produced limited developmental effects, that other mechanisms that decrease maternal weight gain would have the same fetal effects". In fact, decreased food consumption does not appear to be a primary cause of decreased weight gain in the case of ZnPT.

In the Supportive Document on Reproductive Toxicity of the ZnPT Industry CLH consortium – June 30, 2017 (submitted during the initial public consultation by the ZnPT CLH Industry consortium), we showed that food consumption was far less affected than weight gain in pregnant animals. We used food conversion efficiency as a metric of inhibited energy production. Food conversion is the number of grams of food required to produce one gram of body mass. This measure has the advantage that it can be calculated in every study in which food consumption and body weight gain are measured, including developmental toxicity studies. The effects that we saw with analysis of the repeat-dose and prenatal studies on pyrithiones is consistent, dose-related, and at dose levels where there is excessive toxicity, profound. In tables 2 and 3 of Annex 1 to these comments, we summarized the feed conversion efficiency in the 2 Rabbit prenatal oral

(gavage) studies.

4) Mode of Action
During the initial public consultation (May-July 2017) on ZnPT, we submitted 2 significant pieces of information that show that ZnPT does not have intrinsic developmental toxicity:
• First, using rodent whole embryo culture, we showed that neither pyrithione nor its plasma metabolite, 2-methylsulphonylpyridine (2-MSP), have the potential to affect the embryo in the absence of maternal influences, even at concentrations that are comparable to maternal plasma levels at maternally toxic dose levels.

• Second, we provided information on the mechanism of pyrithiones, an inhibition of aconitase which is a Kreb's cycle enzyme, and that this mechanism is preferentially active in the adult, not the embryo. Analysis of the repeat-dose toxicity studies on ZnPT and other pyrithiones provide consistent results on food-conversion efficiency and other consequences of aconitase inhibition, offering conclusive support of this mechanism. This disruption of homeostasis is the direct result of the mode of action of ZnPT on cellular respiration and is stressful to the pregnant animal. Perturbation in maternal intermediary metabolism leads to changes in the nutriture of the embryo. Fluoroacetate, another aconitase inhibitor, produces a transient increase in blood glucose level. We know that hyperglycemia and maternal diabetes are developmentally adverse and can lead to severe skeletal effects (Turck et al. 1998) like those observed under excessive maternal toxicity for ZnPT.

5) Conclusion on Reproductive Toxicity in the "Final Report Amendment No. 1" to the "Prenatal developmental toxicity study of zinc pyrithione in rabbits by oral gavage" (Thor, 2015) - New information
We concur with the conclusion by the study director in the amended study report (Prenatal developmental toxicity study of zinc pyrithione in rabbits by oral gavage" (Thor, 2015)) that there was excessive maternal toxicity in the high dose and six does of the mid-dose group; that all of the developmental toxicity is restricted to the litters of these highly affected animals; and that the maternal toxicity is responsible for the developmental effects. We also concur that omphalocele is a non-specific and relatively common malformation, and provided a peer-reviewed retrospective analysis of the literature supporting this conclusion.

This is consistent with the rest of the evidence on ZnPT: ZnPT only induces developmental toxicity at doses that cause excessive maternal toxicity and there is no evidence of developmental toxicity potential for ZnPT in the absence of maternal effects; developmental toxicity of ZnPT observed is not due to an intrinsic property of ZnPT to induce effects on the embryo but secondary to non-specific effect on the maternal organism due to high toxicity of ZnPT. Therefore, classification of ZnPT as a reproductive toxicant Cat1B is not supported by the evidence, as required by the CLP. Moreover, ZnPT does not have an intrinsic property to cause developmental effects.

Annexes:

Annex 1 : Figures and tables referred in The ZnPT Industry CLH Consortium comments on the targeted consultation on Zinc Pyrithione

Annex 2: Daston, G.P. and Beekhuijzen M. Is Omphalocele a Non-Specific Malformation in New Zealand White Rabbits? In Press, Accepted Manuscript, available online at https://www.sciencedirect.com/science/article/pii/S089062381830042X.

Annex 3: Letter from co-author of Feed Restriction studies (Cappon et al., 2005 and Fleeman et al., 2005)

References:
Beyer, B. K., Chernoff, N., Danielsson, B. R., Davis-Bruno, K., Harrouk, W., Hood, R. D., Janer, G., Liminga, U. W., Kim, J. H., Rocca, M., Rogers, J. & Scialli, A. R. 2011. ILSI/HESI maternal toxicity workshop summary: Maternal toxicity and its impact on study design and data interpretation. Birth Defects Research Part B - Developmental and Reproductive Toxicology, 92, 36-51.

Cappon, G.D., Fleeman, T.L., Chanin, R.E., Hurtt, M. E.: Effects of feed restriction during organogenesis on embryofetal development in rabbit. Birth Defects Res B Dev Reprod Toxicol. 2005 Oct;74(5):424-30.

Turck, PA, Eason, CT and Wickstrom, M 1998 Assessment of the developmental toxicity of sodium
fluoroacetate (1080) in rats. The Toxicologist 42: 258-9.

Fleeman TL, Cappon GD, Chapin RE, Hurtt ME. The effects of feed restriction during organogenesis on embryo-fetal development in the rat. Birth Defects Res B Dev Reprod Toxicol; 2005; 74:442–9.

Giavini, E.; Menegola E. 2012. The problem of maternal toxicity in developmental toxicity studies. Regulatory Toxicology and Pharmacology 62, 568–570

Wise, L. D., Buschmann, J., Feuston, M. H., Fisher, J. E., Hew, K. W., Hoberman, A. M., Lerman, S. A., Ooshima, Y. & Stump, D. G. 2009. Embryo-fetal developmental toxicity study design for pharmaceuticals. Birth Defects Research Part B - Developmental and Reproductive Toxicology, 86, 418-428.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment ZnPT CLH consortium annexes to comments targeted consultation 200318.zip

RAC's response

Noted. There is no new data submitted nor anything substantive that explores possible mechanistic modes of action for Zinc Pyrithione. Suitable HCD was supplied in the original developmental study reports to assess omphalocele. Many of these points were already addressed previously and were considered in depth by RAC.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 19.03.2018 | Belgium | CEPE | Industry or trade association | 13 |

Comment received

The proposed classification would have a significant negative impact on the future availability of the substance

RAC's response

The CLH process does not concern socioeconomic aspects.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 19.03.2018 | Germany | Thor GmbH | Company-Manufacturer | 14 |

Comment received

The final report amendment No. 1 of the prenatal developmental toxicity study of Zinc Pyrithione (ZnPT) in rabbits by oral gavage (Thor, 2015) takes into consideration the evaluation of individual animals. This individual approach was needed to identify the six dams in the mid-dose group (1.5 mg/kg bw/d) that were more adversely affected by the ZnPT treatment than the other animals in the mid-dose group. The amendment now correctly reports that the majority of the developmental effects in the mid-dose group can be assigned to the litters of these six dams. Consequently, the maternal NOAEL was revised from 1.5 mg/kg bw/d (Original study report, Thor, 2015) down to 0.5 mg/kg bw/d (Final report amendment No. 1, Thor, 2017). In light of the provided final report amendment it is evident that the biocidal active substance, ZnPT, does not have an intrinsic property to induce developmental toxicity. The effects observed in the rabbit teratogenicity study are secondary to an excessive maternal toxicity caused by ZnPT. Hence, Thor GmbH disagrees with the data submitter's proposal for classification of ZnPT in Reproductive Toxicity 1B.

In order to facilitate the understanding on how the final report amendment No. 1 ("new information") influences the conclusions made in the original CLH report, Thor prepared an overview on the affected sections in the report.
(Please find attached a PDF-document with formatted text and thus increased readibility)

The following sections* in the original CLH report are affected by the final report amendment No. 1 of the prenatal developmental toxicity study of Zinc Pyrithione in rabbits by oral gavage (Thor, 2015):
*Explanatory note: Excerpts from the original CLH report are represented in "quotation marks", affected parts of the CLH report are highlighted as ">>Text<<" and followed by a comment from Thor ("#Thor comment#") considering the new information.

Section "10.10.4 Adverse effects on development"
1) CLH report, page 77:
"In another prenatal developmental toxicity study performed according to the guidelines (OECD 414/EPA OPPTS 870.3700/EU B.31) and with GLP, zinc pyrithione (purity: >95%) was given to mated female New Zealand White rabbits by oral gavage from GD 7-28 at doses of 0, 0.5, 1.5, and 4 mg/kg (Thor GmbH Art. 95 dossier, 2015). Maternal toxicity was observed in the high-dose group in the form of red/orange discolouration of the urine (in 10 animals), statistically significantly reduced absolute body weight (ranging -8 to -9% during GD 20-29) & body weight gains (ranging -55 to -100% during GD 13-29) and reduced absolute (ranging -15 to -32% during GD 10-23) & relative (ranging -16 to -28% during GD 10-20) food consumption. >>The study author considered the maternal toxicity to be an indirect effect due to a high incidence of resorptions in this group.<<"

#The underlined statement describing the Thor rabbit study is not correct when considering the new information. In the report amendment the study director acknowledged the maternal toxicity in the high-dose group (4.0 mg/kg) and thus, the interpretation that the observed maternal toxicity is an indirect effect is obsolete.
(cf. pages 11, 12, 13, 18, 19 and 20 of the amendment no. 1 to the final report)#

2) CLH report, page 77:

"There was a statistically significant increase in post-implantation loss (67% compared to 8% in controls) and decrease in mean of viable foetuses (33% compared to 92% in controls) in the high-dose group. Such developmental toxicity was also observed in the mid-dose group >>in the absence of maternal toxicity<<, i.e. statistically significant increase in post-implantation loss (23% compared to 8% in controls) and decrease in mean of viable foetuses (77% compared to 92% in controls)."

#The underlined statement describing the Thor rabbit study is not correct when considering the new information. In the report amendment the study director recognised the presence of maternal toxicity in the mid-dose group (1.5 mg/kg). The maternal NOAEL was adjusted to 0.5 mg/kg (low-dose) accordingly and thus, the original interpretation speaking about an absent maternal toxicity in the mid-dose group is obsolete.
(cf. pages 11, 12, 13, 15, 18, 19 and 20 of the amendment no. 1 to the final report)#

3) CLH report, page 77:
"However, for 6 of the 21 does in the mid-dose group the body weight gain was statistically significantly lower during GD 7-29 (58% of the controls) and most of the post-implantation losses in this group were seen in those six does (see Table 63c). The high-dose group had only 9 litters with viable foetuses compared to 19 litters with viable foetuses in the mid-dose group and in controls.
Adverse effects on foetal morphology were observed in both mid- and high-dose groups. External malformations of omphalocele were observed in two foetuses from two litters in the high-dose group and also in two foetuses from two litters in the mid-dose group. Two foetuses (one each from mid and high-dose group) among the four affected foetuses also had an absent tail. >>These external malformations were not found in controls and in only one historical control foetus. The author considered these to be treatment related.<<"

#The underlined statement is no longer correct in its current form as it was amended from the original study report. The study director stated in the report amendment that both findings were noted in the historical control data, omphalocele is regarded as a non-specific response to maternal stress and no further similar type of malformations were noted, and these occurrences were not considered a direct effect of test item treatment. Moreover, omphalocele was observed in 16 studies out of 40 (distributed equally among dose groups) when the complete historical control data set (years 2006 to 2017) was re-examined for omphalocele in any dose group.
(cf. page 16 of the amendment no. 1 to the final report)#

4) CLH report, page 84:
"In another rabbit study with zinc pyrithione (Thor GmbH Art. 95 dossier, 2015), external malformations of omphalocele were observed in two foetuses from two litters each of mid- and high-dose groups. It should be noted that high-dose group had only 9 litters with viable foetuses compared to 19 litters with viable foetuses in the mid-dose group and in controls. Two foetuses (one each from mid- and high-dose group) among the four affected foetuses also had an absent tail. >>These external malformations were not found in controls and in only one historical control foetus.<<"

#The underlined statement is no longer correct in its current form as it was amended from the original study report. The study director stated in the report amendment that both findings were noted in the historical control data, omphalocele is regarded as a non-specific response to maternal stress and no further similar type of malformations were

noted, and these occurrences were not considered a direct effect of test item treatment. Moreover, omphalocele was observed in 16 studies out of 40 (distributed equally among dose groups) when the complete historical control data set (years 2006 to 2017) was re-examined for omphalocele in any dose group.
(cf. page 16 of the amendment no. 1 to the final report)#

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2018 03 19 Thor GmbH comment to targeted public consultation on ZnPT_final.pdf

RAC's response

Noted and considered by RAC. The points raised are discussed in detail in the opinion document.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 19.03.2018 | Germany | Thor GmbH | Company-Manufacturer | 15 |

Comment received

In February 2018, the Scientific Committee on Consumer Safety (SCCS) adopted an Opinion (SCCS/1593/2018) that serves as addendum to the scientific opinion on Zinc Pyrithione (ZnPT). The scope was to re-assess the safety of ZnPT as an anti-dandruff agent in rinse-off hair care products at a maximum concentration of 2% considering that new ZnPT data became available with the CLH report submitted by the Swedish Chemicals Agency (KemI).
The SCCS concludes that "The newly provided studies on fertility and developmental toxicity […] did not lead to changes of point of departure for risk assessment […]". Here, the newly provided studies comprise the prenatal developmental toxicity study of ZnPT in rabbits by oral gavage (Thor, 2015) and the relevant final report amendment No. 1 that is open for this targeted public consultation. The Committee considers the use of rinse-off hair products containing 2% ZnPT as anti-dandruff agent to be safe.

Although as the Committee clearly states in its Opinion: "[…] the expected SCCS Opinion is a risk assessment and not a hazard assessment […]", based on the fact that the new information does not change the outcome of the risk assessment (performed in SCCS/1502/13) it can be inferred that ZnPT does not pose an unacceptable risk to the consumer. Consequently, the assessment of the SCCS expert group does not support the data submitter's proposal to classify ZnPT as reproductive toxicant Category 1 B, as this classification would represent an unacceptable risk.

It is also noteworthy that for setting the specific concentration limit (SCL) for skin sensitisation of the biocidal active substance, MIT, the Risk Assessment Committee (RAC) considered the SCCS Opinion on MIT (SCCS/1557/15) (cf. RAC Opinion CLH-O-0000001412-86-105/F, adopted 10 March 2016) as very relevant. This approach was taken although the CLP Guidance clearly describes the SCL for skin sensitisation as hazard-based value (cf. section 3.4.2.2.5. Setting of specific concentration limits in the Guidance on the Application of the CLP Criteria, Version 5.0 – July 2017). In the interests of a consistent and harmonised procedure, and following the precedence of MIT, the SCCS Opinion on ZnPT should be taken into account by RAC. Or, vice versa, if RAC now ignored the SCCS Opinion on ZnPT, the procedure for MIT would need a revision.

RAC's response

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| The current targeted public consultation focus on the documents open in the call. Please note that RAC makes an independent assessment of the data provided. Another committee may come to a different conclusion. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 19.03.2018 | Germany | German Paint and Printing Ink Association (VdL) | Industry or trade association | 16 |
| Comment received | | | | |
| The proposed classification as reprotoxic category 1B has the legal consequence that ZnPT would fall under the exclusion criteria under the biocides legislation (regulation (EU) No. 528/2012) according to article 5. Substances which fall under the exclusion criteria shall not be approved, unless some very specific conditions are met (for instance negligible risk).<br><br>Furthermore, the classification has severe legal consequences for the substance approval and the authorization of the biocidal product. Approval as a biocidal active may only be for an initial period of 5 years (compared to 10 years otherwise). Biocidal products classified as reprotoxic category 1B shall not be authorized for making available on the market for use by the general public (article 19). This would already be the case at a concentration of 0.3% in the biocidal product. Moreover a Union authorization is not possible. Thus, it is reasonable to expect that the proposed classification will in the end result in ZnPT being no longer available for paints and coatings.<br><br>CLP classification is hazard-based and hence the actual risk is not considered. BPR exclusion criteria are also hazard-based. The use of ZnPT as biocide active substance (PT6 and PT7) is considered as safe as there is no relevant exposure - neither during the application of the paint nor during the service life of a painted surface. The proposed CLP classification would thus lead to the ban of a safe use, which is unreasonable and disproportionate.<br><br>We also would like to point out that the Scientific Committee on Consumer Safety stated in its current addendum to the scientific opinion on ZnPT (SCCS/1593/2018) that the "newly provided studies on fertility and developmental toxicity did not lead to changes of point of departure for risk assessment compared to SCCS/1512/13." It concludes that ZnPT "is considered safe when used at a concentration up to 2.0% as an antidandruff agent in rinse-off hair care products." This also demonstrates that there is no risk for the consumer.<br><br>Hence, due to the high importance of the substance for our industry, we strongly recommend considering any newly provided information by the suppliers on this topic. | | | | |
| RAC's response | | | | |
| The CLH process does not concern socioeconomic or risk aspects. | | | | |

PUBLIC ATTACHMENTS
1. ZPT Buschmann.pdf [Please refer to comment No. 8]
2. Rabbit ZnPT ECHA comments.docx [Please refer to comment No. 9]
3. ZnPT CLH consortium annexes to comments targeted consultation 200318.zip [Please refer to comment No. 12]
4. 2018 03 19 Thor GmbH comment to targeted public consultation on ZnPT_final.pdf [Please refer to comment No. 14]