Review of Zinc Pyrithione (CAS: 13463-41-7, ZnPT) under the harmonised classification under Regulation (EC) 1272/2008, on Classification, Labelling and Packaging of substances and mixtures.

Comments provided by the Article 95 (EU No. 528/2012 Biocidal Products Regulation) applicant Thor GmbH on KemI's proposed classification and labelling of ZnPT as reproductive toxicant category 1B.

Thor GmbH welcomes the opportunity to provide comments on the classification proposal for Zinc Pyrithione (ZnPT).

In providing our comments, we refer to the Regulation (EC) 1272/2008, on classification, labelling and packaging of substances and mixtures (CLP), and the most recent Guidance on the Application of the CLP Criteria Version 5.0[1], (CLP Guidance) released by ECHA in July 2017.

Comment on toxicity to reproduction

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.

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[1] Guidance on the application of the CLP Criteria: Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures.

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.

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 "*italic*", affected parts of the CLH report are "underlined" and followed by a box with comments from Thor 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. [Emphasis added]

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 <u>in the absence of maternal toxicity</u>, 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). [Emphasis added]

> 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.
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> (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. <u>These external malformations were not found in controls and in only one historical control foetus. The author considered these to be treatment related</u>. [Emphasis added]

> 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.
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> (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. <u>These external malformations were not found in controls and in only one historical control foetus</u>. [Emphasis added]

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)