Critical Review of Reproductive Toxicity data of Zinc pyrithione (ZPT)

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 endorse 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.
This amendment can be summarized as follows:
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.
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.

The amendment mainly focuses on three points, namely

1. Correct interpretation of **body weight** data in the medium dose group as an **expression of maternal toxicity**
2. Clear **link between maternal toxicity** data in individual animals **and the increase in postimplantation loss** in the medium dose group.
3. Improved interpretation of **omphalocele** in the high dose group as a **consequence 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 expressed as decreased body weight gain at the beginning of treatment. This is now correctly interpreted as maternal toxicity rather than an indirect consequence of embryofetal 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 **postimplantation 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 presence, 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 **omphalocele in rabbits** can be induced by **maternal food restriction** and it also occurs **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 toxicity**, they are common findings and can also be caused by maternal food restriction

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.

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