

## BASF-Comment on the lack of teratogenic potential of pendimethalin in rabbits

In section 4: Justification that action is needed at community level (page 9)

Further detail on need of action at Community level:

The CLH dossier states:

*“Indeed, in the developmental toxicity study in rabbits, increased incidence of less than twelve pairs of ribs and missing/incomplete vertebrae were observed in the absence of maternal toxicity.”*

The phrase is slightly misleading in that it leaves out the fact, that both findings are largely seen in a single high dose litter (#27928). This litter is clearly an outlier since it displays multiple malformations and skeletal variations, as well as two additional resorptions (see below). All but one surviving pup originate from a single uterus horn, in which in the two resorptions were seen.

It is not uncommon, to exclude such unusual litters from the evaluation of toxicological effects. If this litter is taken out of the evaluation, the incidence for less than twelve pairs of ribs and missing/incomplete vertebrae do no longer follow a dose response curve or, in case of the vertebrae findings, are no longer seen at the top dose.

The RMS has provided the data for developmental skeletal anomalies in rabbits in table 14 (page 25/26) including litter #27928. The RMS correctly points out in the footnote, that:

*“Three out of four fetuses came from one litter (#27928). The observed fetuses with missing/incomplete vertebrae also come from this litter.”*

For the reviewer’s convenience it would be good to provide table 14 with the respective incidence data excluding litter #27928.

This could for example look like:

| Dose (mg/kg bw/day)                          | 0   | 15  | 30  | 60                |
|--|-----|-----|-----|-------------------|
| Number of fetuses examined                   | 111 | 106 | 118 | 107               |
| Number of litters examined                   | 17  | 17  | 17  | 17                |
| Number of fetuses with skeletal anomalies    | 0   | 0   | 2   | 5                 |
| Foetuses with less than twelve pairs of ribs |     |     |     |                   |
| - Fetal incidence                            | 0   | 0   | 1   | 4(1) <sup>1</sup> |
| - Litter incidence                           | 0   | 0   | 1   | 2(1) <sup>1</sup> |
| Foetuses missing/incomplete vertebrae        |     |     |     |                   |
| - Fetal incidence                            |     |     |     |                   |
| - Lumbar                                     | 0   | 0   | 1   | 2(0) <sup>1</sup> |
| - Sacral (incomplete)                        | 0   | 0   | 0   | 2(0) <sup>1</sup> |
| - Caudal                                     | 0   | 0   | 0   | 3(0) <sup>1</sup> |
| - Litter incidence                           |     |     |     |                   |
| - Lumbar                                     | 0   | 0   | 1   | 1(0) <sup>1</sup> |
| - Sacral (incomplete)                        | 0   | 0   | 0   | 1(0) <sup>1</sup> |
| - Caudal                                     | 0   | 0   | 0   | 1(0) <sup>1</sup> |

<sup>1</sup> Three out of four foetuses came from one litter (#27928). The observed foetuses with missing/incomplete vertebrae also come from this litter. Pup and litter incidences excluding litter 27928 are provided in brackets.

A detailed argumentation is provided in the Annex I to the CLH dossier, including two independent expert evaluations coming to the conclusion that pendimethalin treatment does not lead to a teratogenic effect in rabbits.

On page 55/56 of Appendix I the incidences of other skeletal findings are discussed with and without litter 27928. In litter 27928 7/10 foetuses displayed multiple morphological changes. One of the fetuses from this litter also displayed a missing tail.

The number of affected litters are given in brackets

| Dose (mg/kg bw/day)                  | 0     | 15    | 30    | 60    |
|--------------------------------------|-------|-------|-------|-------|
| <b>Including female # 27928</b>      |       |       |       |       |
| Missing tail                         | -     | -     | -     | 1 (1) |
| <12/12 ribs                          | -     | -     | 1 (1) | 4 (2) |
| Fused/forked ribs                    | 3 (2) | 1 (1) | 1 (1) | 8 (3) |
| Malaligned thoracic arches ad centra | 6 (4) | 2 (2) | 3 (3) | 9 (3) |
| 0-2 caudal vertebrae                 | -     | -     | -     | 3 (1) |
| <b>Excluding female # 27928</b>      |       |       |       |       |
| Missing tail                         | -     | -     | -     | -     |
| <12/12 ribs                          | -     | -     | 1 (1) | 1 (1) |
| Fused/forked ribs                    | 3 (2) | 1 (1) | 1 (1) | 2 (2) |
| Malaligned thoracic arches ad centra | 6 (4) | 2 (2) | 3 (3) | 2 (2) |
| 0-2 caudal vertebrae                 | -     | -     | -     | -     |

Based on the available data, litter 27928 can not be considered to represent a normal litter and should therefore be excluded from the evaluation.

Recent evaluations of the pendimethalin data package performed by the JMPR and JMAFF (Japan) after the evaluation of the data by EFSA came to the conclusion that pendimethalin does not have a teratogenic potential in rabbits.

In conclusion BASF is of the opinion, that litter 27928 should be excluded from the evaluation of the rabbit teratogenicity study. The resulting incidence numbers would not justify the conclusion that pendimethalin has a developmental toxic potential in the rabbit.