

Clethodim STOT RE Cat 2 Classification response from applicant

Rat developmental study

The findings in the rat prenatal developmental toxicity study have been previously evaluated by RAC in the context of a proposed classification for STOT RE and were not considered to be relevant or sufficiently severe to warrant classification. It was concluded by RAC (2015) that *'In the rat study, the effects seen in the highest dose group (700mg/kg bw/d) were not considered relevant for classification due to high maternal mortality (20%) and the effects in the next top dose (350mg/kg bw) were not severe enough for classification'*.

In the pilot developmental study rats were dosed at a maximum dose level of 500 mg/kg/day, clinical signs of salivation were observed at 300 and 500 mg/kg bw/day and no mortalities were observed. In the prenatal developmental toxicity study in rats the highest test dose was 700 mg/kg bw/day, which exceeded the highest dose level tested (500 mg/kg bw/day) in the pilot rat study.

Excessive salivation was the most common clinical observation at 700 mg/kg bw/day in line with the clinical observations seen at 500 and 300 mg/kg bw/day. Additional clinical signs were also observed at 700 mg/kg bw/day and at 350 mg/kg bw/day in the prenatal developmental study in rats, and high mortality was observed at 700 mg/kg bw/day. These data suggest that the MTD lies between 500 and 700 mg/kg bw/day and consequently the MTD has been exceeded in the rat developmental toxicity study.

According to Regulation EC No. 1272/2008 (the CLP Regulation), Section 3.9.2.1: *" Substances are classified as specific target organ toxicants following repeated exposure by the use of expert judgement (see 1.1.1), on the basis of the weight of all evidence available, including the use of recommended guidance values which take into account the duration of exposure and the dose/concentration which produced the effect(s) "*.

The dataset for clethodim includes robust, CLP and test guideline compliant 28-day and 90-day repeated oral dose toxicity studies that do not provide evidence to support target organ toxicity:

In a 90-day oral toxicity study (Vol. 3, B.6.3.2/01) in female rats dosed with clethodim at 2.8, 30, 159 and 341 mg/kg bw/day and male rats dosed at 2.3, 25, 134 and 279 mg/kg bw/day no treatment related deaths occurred during the study and systemic effects were observed. According to Regulation EC No. 1272/2008 (CLP), section 3.9, Annex I: 3.9.2.9.7 the guidance values to assist in Category 2 classification based on a 90-day toxicity study in the rat (oral route) in mg/kg bw/day is $10 < C \leq 100$. No mortalities were observed for 90 days exposure within the CLP guidance values.

In a 28-day oral toxicity study (Vol. 3, B.6.3.1/01) in female rats dosed with clethodim at 0.29, 13.9, 70.6, 291 and 554 mg/kg bw/day and males dosed at 0.26, 12.5, 65.6, 216 and 515 mg/kg bw/day no treatment related deaths occurred and systemic effects were observed. According to Regulation EC No. 1272/2008 (CLP), section 3.9, Annex I: 3.9.2.9.7 the extrapolated guidance values to assist in Category 2 classification based on a 28-day toxicity study in the rat (oral route) in mg/kg bw/day is $30 < C \leq 300$. No mortalities were observed following 28 days exposure to clethodim within the CLP guidance values.

Based on a weight of evidence approach, the findings from the 90-day and 28-day rat studies further support the rationale that a STOT RE category 2 classification is not warranted.

Rabbit developmental study

Mortalities were observed in a rabbit pilot developmental study (Vol. 3, B.6.6.2.3/01) following 13 days exposure (gestational days 7-19) to clethodim at 300 and 500 mg/kg bw/day. Two out of seven pregnant 300 mg/kg/day dose group rabbits died, and one of seven pregnant 500 mg/kg/day dose group rabbits

aborted and died. For all animals where mortality occurred, daily feed consumption was inhibited, and weight loss was apparent.

In several other clethodim studies it has been reported that poor palatability of clethodim potentially impacted food consumption, and therefore the feed inhibition and weight loss observed in the rabbit pilot developmental study may have been a result of palatability issues rather than a toxic effect of clethodim.

The death of one animal at 500 mg/kg bw/day was reported to have been interrelated with a possible intubation accident during administration and the rabbit had clonic convulsions and died within 15 minutes of intubation.

Therefore, considering the mortalities observed: no dose-response relationship was observed; the death of one animal in the highest dose group (500 mg/kg bw/day) was probably due to experimental error and, taking into account the impact of poor palatability, there is no clear evidence that the mortalities observed were due to the test substance and are more likely to be incidental or secondary to other effects.

In a rabbit developmental study (Vol. 3, B.6.6.2.4/01) following 13 days exposure (gestational days 7-19) to clethodim at 25, 100 and 300 mg/kg bw/day, no deaths attributable to administration of clethodim were observed. This further casts doubt on the relevance of the mortalities observed in the rabbit pilot study, as the mortalities observed at 300 mg/kg/day were not reproduced in the rabbit developmental study.

In addition, it was concluded by RAC (2015) that 'In the rabbit, no treatment-related effects were seen'.

When considered as part of a WoE approach, taking into account the absence of evidence clearly supporting specific, target organ toxicity in the rat studies, no substantive evidence can be additionally drawn from the rabbit developmental toxicity studies to support the classification.