Registration Decision RD2019-17

Mefentrifluconazole and related end-use products

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Registration Decision Statement[1] for Mefentrifluconazole

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is granting registration for the sale and use of Revysol Fungicide Technical, BAS 752 RC, Belyan, Cevya, Lenvyor, Maxtima, and Relenya, containing the technical grade active ingredient mefentrifluconazole, to control various fungal pests in field crops, fruits, specialty crops and golf course turf.

This decision is consistent with the Proposed Registration Decision PRD2019-09, *Mefentrifluconazole and related end-use products*, which contains a detailed evaluation of the information submitted in support of this registration. The evaluation found that, under the approved conditions of use, the health and environmental risks and the value of the pest control product(s) are acceptable. See Appendix I for a summary of comments received during the consultation process as well as Health Canada's response to these comments.

Other Information

The relevant test data on which the decision is based (as referenced in PRD2019-09) are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (hc.pmra.info-arla.sc@canada.ca).

Any person may file a notice of objection[2] regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides section Canada.ca website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

1 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act.*

2 As per subsection 35(1) of the *Pest Control Products Act.*

Appendix I Comments and Responses

1.0 Comment from the registrant related to a reproductive toxicity effect retained by the PMRA in the 2-generation reproductive toxicity study in the rat

The registrant considers the reduction of implantation site number in F1 high-dose females of the 2-generation reproductive toxicity study to be incidental, therefore not a treatment-related finding. The registrant argues that a) the lower number of implants in the F1 dams is within historical range, b) there was no effect on male or female reproductive organs, including sperm analysis and differential ovarian follicle count, in the F1 animals, and c) no such effects was observed in the F0 animals. To support this claim, the registrant also mentioned that no dose-response was observed in F1 generation and the registrant suggested that the effect noted was driven by one female with a low number of implantations (1 implant). Consequently, the registrant considers that the weight of evidence indicates a chance finding and that the slight reduction in mean number of implantation sites in F1 generation high-dose group is incidental and not a treatment-related effect.

PMRA Response:

Although no effects on male or female reproductive organs were observed, including sperm analysis and differential ovarian follicle count in the F0 animals, the PMRA cannot exclude the possibility that the dams from the second generation exposed to the test substance could be more sensitive than those of the first generation. Also, a traditional dose-response relationship may not always be observed for endpoints, depending on the toxicological profile of the test substance and the dose range used in the study. In this case, the effect observed at the high-dose was determined to be the reproductive lowest observed adverse effect level (LOAEL). A different (wider range) dose selection may have produced a dose-response relationship for the assessed end-point.

The PMRA re-calculated the implantation site incidences for the F1 dams from the high-dose group excluding animal #388, which was an outlier according to the registrant. The result, including or excluding animal #388, shows a statistically significant decrease in the number of implantation sites in F1 animals of the high-dose group. Furthermore, to calculate the historical control data range, the PMRA took into account only the studies performed at the test facility within two years of the main study period which comprised six historical control studies (2011-2014) for which comparison with the main study is possible. From these studies, an average of 12.2 ± 1.0 implantation sites in F1 animals was noted within a range of 11.1 to 13.9 implantation sites. Consequently, the number of F1 implantation sites (with or without animal #388) is outside the historical control data range. In conclusion, the PMRA still considers the decreased number of implantation sites in the F1 generation treatment-related and adverse.

Implantation Site Incidences

Dose (mg/kg bw/d)	0	25	75	200	Historical control data mean ± SD [range]
F0	12.3 ± 2.5	11.4 ± 2.7	12.0 ± 1.7	11.8 ± 2.5	12.1 ± 0.4 [11.3-12.8] 9 studies (n = 23-25)
F1	12.0 ± 1.8	11.4 ± 2.1	12.3 ± 1.9	**10.0 ±2.8*** Including #388 or **10.4 ± 2.1*** Excluding #388	12.2 ± 1.0 [11.1-13.9] 6 studies (n = 23-25)

* $p < 0.05$

2.0 Comment from the registrant related to the placental weight increase in the developmental toxicity study in the rat

The registrant noted that the observation of increased placental weight is mentioned only once in Section 3.1.1 of the PMRA document. This observation is not discussed elsewhere in the document. Since this is not an adverse effect, the registrant suggests to delete the mention to this effect in the document.

PMRA Response:

The PMRA acknowledges the fact that the observation of increased placental weight in the developmental toxicity study in the rat at the high dose is not to be considered an adverse effect. It was neither discussed in the toxicology summary section nor reported in the toxicity profile table. The PMRA agrees that the mention of this observation was not required in PRD2019-09.