Registration Decision RD2021-01

Trifludimoxazin, Vulcarus and Voraxor

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Registration decision statement[1] for trifludimoxazin

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is granting registration for the sale and use of Tirexor Herbicide Technical, Vulcarus and Voraxor, containing the technical grade active ingredient trifludimoxazin, to control weeds in barley, corn, field pea, soybean, wheat, lentil, and chemfallow.

This decision is consistent with the Proposed Registration Decision PRD2020-15, *Trifludimoxazin, Vulcarus and Voraxor,* 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 products 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 PRD2020-15, *Trifludimoxazin, Vulcarus and Voraxor*) 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 and Pest Management portion of the Health Canada's website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

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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

A. Comment on modelling of drinking water concentrations

A comment was submitted regarding an adsorption coefficient value normalized to organic carbon (K_{oc}) used in Health Canada's modelling of drinking water concentrations. The registrant stated that the PMRA-selected K_{oc} of 0.52 mL/g for use in the Pesticides in Water Calculator (PWC) model is not clear, as the lowest K_{oc} value across all compounds (parent and metabolites) is 33.1 mL/g.

Health Canada's response: The value of 0.52 mL/g used by Health Canada is in fact a K_d value (and not a K_{oc} value) for the major transformation product, M850H003. A K_d value was used for modelling instead of a K_{oc} value because the available sorption data show no relationship between sorption and soil organic carbon content. When considering trifludimoxazin and the three transformation products with which it was combined in drinking water modelling, the K_d value of M850H003 was used as it is the most mobile in soil. The K_d value of 0.52 mL/g for M850H003 was calculated by Health Canada and differs from the value reported by the registrant (0.35 mL/g).

B. Comments on the toxicology review

Comments were submitted regarding the extended one-generation reproductive toxicity study in the rat.

(1) Comment: The registrant commented that it was their opinion that the reduction in auditory startle response in high-dose males was a consequence of high outlier data in the control group males. Additionally, the registrant referenced the lack of similar effect in females and the lack of corroborating neurobehavioural effects during other assessments performed during the study. The registrant noted that an auditory startle response effect was reported in both males and females in the Toxicity Profile Table (Appendix I, Table 5 in PRD2020-15, *Trifludimoxazin, Vulcarus and Voraxor*).

Health Canada's response: While removal of the high outlier data reduces the group means and variability around the means for amplitude and latency, it also reduces the group sample size. Additionally, a low outlier value in the control group males could also arguably be excluded on the same grounds. Removing all potential outliers would not only significantly reduce the sample size, but could also lead to additional issues with the overall quality of data. For example, removing the high outlier data mutes the habituation response in the control group. The non-outlier data from the remaining seven animals suggests poor habituation to the auditory startle stimulus, leading to uncertainty in the reliability of the test results. Therefore, removal of the outlier data from the control group when analyzing the auditory startle data was not considered to aid in the interpretation of the data.

Although comparisons between sexes and to other neurobehavioural assessments in the database can be considered in a weight-of-evidence approach, lack of effects in both sexes is not a valid reason for dismissing treatment-related effects. Furthermore, as discussed below, a treatment-related effect on brain morphometric measurements in high-dose males could not be excluded.

These considerations, combined with the observation of other indications of neurotoxicity in the trifludimoxazin toxicology database, lend weight to the conclusion that a relationship to treatment for the reduced auditory startle response in high-dose males cannot be dismissed.

The auditory startle effect was considered potentially treatment-related in high-dose males and the inclusion of the female symbol with this effect in the Toxicity Profile Table was in error.

The information provided was not considered sufficient to revise the previous assessment of the auditory startle data.

(2) Comment: The registrant commented that it was their opinion that the observed decreases in multiple brain morphometrics in high-dose males were coincidental as similar effects were not seen bilaterally (both right and left), the decreases were less than 10% different from controls, and there were no effects observed in females. The registrant performed a statistical analysis using females as a covariate, which reduces the effect of treatment. Additionally, the registrant noted that corpus callosum measurements are known for high variability.

Health Canada's response: Decreases in several brain morphometric measurements were observed in high-dose males relative to controls, including the frontal cortex, nucleus caudatus, and corpus callosum. For those areas with bilateral measurements, decreases relative to controls were noted for tissues collected from both the left and right hemispheres. It was noted that the decreases reached statistical significance on only one side and were of greater magnitude than the contralateral side. Concerning the corpus callosum measurements, the variability in the data was noted. However, given the consistency of the brain morphometric findings in high-dose males, the above-noted effects on auditory startle response, and other indications of neurotoxicity in the trifludimoxazin toxicology database, an effect of treatment on the brain morphometric measurements of high-dose males could not be ruled out. Further, as noted above, the lack of effects in females is not a valid reason for dismissing treatment-related effects observed in males.

The information provided was not considered sufficient to revise the previous assessment of the morphometric data.