Registration Decision RD2019-09

Dinotefuran and Related End-use Products

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Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6607 D
Ottawa, Ontario K1A 0K9

Internet: canada.ca/pesticides
hc.pmra.publications-arla.sc@canada.ca
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
hc.pmra.info-arla.sc@canada.ca

Canada

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Registration Decision Statement[1] for Dinotefuran

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 Dinotefuran Technical and the following three end-use products, Vectra 3D for Dogs Weighing 25.1 to 43 kg, Vectra 3D for Dogs and Puppies Over 7 Weeks of Age Weighing 9.1 to 25 kg and Vectra 3D for Dogs and Puppies Over 7 Weeks of Age Weighing 4.6 to 9 kg, containing the technical grade active ingredient dinotefuran, to repel and/or kill ticks and specific insect and mite pests on dogs and puppies. In addition, the PMRA is granting registration for the sale and use of the following three end-use products, Seclira Pressurized Insecticide (former name Prescription Treatment Brand Alpine Pressurized Insecticide), Seclira Dust Insecticide (former name Prescription Treatment Brand Alpine Dust Insecticide) and Seclira Cockroach Gel Bait Reservoir (former name Prescription Treatment Brand Alpine Cockroach Gel Bait Reservoir), containing the technical grade active ingredient dinotefuran, to kill several structural pests found inside and/or on the exterior surfaces of commercial, industrial and residential structures and inside transportation vehicles.

This decision is consistent with the Proposed Registration Decision PRD2019-01, *Dinotefuran 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 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 PRD2019-01) 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 of Canada.ca (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

1.0 Toxicology Assessment Comments

Comment relating to the findings of thyroid C-cell adenomas in the 2-year chronic toxicity/oncogenicity study in rats

The applicant contends that there was no treatment-related increase in the incidence of thyroid C-cell adenomas in male rats in the 2-year dietary chronic toxicity/oncogenicity study conducted with dinotefuran. The applicant states that, although there was a statistically significant increase in the incidence of this tumour in male rats, the incidence was within the historical control range and this tumour type is a common neoplastic lesion in the rat. The applicant also notes that the combined incidence of thyroid C-cell adenomas and carcinomas was not significantly higher in treated rats when compared to controls. The applicant is not requesting re-evaluation of this study at this time, but notes that such a request would be included in the event of future registration applications.

PMRA Response

As outlined in PRD2019-01, following long-term dietary exposure to dinotefuran, an increased incidence of thyroid C-cell adenomas was noted in high-dose male rats when compared to the concurrent control incidence. The incidence in high-dose males was also slightly above the upper end of the historical control range for this tumour type. The PMRA agrees that there was no corresponding increase in the incidence of thyroid C-cell carcinoma. It was noted by the PMRA in PRD2019-01 that the incidence of thyroid C-cell adenomas in male rats was increased at a dose level that approached the limit dose of testing; as such, the endpoints selected for the non-cancer risk assessment were considered protective of these findings.

Comment relating to the NOAEL and LOAEL in the 1-year dog study

The applicant contends that the effects on the thymus in the 1-year dog study, which the applicant notes formed the basis of the LOAEL established by the PMRA, are not toxicologically relevant based on the lack of corroborating evidence such as alterations in hematology parameters, histopathological lesions, or toxicity to the hematopoietic system. The applicant further notes that no treatment-related effects on the spleen or thymus were noted in immunotoxicity studies conducted with dinotefuran, including a developmental immunotoxicity study. The applicant is not requesting re-evaluation of this study at this time, but notes that such a request would be included in the event of future registration applications.

PMRA Response

The LOAEL established by the PMRA for the findings in the 1-year dog study conducted with dinotefuran was based only in part on effects on the thymus. The LOAEL in the 1-year dog study established by the PMRA was based on decreased food efficiency and decreased thymus weights in both sexes, an increased incidence of thymic cysts in males, and decreased body weight and body weight gain as well as red blood cell effects in females. Decreased thymus weight was also observed in the rat after both long-term dietary dosing and short-term inhalation exposure, as

well as in offspring in the reproductive toxicity and developmental immunotoxicity studies conducted in rats. Based on these collective findings, the LOAEL in the 1-year dog study was determined by the PMRA to be 111/108 mg/kg bw/day in males/females.

Comment relating to NOAELs in the 18-month mouse oncogenicity study, the rabbit developmental toxicity study, and the rat developmental neurotoxicity study

The applicant notes that the NOAELs established by the PMRA in the 18-month mouse oncogenicity study, the rabbit developmental toxicity study, and the rat developmental neurotoxicity study are different from those established by the USEPA and summarized in an assessment that was released in 2017, and contends that the USEPA assessment more accurately reflects the data. The applicant is not requesting re-evaluation of these studies at this time, but notes that such a request would be included in the event of future registration applications.

PMRA Response

For any future application involving a major expansion of use or for re-evaluation activities related to dinotefuran, conclusions reached previously by the PMRA would be re-assessed if new scientific information becomes available, and to ensure any changes in evaluation processes are reflected in the new assessment. Conclusions reached by international regulatory authorities available at the time of review are also considered by the PMRA as part of its evaluation activities. However, differences may still exist between regulatory authorities in the interpretation of toxicology data or in the application of jurisdiction-specific science policy.

2.0 Textual Comments

Comment

On page 13, the dissociation constant is noted as 12.6. Please amend to read “12.6 at 20°C”.

PMRA Response

The PMRA acknowledges that the dissociation constant can be expressed as “12.6 at 20°C” in the table “Technical Product – Dinotefuran Technical” in Section 1.2 on page 9.

Comment

The second table on page 55 is without a title.

PMRA Response

The PMRA acknowledges that the title is missing for the second table in Appendix 1 on page 55. The title should be “Table 4 Toxicology Reference Values for Use in Health Risk Assessment for Dinotefuran”