Registration Decision RD2016-23

Buprofezin

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

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

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Registration Decision Statement[1] for Buprofezin

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is granting full registration for the sale and use of Buprofezin Technical and Applaud Insect Growth Regulator, containing the technical grade active ingredient buprofezin, to control whiteflies on greenhouse vegetables (cucumbers, peppers and tomatoes) and greenhouse ornamentals (excluding cut flowers).

This decision is consistent with the Proposed Registration Decision PRD2016-07, *Buprofezin,* 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 products have value and do not present an unacceptable risk to human health or the environment. See Appendix I for a summary of comments received during the consultation process as well as the PMRA's response to these comments.

Other Information

The relevant test data on which the decision is based (as referenced in Decision PRD2016-07, *Buprofezin,* 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 (pmra.infoserv@hc-sc.gc.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 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. Comments relating to the findings in the rat 28-day inhalation toxicity study

One commenter expressed disagreement with the NOAEC of 0.1 mg/L established by the PMRA in the rat 28-day inhalation toxicity study. The commenter argued that the liver findings (increased weight, hypertrophy, increased triglycerides, total protein and globulin) observed at the highest dose level (0.5 mg/L) should be considered non-adverse as the clinical chemistry changes were slight and there were no necrotic or degenerative changes in the liver. The commenter was also of the opinion that many of the other changes (including reduced body and spleen weights, increased adrenal gland weights and hypertrophy of adrenal cortex) should not be considered adverse as they reflect the stress associated with treatment with higher chamber concentrations of the test chemical and are not indicative of direct toxicity. It was further noted by the commenter that there was a lack, or minimal extent of, accompanying histopathology findings in the affected organs. As further support that effects on the spleen were a systemic response to stress, the commenter referred to the results of the rat 28-day immunotoxicity study. In that study, decreases in spleen weight and plaque-forming counts were only observed at a dose producing statistically significant reductions in body weights. In light of the above information, the commenter argued that the 28-day inhalation toxicity study NOAEC should be revised to 0.5 mg/L.

PMRA Response

Reductions in male body weights (approximately 6% when compared to controls) as well as body weight gains (approximately 17% when compared to controls) were observed at the highest dose level in the 28-day inhalation toxicity study. The magnitude of the decrease in body weight gradually increased over each weekly reporting interval attaining 6% by study termination. The PMRA generally considers body weight reductions ≥5% of toxicological significance from the perspective of establishing a point of departure. On the basis of the body weight reduction in males at the highest dose level, the PMRA maintains the overall study NOAEC at 0.1 mg/L, irrespective of the other effects (such as liver findings, spleen weights) discussed below.

When assessing the weight of evidence for liver toxicity in a study, the PMRA considers the collective information. As a general rule, the PMRA considers liver hypertrophy and corresponding increases in liver weight adverse when these findings are accompanied by alterations in liver clinical chemistry parameters, and/or histopathology. The treatment-related elevations in liver-associated clinical chemistry parameters in the 28-day rat inhalation study were slight in magnitude, and upon re-examining the findings, the PMRA acknowledges that an argument can be made that the effects on the liver at the highest dose level are non-adverse. That said, the high dose was associated with adverse effects on body weight as noted above.

The PMRA acknowledges the physiological stress to animals that are maintained in exposure chambers under the conditions of inhalation toxicity testing, as well as the fact that changes in weights of organs such as the spleen and adrenal gland can be a part of the normal response to such stress. Despite this, effects on these organs in the rat 28-day inhalation study were only observed at the highest dose level.

As for the commenter's claim that decreases in spleen weight and plaque-forming counts were only observed in the 28-day immunotoxicity study at a dose producing statistically significant reductions in body weights, the PMRA notes that body weight reductions in that study were pronounced in both sexes. Decreased spleen and plaque-forming counts were only observed in females, however.

Revisions to appropriate documentation will be made to clarify the Agency's position regarding the body weight and liver findings noted above.

2. Comments relating to the developmental thyroid toxicity

A commenter disagreed with the PMRA's interpretation of the offspring findings in the developmental thyroid toxicity study. The commenter was of the opinion that the data supported an offspring NOAEL of 10 mg/kg bw/day (lowest dose level), whereas the PMRA established the LOAEL for offspring at this dose level. The commenter's argument was focused on the PMRA's interpretation of body weight, as well as the thyroid stimulating hormone (TSH) findings when considered within the context of thyroid weight changes.

Decreases in offspring body weight

In general, the commenter's concern related to interpretation/degree of adversity of body weight findings in low-dose offspring on postnatal day (PND) 4, PND7, and PND13. The commenter was of the opinion that the body weight decreases observed in male pups on PND4 did not follow a dose response and that they were the result of a litter size effect; that is, they reflected the fact that litters of larger size tend to have smaller fetal weights. For these reasons, they felt that the body weight decreases should not be considered related to treatment with buprofezin. As additional evidence supporting the litter size effect, the commenter cited the absence of similar findings in low-dose offspring after litter size adjustment on PND4. The commenter also cited the lack of statistical significance for this finding, as well as for the decreased offspring weights at PND7 and PND13, as further support for this position.

PMRA Response

The PMRA recognizes that an inverse relationship generally exists between litter size and fetal weight. However, the mean body weight of pups of the low-dose group on PND0 was not markedly lower than control values, despite the fact that the mean litter size was 7% larger, suggesting that increased litter size was not the cause of the lower body weights. Contrary to the commenter's claim that a similar effect on body weight was not observed in low-dose pups after litter size adjustment on PND4, body weights were decreased 7-8% after litter size standardization on PND4 and PND7; mean litter sizes at these time points were only 3% higher than respective control values. As mentioned in an earlier comment, the PMRA generally considers reductions of ≥5% in body weight of toxicological relevance in establishing a point of departure. With regards to the commentary that such decreases should be considered non-adverse as they occurred in the absence of statistical significance, the PMRA takes into account the statistical significance of toxicological findings, but notes that a lack of statistical significance does not necessarily indicate a lack of biological significance. Finally, reductions in body weights of pups in the developmental thyroid toxicity study that were not gavage-dosed, but

continued to nurse, as well those that were directly gavage-dosed, indicate that residues of buprofezin were transferred through maternal milk to the pups. The commenter shared this position within the context of interpretation of the body weight data for the higher doses. Collectively, the information supports PMRA's position that the effects on pup body weight at the lowest dose level are treatment-related and adverse. The transiency of the bodyweight findings was a consideration in the PMRA's overall level of concern for this endpoint; however, as noted above, the strength of the findings met the PMRA's criterion for adversity. These results were taken into consideration with the other findings, further elaborated below, in determining the overall point of departure for health risk assessment.

Increased TSH levels in offspring and decreased thyroid weights in male fetuses

Regarding TSH levels of the low-dose group, the commenter did not share the PMRA's interpretation that the findings in culled pups (PND4) and dosed weanlings (PND21) were treatment-related as they were not statistically significant from controls, and were not accompanied by thyroid histopathology, statistically significant decreases in thyroid weight, or reduced T4 levels. The commenter further noted that even if relation to treatment was not excluded, the very slight increases in TSH levels should be considered non-adverse as they were either within normal variation or an adaptive response.

The commenter also noted that increased thyroid weights in male fetuses were not accompanied by increases in TSH levels, and therefore the increase in fetal thyroid weight should not be considered adverse. Finally, it was claimed that when looking at the findings at the higher doses, increased thyroid weights in male fetuses should be considered equivocal as there was no dose response, and they were not accompanied by changes in thyroid hormone levels or histopathology.

PMRA Response

The commenter did not provide information to support the contention that the observed increases in TSH were within the normal range for these animals, and thus the findings could not be dismissed. In terms of the thyroid weight findings, the PMRA does not concur with the assertion that the increases in thyroid weights of male fetuses at higher doses are not treatment-related. Although the increases in thyroid weights were not clearly dose-responsive, alterations in thyroid response were observed at these doses, namely, increased thyroid follicular hypertrophy and cell height, decreased thyroid colloid area, and increased TSH levels. The PMRA concurs with the commenter that there were no changes in TSH levels in low-dose male fetuses. However, the PMRA maintains its opinion that effects on thyroid weights in low-dose male fetuses are equivocal based on the collective thyroid evidence in offspring. Revisions to appropriate Agency documentation will be made for increased clarity.

Overall PMRA comments on developmental thyroid toxicity study

In determining the point of departure for adverse effects in offspring in the developmental toxicity thyroid study for buprofezin, all supporting evidence in the toxicology database was taken into consideration as well as the comments received above. The PMRA maintains that the lowest dose (10 mg/kg bw/day) represents an adverse effect level.

The thyroid, a target organ of toxicity for buprofezin, plays a critical role during development and the overall evidence indicates that an adverse outcome on the developing young at the lowest dose level of the developmental thyroid toxicity study cannot be ruled out.

Therefore, the PMRA opined that the evidence was sufficient to set the lowest dose as a LOAEL, rather than a NOAEL. However, in the consideration of toxicological endpoints for use in risk assessment, the PMRA felt that application of an additional factor for the use of a LOAEL was not warranted for exposure scenarios for which the offspring LOAEL from the developmental thyroid toxicity study was used. The effects on thyroid and body weights of offspring in this study occurred in the absence of maternal toxicity, suggesting that the young animal was more sensitive than the adult animal to buprofezin toxicity. The PMRA reasoned, however, that the PCPA factor could be reduced to 1-fold on the strength of the overall findings at the time of the initial assessment, and maintains this position.

3. Comments relating to the toxicological endpoints selected for human health risk assessment

A comment was received which disagreed with the selection of the offspring LOAEL from the developmental thyroid toxicity study for use as the short- and intermediate-term dermal toxicity endpoint in the human health risk assessment. The commenter was of the opinion that pups were not more susceptible than adults to the effects of buprofezin on the thyroid. As a result, the commenter argued that PMRA's premise that the repeat-dose dermal toxicity study did not allow for assessment of the relevant endpoint in the subpopulation of concern (that is, potential thyroid effects in the developing young) was not valid. The commenter felt that the NOAEL of 300 mg/kg bw/day from the 24-day dermal toxicity in rats should be used for the short- and intermediate-term dermal risk assessment.

A comment was also received which disagreed with the selection of the offspring LOAEL from the developmental thyroid toxicity study for use as the short- and intermediate-term inhalation toxicity endpoint in the human health risk assessment. The reasons for this position were the same as noted for the dermal toxicity endpoint. It was the commenter's opinion that the NOAEC from the 28-day inhalation toxicity study in rats was most appropriate for inhalation risk assessment.

PMRA Response

The PMRA could not rule out the potential for an adverse outcome on the developing young at the lowest dose level of the developmental thyroid toxicity study for the reasons previously noted. Therefore, the Agency maintains its position regarding the toxicology endpoints for dermal and inhalation risk assessment as outlined in PRD2016-07.