Registration Decision RD2012-15

Spiromesifen

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Registration Decision for Spiromesifen

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is granting renewel of the conditional registration for the sale and use of Spiromesifen Technical Insecticide/Miticide, Forbid 240 SC Insecticide/Miticide and Oberon Flowable Insecticide-Miticide containing the technical grade active ingredient spiromesifen to control mites and whiteflies on greenhouse and outdoor ornamentals, on greenhouse and field vegetables as well as on strawberries.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

These products were proposed for a renewel of the conditional registration in the consultation document[1] Proposed Registration Decision PRD2011-19, *Spiromesifen*. This Registration Decision[2] describes this stage of the PMRA's regulatory process for spiromesifen and summarizes the Agency's decision, the reasons for it and provides, in Appendix I, a summary of comments received during the consultation process as well as the PMRA's response to these comments. This decision is consistent with the proposed registration decision stated in PRD2011-19.

For more details on the information presented in this Registration Decision, please refer to the Proposed Registration Decision PRD2011-19, *Spiromesifen*, which contains a detailed evaluation of the information submitted in support of this registration.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[3] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions of registration. The Act also requires that products have value[4] when used according to label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act.*

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

3 "Acceptable risks" as defined by subsection 2(2) of *Pest Control Products Act.*

4 "Value" as defined by subsection 2(1) of *Pest Control Products Act* "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact".

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What is Spiromesifen?

Spiromesifen is a foliar applied, contact insecticide used to control mites and whiteflies. It is applied to greenhouse vegetables and ornamentals, field corn, cucurbits, leafy greens, leafy brassicas, tuberous and corm vegetables, fruiting vegetables, alfalfa and strawberries using ground, and in some instances, aerial application equipment. Spiromesifen inhibits lipid biosynthesis in target insects and is effective against all immature life stages. It may have indirect effects on adults of some target pest species.

Health Considerations

Can Approved Uses of Spiromesifen Affect Human Health?

Spiromesifen is unlikely to affect your health when used according to the label directions.

People could be exposed to spiromesifen through diet (food and water) or when handling and applying Forbid 240 SC Insecticide/Miticide and Oberon Flowable Insecticide-Miticide. When assessing health risks, the PMRA considers two key factors: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers).

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose at which no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when products containing spiromesifen are used according to the label directions.

The technical grade active ingredient spiromesifen caused allergic skin reactions in animals. Consequently, the statement "Potential Dermal Sensitizer" is required on the label for the technical grade active ingredient. The end-use products Forbid 240 SC Insecticide/Miticide and Oberon Flowable Insecticide-Miticide caused slight toxicity in animals when inhaled. Consequently, the statement "Caution—Poison" is required on the label for the end-use products. Spiromesifen did not cause cancer in animals and was not genotoxic. Health effects in animals given daily doses of spiromesifen over long periods of time included effects on the spleen, liver, uterus, thyroid gland and adrenal gland. When spiromesifen was given to pregnant animals, effects on the developing fetus were observed at doses that were toxic to the mother, indicating that the fetus is not more sensitive to spiromesifen than the adult animal. Effects on the young

animal, however, were slightly more severe than those observed in parental animals after the parental animals were given daily doses of spiromesifen before mating, during pregnancy and while providing nourishment to the young animal through lactation. Signs of potential neurotoxicity were observed at doses that caused other effects in test animals. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests. Only those uses where exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Aggregate chronic dietary intake estimates (food plus water) revealed that children (1 to 2 years old), the subpopulation which would ingest the most spiromesifen relative to body weight, are expected to be exposed to less than 41% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from spiromesifen is not of concern for all population subgroups.

Animal studies revealed no acute health effects. Consequently, a single dose of spiromesifen is not likely to cause acute health effects in the general population (including infants and children).

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for The *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using spiromesifen on various fruit and vegetable crops were acceptable. The reviews for this active ingredient can be found in the Evaluation Report, ERC2007-08, *Spiromesifen*, and in the Evaluation Report (Application Number 2008-5063) located within the PMRA Public Registry on the Health Canada Website. The MRLs for this active ingredient can be found in the Established Maximum Residue Limit documents EMRL2008-17, *Spiromesifen* and EMRL2011-29, *Spiromesifen*.

Workplace Risks From Handling Forbid 240 SC Insecticide/Miticide and Oberon Flowable Insecticide-Miticide

Occupational risks are not of concern when Forbid 240 SC Insecticide/Miticide and Oberon Flowable Insecticide-Miticide are used according to the label directions, which include protective measures.

Farmers and pesticide applicators mixing, loading or applying Forbid 240 SC Insecticide/Miticide and Oberon Flowable Insecticide-Miticide as well as workers entering fields or greenhouses of recently treated crops can come in direct contact with spiromesifen on the skin or through inhalation of spray mists. Therefore, the label specifies that anyone mixing or loading Forbid 240 SC Insecticide/Miticide and Oberon Flowable Insecticide-Miticide must wear a long-sleeved shirt, pants, chemical-resistant gloves, a respirator with appropriate filter and goggles or

a face shield and that anyone applying the product must wear a long-sleeved shirt and pants. Based on these label statements, risks to farmers, applicators or workers are not a concern.

For members of the general population that are at pick-your-own facilities, exposure is not of concern because there were no acute concerns for spiromesifen identified in the toxicological database.

Environmental Considerations

What Happens When Spiromesifen Is Introduced Into the Environment?

Spiromesifen is toxic to terrestrial plants and aquatic organisms, therefore, buffer zones are required during application.

Spiromesifen enters the environment when used as an insecticide on a variety of crops including field corn, cucurbits, leafy greens, leafy brassicas, tuberous and corm vegetables, fruiting vegetables, alfalfa and strawberries. Spiromesifen is not persistent to moderately persistent in soil (depending on soil characteristics) and slightly persistent in water, while the major transformation product, BSN 2060-enol, is persistent in water, and slightly to moderately persistent in soil (depending on soil characteristics). Spiromesifen is not expected to leach through the soil profile beyond 30 cm; and therefore is not expected to enter groundwater. In contrast, BSN 2060-enol is mobile and expected to leach and enter groundwater. Based on its low volatility, spiromesifen residues are not expected in the air.

During the original review (reported in the Evaluation Report, ERC2007-08, *Spiromesifen*) it was determined that spiromesifen does not present a risk to wild mammals, birds, adult bees, marine invertebrates, algae and aquatic plants. However, spiromesifen does affect terrestrial plants, predators and parasites, daphnia, freshwater and marine fish, and amphibians in adjacent areas. Therefore, to protect from the effects of spray drift, buffer zones were required on the label to protect sensitive aquatic species and non-target plant species in adjacent habitats.

During this review of spiromesifen, a number of additional field and semi-field bee hive studies were submitted for review. From these studies, it was determined that spiromesifen poses a potential risk to honeybee brood. If applied to blooming plants, it may be possible that nectar and pollen can be brought back to the hive resulting in exposure to spiromesifen. In the studies, there was also indication of hive recovery. Therefore, in order to further characterize the potential risk to bee brood, additional information is being requested from the registrant to address the above mentioned concerns.

Value Considerations

What Is the Value of Forbid 240 SC Insecticide/Miticide and Oberon Flowable Insecticide-Miticide?

Spiromesifen, an insecticide/miticide, controls specific mites and whiteflies on greenhouse vegetables and ornamentals, field corn, cucurbits, leafy greens, leafy brassicas, fruiting vegetables, alfalfa, tuberous and corm vegetables, and strawberries.

A single application of spiromesifen provides control of specific mites and whiteflies on a variety of crops, in both greenhouses and outdoors. It is also compatible with current management practices and conventional crop production systems. Growers are familiar with the monitoring techniques to determine if and when applications are needed. Spiromesifen is the active ingredient found in two end-use products, Forbid 240 SC Insecticide/Miticide and Oberon Flowable Insecticide-Miticide.

One other registered miticide, spirotetramat, from the same resistance management class as spiromesifen can be applied to several vegetable crop groups to control whiteflies. While spiromesifen offers a new class for resistance management purposes to some crops, prudent rotation and alternation will be required to prevent the onset of resistance where both active ingredients are registered.

Measures to Minimize Risk

Registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures on the label of Forbid 240 SC Insecticide/Miticide and Oberon Flowable Insecticide-Miticide to address the potential risks identified in this assessment are as follows:

Key Risk-Reduction Measures

Human Health

As there is a concern with users coming into direct contact with spiromesifen on the skin or through inhalation of spray mists, anyone mixing or loading Forbid 240 SC Insecticide/Miticide or Oberon Flowable Insecticide-Miticide must wear a long-sleeved shirt, pants, chemical-resistant gloves, a respirator with appropriate filter and goggles or a face shield. Anyone applying these products must wear a long-sleeved shirt and pants.

Environment

Buffer zones are required for Oberon Flowable Insecticide-Miticide to protect susceptible non-target plant species and susceptible aquatic organisms. The distance allowed depends on the type of spray equipment used to apply the product, the type of habitat and the crop being sprayed with the product (please refer to the label).

Hazard statements to identify potential effects on bee brood and limitations for application during bloom will be required on both end-use product labels.

Other Information

The relevant test data on which the decision is based (as referenced in PRD2011-19, *Spiromesifen)* 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[5] 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 Pesticide and Pest Management portion of the Health Canada's website (Request a Reconsideration of Decision, www.hc-sc.ca/cps-spc/pest/part/protect-proteger/publi-regist/index-eng.php#rrd or contact the PMRA's Pest Management Information Service.

[5]As per subsection 35(1) of the *Pest Control Products Act.*

Appendix I Comments and Responses

Comments received on the document Proposed Registration Decision PRD2011-19, *Spiromesifen,* indicated that the overall conclusion of harm to bee broods in the field as a result of exposure to spiromesifen were incorrect. Specifically noted were the following four main points:

- The conclusion of decreased egg production was incorrect. Overall, there are no effects on ovi-position in the semi-field or field studies.
- The conclusion of brood effects in field environments should not have been based on cotton field study since there was observational error. The melon field study indicated no harm to bee brood or larvae.
- The conclusion that bee brood observations were insufficient in the field studies in comparison to the semi-field studies is incorrect.
- The conclusion of decreased hive weight, drone mortality and increased foraging activity as being biologically relevant and related to exposure to spiromesifen is incorrect.

Response:

The PMRA has reviewed four higher-tier spiromesifen studies, which included two semi-field studies (a tent buckwheat study and a greenhouse zucchini study) and two field studies (a cotton study and a melon study). The following reply is based on the review of these four studies.

Decreased egg production

Indication of lower egg numbers in treated hives compared to control hives was observed in the greenhouse study, cotton study and buckwheat study. The results of the greenhouse study indicated that there was no impact on oviposition; however, as noted by the PMRA reviewer and study author, fewer eggs were found in the exposed hives at the end of the study period. Thus, the observation of lower egg numbers is reported in the evaluation of spiromesifen. Although problems with the cotton study design led to difficulty interpreting data and increased data variability due to observational error (of up to 20%), mean numbers of eggs and larvae were lower in exposed hives as compared to control hives (25 eggs and 99 larvae in the control compared to 7 eggs and 22 larvae in the treated hive), and a decrease in egg number after the second application (64 eggs in the control compared to 21 eggs in the treated group). Thus, indication of lower egg numbers was observed. The results of the buckwheat study indicated that there were fewer eggs and larvae in the treatment groups compared to controls during the study, however, there was also recovery of numbers after bees were allowed to forage freely (on uncontaminated food). Therefore, it is unclear if the increase in egg numbers after confinement was due to reduced stress, or a lack of a contaminated food source, especially in light of the statistically significant decrease in larval survival in the treated hives.

Conclusion of brood effects

A weight of evidence approach was used to evaluate the potential risk of spiromesifen to bee broods. The PMRA conclusion of brood effects in hives, as stated in PRD2011-19 was based on effects observed in all of the submitted studies (including both semi-field and field) and was not based solely on the cotton study. The cotton study was used as part of the assessment process.

There were reduced egg and larvae numbers in treatment hives in the cotton study, however, the PMRA does recognize that "based on the methodology used for counting, potential errors (up to 20%) was expected." Thus, among other uncertainties related to study design, data interpretation of the brood effects was difficult in the cotton study. As noted by the PMRA reviewer and the study author, larval mortality was observed in both the greenhouse study and buckwheat study when bees were exposed to spiromesifen. The results of the melon study were also reported by the PMRA and showed little difference between the control and treatment hives (approximately 55 to 57% success in both control and treated hives); however, the interpretation of data in the melon study was difficult due to a number of uncertainties related to the study design. Some of the key uncertainties/study design concerns included cross contamination (spiromesifen detected in control hives), presence of other potentially toxic chemicals present in the hives, lower application rate compared to the Canadian use pattern, frequency of brood inspection, problems with queens in the study, and the study was conducted late in the season when the bees were potentially preparing for overwintering and overwintering conditions (Arizona and California) not relevant to Canadian conditions. Based on the high number of uncertainties in the two field studies, the evaluation of potential brood effects was based primarily on semi-field and field studies. All of the uncertainties and study interpretation are presented in Appendix I of PRD2011-19. Additional data submitted as part of the comments received included information related to the melon study addressing some of the above mentioned concerns, as presented to the United States Environmental Protection Agency and California Department of Pesticide Regulation. However, the submitted comments and data did not alleviate all of our concerns.

Overall, brood effects were confirmed in the semi-field studies and potential effect on bee broods in the field could not be excluded based on submitted comments and data.

Conclusion of brood observations (related to potential recovery of hives)

The PMRA is not referring to replicates in PRD2011-19, nor doing a comparison between the field and semi-field studies. The PMRA was commenting that the length and the number of observations post-exposure to determine hive recovery/health was too low. The PMRA did not indicate hive recovery in the "field" in the PRD2011-19, as there were too many uncertainties related to the field study design; rather, it was referring to potential recovery in the semi-field studies, as reported in Appendix I of PRD2011-19. In the greenhouse study, the survival of the third egg cohort (colonies transferred from the greenhouse) was increasing compared to the second egg cohort (exposed after second application of spiromesifen). In the buckwheat study, the percent eggs increased from 0% on September 26th to 5.33% on October 2nd (which was comparable to control values). Based on a short timeframe for observations indicating recovery of the bee brood, it is unclear if recovery would take place under conditions of use in the field.

Conclusion of decreased hive weight, drone mortality and increased foraging and biological significance

Statistically significant lower hive weight gain was observed in hives exposed to spiromesifen in the cotton study (untreated hives gained 28 pounds compared to 6 pounds in the treated hives), as observed by the study author and the PMRA evaluator. Hive weight could be the result of lower foraging, and thus lower honey and nectar stores, decreased number of eggs, larvae or pupae, and decreased food consumption and is thus, considered biologically relevant. Dead adult normal wing drones were statistically significantly higher in treated hives in the melon study.

The death of any bee in the colony (queen, foraging bee, drone bee, or brood) is considered biologically relevant. High death rate of drones may indicate the presence of a biological or non-biological stress in the hive. A change in foraging activity was observed in the buckwheat, greenhouse, cotton and melon study. Foraging activity is a behavioral endpoint related to the biological activity of bees which may be affected by colony stress, and the nutritional needs of the hive. Thus, these observations noted during the review of spiromesifen, are considered biologically relevant. The potential link between these observations and exposure to spiromesifen cannot be excluded based on the data provided.

Overall conclusion

The comments and data reviewed in this document did not provide sufficient evidence to change the previous assessment. As identified in PRD2011-19, in order to mitigate for the current uncertainties, the PMRA is proposing to minimize potential exposure using label mitigation measures.