Proposed Registration Decision PRD2012-31

# Spinetoram

*(publié aussi en français)*

**21 December 2012**

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6604-E2
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

Canada

ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2012-31E (print version)
H113-9/2012-31E-PDF (PDF version)

# Table of Contents

# Overview

## Proposed Registration Decision for Spinetoram

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Spinetoram Technical Insecticide, Radiant SC Insecticide and Delegate WG Insecticide, containing the technical grade active ingredient spinetoram, to control or suppress a variety of foliage-feeding insect pests in orchard, vineyard, and field crops.

Spinetoram Technical Insecticide, (Registration Number 28776), Radiant SC Insecticide (Registration Number 28777) and Delegate WG Insecticide (Registration Number 28778) are conditionally registered in Canada. The detailed review for Spinetoram Technical Insecticide, Radiant SC Insecticide and Delegate WG Insecticide can be found in Evaluation Report ERC2008-01, *Spinetoram (XDE-175)*. The current applications were submitted to convert Spinetoram Technical Insecticide, Radiant SC Insecticide and Delegate WG Insecticide from conditional registration to full registration.

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.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Spinetoram Technical Insecticide and Radiant SC Insecticide and Delegate WG Insecticide.

## 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[1] 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 proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

---

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

2 "Value" as defined by subsection 2(1) of the *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.

Before making a final registration decision on spinetoram, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on spinetoram, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

## What Is Spinetoram?

Spinetoram is a non-systemic insecticide derived from the fermentation of *Saccharopolyspora spinosa*. The end-use products Radiant SC Insecticide and Delegate WG Insecticide are applied using ground-based foliar application equipment to control a variety of insect pests on a wide range of fruit, vegetable and cereal crops. Spinetoram affects insects through both contact and ingestion, but is most active through ingestion.

## Health Considerations

### Can Approved Uses of Spinetoram Affect Human Health?

**End-use products containing spinetoram are unlikely to affect your health when used according to label directions.**

Exposure to spinetoram may occur through diet (food and water) or when handling and applying the end-use products. When assessing health risks, two key factors are considered: the levels where 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). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

---

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

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where 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 using pesticide products according to label directions.

In laboratory animals, the technical grade active ingredient spinetoram was of low acute toxicity via the oral, dermal and inhalation routes of exposure. It was non-irritating to the eyes and skin, but considered to be a potential skin sensitizer. Consequently, the statement "Potential Dermal Sensitizer" is required on the label. Based on the acute toxicity data, no hazard labelling was necessary for the end-use products Radiant SC Insecticide or Delegate WG Insecticide.

Spinetoram did not cause cancer in laboratory animals and was non-genotoxic. There was no indication that spinetoram caused damage to the nervous system. Health effects in animals given repeated doses of spinetoram included effects on the thyroid gland, lymphoid tissues, kidneys, spleen and blood system. Spinetoram did not cause birth defects in laboratory animals. When spinetoram was given to pregnant animals, fetal death was observed at doses which were also toxic to the mother, as demonstrated by difficulty in delivering their young. The potential for increased sensitivity of the lungs following repeated inhalation exposure necessitated the application of extra protective factors in the inhalation risk assessment to further reduce the allowable level of human exposure to spinetoram.

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.

## Residues in Water and Food

### Dietary risks from food and water are not of concern

Aggregate refined dietary intake estimates (food plus water) revealed that the general population and children, the subpopulation which would ingest the most spinetoram relative to body weight, are expected to be exposed to less than 11.3% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from exposure to spinetoram residues is not of concern for any of the population sub-groups.

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 under the authority of the *Food and Drugs Act* 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.

Processing studies conducted on oranges and grapes in the United States and France, using the end-use product containing spinetoram, were acceptable. The MRLs for this active ingredient are accessible on the PMRA's MRL webpage. The MRLs for grape juice, raisins, and citrus oil will be revised to reflect the results of the submitted processing studies.

### Occupational Risks From Handling Radiant SC Insecticide and Delegate WG Insecticide

**Occupational risks are not of concern when Radiant SC Insecticide and Delegate WG Insecticide are used according to the proposed label directions, which include protective measures.**

The label will specify that anyone mixing or loading Radiant SC Insecticide or Delegate WG Insecticide, or performing clean-up or repair activities, must wear coveralls over long-sleeved shirt and long pants, shoes plus socks and chemical-resistant gloves. Workers applying either product must wear long-sleeved shirt and long pants, shoes and socks and chemical-resistant gloves. Taking into consideration these label requirements, risk to workers handling Radiant SC Insecticide or Delegate WG Insecticide is not of concern.

## Environmental Considerations

### What Happens When Spinetoram Is Introduced Into the Environment?

Spinetoram rapidly transforms in the terrestrial and aquatic environment. The parent compound and its major transformation product, N-demethyl-J, are non-persistent in the environment and have a low potential for residue carryover. They also have a low potential to leach and contaminate groundwater. Based on its low volatility, spinetoram residues are not expected in the air.

Spinetoram may pose a risk to bees, predatory and parasitic arthropods, non-target terrestrial plants, wild mammals, freshwater invertebrates (daphnids and benthic organisms); therefore, statements on the product labels are required to inform users of the potential risks. In order to minimize the potential for exposure resulting from off-field spray drift, no-spray buffer zones are required between the treated area and downwind terrestrial habitats.

## Value Considerations

### What Is the Value of Radiant SC Insecticide and Delegate WG Insecticide?

**Radiant SC Insecticide and Delegate WG Insecticide control or suppress a variety of insect pests of fruit, vegetable and cereal crops.**

Application of Radiant SC Insecticide or Delegate WG Insecticide provides control or suppression of a variety of insect pests of fruit, vegetable and cereal crops and is 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.

One other active ingredient in the same class as spinetoram is registered for some of the same uses; however, spinetoram is registered for use against a broader range of pests. Spinetoram provides a new alternative active ingredient for uses that have traditionally relied on older classes of chemistry as well as uses that have few other registered alternatives.

## Measures to Minimize Risk

Labels of registered pesticide products 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 being proposed on the label of Radiant SC Insecticide and Delegate WG Insecticide to address the potential risks identified in this assessment are as follows.

### Key Risk-Reduction Measures

### Environment

Spinetoram can pose a risk to bees, predatory and parasitic arthropods, wild mammals and freshwater invertebrates (daphnids and benthic organisms). Label statements informing the users of the potential risks to these organisms are specified on the product labels.

Spray drift of spinetoram can pose a risk to non-target terrestrial plants. To minimize potential exposures via spray drift, no-spray buffer zones of one to two metres are required to protect sensitive terrestrial habitats. These no-spray buffer zones are specified on the product labels.

## Next Steps

Before making a final registration decision on spinetoram, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency’s response to these comments.

## Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on spinetoram (based on the Science Evaluation Section of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

# Science Evaluation

## Spinetoram

## 1.0 The Active Ingredient, Its Properties and Uses

Refer to the PMRA Evaluation Report ERC2008-01, *Spinetoram (XDE-175)* for a detailed assessment of the active ingredient.

The outstanding storage stability and corrosion characteristics study has been provided and found acceptable. The product chemistry for Radiant SC Insecticide and Delegate WG Insecticide have been completed.

### 1.1 Directions for Use

The active ingredient spinetoram is formulated into two commercial class end-use products, Radiant SC Insecticide and Delegate WG Insecticide. These products may be applied using conventional ground application equipment at application rates and re-application intervals that vary depending on the pest and crop (Table 1.1.1). Both products were initially registered for the same uses and the same application rate of active ingredient per hectare for any given use (see ERC2008-01, *Spinetoram (XDE-175)*). Several additional uses have been added to the label of Delegate WG Insecticide, but not to the label of Radiant SC Insecticide, since the products were initially registered. All uses are limited to a maximum of three applications per year.

**Table 1.1.1 Application Rates and Re-application Intervals for Spinetoram**

| Pest(s) | Crop(s) | Application Rate (g a.i./ha) | Re-application Interval |
|---|---|---|---|
| Apple Maggot (suppression)<br>Codling Moth<br>Plum Curculio (suppression) | Pome Fruits | 105 | 14 days |
| Armyworm | Cereals<br>Soybean | 25-50 | 5 days |
| Asparagus Beetle (suppression) | Asparagus (ferns only) | 35-70 | 5 days |
| Blackheaded Fireworm[1]<br>Sparganothis Fruitworm[1]<br>Cranberry Tipworm (suppression) [1] | Lowbush Cranberry[1] | 105 | 7 days |
| Blueberry Flea Beetle[1] | Bushberries | 50 | 6 days |
| Blueberry Spanworm (suppression) | Bushberries | 25-50 | 6 days |

| Pest(s) | Crop(s) | Application Rate (g a.i./ha) | Re-application Interval |
|---|---|---|---|
| Cabbage Looper | Fruiting Vegetables and Okra<br>Leafy Vegetables (non-Brassica) | 35-50 | 5 days |
| Cabbage Looper<br>Imported Cabbageworm<br>Diamondback Moth | Cole Crops (Brassica Leafy Vegetables)<br>Leaves of Root and Tuber Vegetables<br>Root Vegetables | 35-50 | 5 days |
| Codling Moth<br>Walnut and Butternut Curculios[1]<br>Walnut Husk Fly[1] | Tree Nuts[1] | 105 | 14 days |
| Colorado Potato Beetle[1] | Potato[1] | 40-60 | 7 days |
| European Corn Borer[1] | Potato[1] | 40 | 7 days |
| Eyespotted Bud Moth[1] | Pome Fruits | 52.5-105 | 14 days |
| Fruittree and European Leafrollers[1] | Pome Fruits<br>Tree Nuts[1] | 52.5-105 | 14 days |
| Grape Berry Moth (suppression) | Grape | 70 | 5 days |
| Obliquebanded Leafroller | Caneberries | 25-50 | 5 days |
| Obliquebanded and Threelined (Pandemis) Leafrollers | Pome Fruits<br>Stone Fruits<br>Tree Nuts[1] | 52.5-105 | 14 days |
| Obliquebanded Leafroller[1]<br>Winter Moth[1] | Highbush Blueberry (Bushberries) | 25-50 | 6 days |
| Onion Thrips (suppression)[1]<br>Leek Moth (suppression)[1] | Bulb Vegetables[1] | 25-84 | 7 days |
| Oriental Fruit Moth | Pome Fruits<br>Stone Fruits | 105 | 14 days |
| Spotted and Western Tentiform Leafminers | Pome Fruits | 52.5-105 | 7 days |
| Thrips (suppression) | Strawberry | 50-70 | 3 days |

[1] Use added to the label of Delegate WG Insecticide (only) subsequent to initial registration.

### 1.2 Mode of Action

Refer to the PMRA Evaluation Report ERC2008-01, *Spinetoram (XDE-175)* for a description of the mode of action.

## 2.0 Methods of Analysis

### 2.1 Methods for Analysis of the Active Ingredient

The analytical methods provided for the analysis of the active ingredient and the impurities have been validated and assessed to be acceptable.

Refer to the PMRA Evaluation Report ERC2008-01, *Spinetoram (XDE-175)* for a detailed assessment of the methods of analysis.

## 3.0 Impact on Human and Animal Health

### 3.1 Toxicology Summary

A detailed review of the toxicological database for spinetoram is summarized in Evaluation Report ERC2008-01, *Spinetoram (XDE-175)*. Spinetoram is derived from the same soil bacteria as another currently registered pesticide active ingredient, spinosad (Regulatory Note REG2001-10, *Spinosad Success™ 480SC Naturalyte Insect Control Product, Conserve™ 480SC Naturalyte Insect Control Product*). Structurally, the two compounds are almost identical.

Certain core toxicology studies for spinetoram were either in progress or not yet conducted at the time of the initial registration petition. A request by the registrant to bridge the requirements for these studies to the spinosad database, pending their completion, was accepted in principle by the PMRA. This acceptance was based on an initial assessment showing a similar toxicity profile for both compounds.

As described in Evaluation Report ERC2008-01, *Spinetoram (XDE-175)*, spinetoram was not considered carcinogenic, genotoxic or neurotoxic. There was no indication of increased susceptibility of the young in the developmental toxicity studies, although fetal death was observed at maternally toxic doses in the rat reproduction study. The most consistent finding following repeated dosing in rats, mice and dogs was vacuolation and/or aggregates of macrophages in a variety of tissues, including thyroid gland, kidneys, spleen, lungs and hematopoietic system, but primarily those of the lymphoid system. The vacuolation appeared to be consistent with effects produced by cationic amphiliphic drugs (CADs) which induce phospholipidosis. Scientific literature on CADs indicate that lung macrophages may be more susceptible to the effects of spinetoram due to the high phagocytic activity towards phospholipids in the alveolar lining (Pauluhn, 2004; Halliwell, 1997; Reasor, 1988; Lüllmann et al, 1975). The potential for increased sensitivity of the lungs following repeated inhalation exposure necessitated the application of extra protective factors in the inhalation risk assessment to further reduce the allowable level of human exposure to spinetoram.

The following confirmatory toxicology studies/information with spinetoram were required at the time of issuance of the conditional registration: the 2-year chronic toxicity/carcinogenicity study in rats, a 90-day inhalation study, and information identifying the contents of the vacuoles (histochemical analysis) observed in various tissues of lymphoid and endocrine systems. The 2-year chronic toxicity/carcinogenicity study in rats and a request to waive the requirement for the 90-day inhalation toxicity study, that included literature references to address the content of the vacuoles, were received for review by the PMRA. The current assessment takes into account this newly submitted information as well as knowledge of the spinosad toxicology database. The toxicology profile of spinosad is described in Regulatory Note REG2001-10, *Spinosad Success™ 480SC Naturalyte Insect Control Product, Conserve™ 480SC Naturalyte Insect Control Product*.

The 2-year chronic toxicity/carcinogenicity study in rats provided evidence that spinetoram was not carcinogenic. Treatment-related effects at the two highest doses included a slight decrease in body weight and body weight gain in males. Increased heart (both sexes) and liver (females) weights were also observed at these doses. Histopathological findings at the two highest doses included an increase in vacuolation of epithelial cells of the thyroid follicles in both sexes, and increased incidences of aggregates of macrophages/histiocytes in the mesenteric and mediastinal lymph nodes, white pulp of the spleen, and Peyer's patches of the ileum (females only). At the highest dose, effects also included increased incidences of macrophages/histiocytes in the mesenteric lymph nodes of males, and multifocal aggregates of alveolar macrophages and bilateral retinal degeneration and vacuolation of retinal cells in females. These study findings were largely consistent with those observed in the spinosad 2-year rat study. In addition, the study with spinetoram included a neurotoxicity component that indicated there were no histopathological findings in any of the examined neurological tissues.

The rationale presented in the inhalation study waiver request did not adequately address the concern that lung tissues may be more susceptible to the effects of spinetoram following repeated inhalation exposure. The literature suggests that the behaviour of CADs is not a class-wide phenomenon as there are various effects and degrees of severity of response among CADs (Shayman, 2012; Lüllmann, 1975; Halliwell, 1997; Lüllmann, 1978; Schneider,1992; Reasor, 1988). The literature references cited by the registrant with respect to lung macrophage susceptibility were specific to the oral route of exposure. This information did not address how the severity or magnitude of the response may change following inhalation dosing. In addition, it did not address functional consequences that may arise as a result of this change. A 90-day inhalation study was not available in the spinosad database. A summary of a 14-day inhalation study using spinosad, cited by the registrant in the waiver request but not submitted to the PMRA, utilized dose concentrations that were too low to elicit any response. Since lung alveolar macrophages may have a pronounced susceptibility to the effects of CADs, likely due to their continuous phagocytic uptake of phospholipid-rich surfactant material from the alveolar lining, there remains uncertainty as to the toxicity of spinetoram following repeat inhalation exposure. Therefore, a database uncertainty factor of 3-fold is appropriate for assessing the risk associated with repeat-dose inhalation scenarios.

The registrant did not provide any new studies which characterized the contents of the vacuoles. The overall findings in the supporting toxicology databases for spinetoram and spinosad suggest that these technical grade active ingredients behave in the same manner as CADs as described in the supporting literature, for which the content of the vacuoles is well understood. No observable adverse effect level (NOAELs) for these findings have been identified in the database for oral studies of various durations and in various species, as well as following repeated dermal exposure.

Results of the 2-year chronic toxicity/carcinogenicity study with spinetoram are summarized in Appendix I, Table 2. In addition, there were minor editorial errors in the mouse oncogenicity study results contained in the Toxicity Profile table of Evaluation Report ERC2008-01, *Spinetoram (XDE-175)*. Consequently, the amended version is included in Table 2 of the current document. The toxicology endpoints for human health risk assessment were revisited in light of the newly submitted information, as well as in consideration of the combined findings in both the spinosad and spinetoram databases, and are summarized in Appendix I, Table 3.

**Incident Reports**

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set timeframe. Information on the reporting of incidents can be found at the PMRA website. Incidents from Canada and the United States were searched and reviewed for spinetoram. As of 3 October 2012, there were no incidents related to spinetoram in the PMRA incident reporting database; however, there was one human incident reported for spinosad. A resident of the United States reported irritated eyes after being exposed, during application, to an end-use product containing spinosad. No changes are required to the risk assessment as a result of this information.

### 3.1.1 Pest Control Products Act Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for spinetoram. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of the young in the developmental toxicity studies. In the 2-generation rat reproductive toxicity study, an increased incidence of post-implantation loss and late resorbing/retained fetuses, was observed at the highest dose tested; however, this occurred in the presence of maternal toxicity (dystocia and animal sacrifice due to moribund condition).

Overall, the database is adequate for determining the sensitivity of the young, and effects on the young are well-characterized. Although the fetal effects in the reproduction study were considered serious endpoints, the concern was tempered by the presence of maternal toxicity suggesting that a 3-fold *Pest Control Products Act* factor would be required. However, the endpoints selected for risk assessment provide an intrinsic margin to the endpoint of fetal loss. Consequently, the *Pest Control Products Act* factor has been reduced to 1-fold.

### 3.2 Acute Reference Dose (ARfD)

An endpoint of concern attributable to a single oral exposure was not identified in the oral toxicity studies, and thus an acute reference dose is not required.

### 3.3 Acceptable Daily Intake (ADI)

To estimate the risk of repeated dietary exposure, the 1-year dietary dog study with spinetoram with a NOAEL of 2.49 mg/kg bw/day was selected. At the lowest observable adverse effect level (LOAEL) of 5.36 mg/kg bw/day, arteritis accompanied by necrosis of the arterial wall in various tissues was observed. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. **The composite assessment factor (CAF) is 100.**

The ADI was calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{2.49 \text{ mg/kg bw/day}}{100} = 0.03 \text{ mg/kg bw/day of spinetoram}$$

The ADI provides a margin of > 300 to the NOAEL for increased post-implantation loss and late resorbing/retained fetuses in the reproduction study. The selection of this ADI is considered to be protective of all populations, including the unborn children and nursing infants of exposed women.

**Cancer Assessment**

There was no evidence of carcinogenicity and, therefore, a cancer risk assessment was not necessary.

### 3.4 Occupational and Residential Risk Assessment

Refer to the PMRA Evaluation Report ERC2008-01, *Spinetoram (XDE-175)* for a detailed assessment of the occupational and residential risk assessment.

### 3.4.1 Toxicological Endpoints

**Short-, Intermediate- and Long-term Dermal**

A 28-day dermal study in rats with spinetoram was considered the most appropriate study for dermal risk assessment for all durations. The study was well-conducted and included histopathological examination of the target tissues of toxicity, including kidney and thyroid. No treatment-related effects were observed up to the limit dose of 1000 mg/kg bw/day. This study was also considered appropriate for the intermediate- and long-term scenarios as there did not appear to be any significant durational effect observed in the database. However, this study was not designed to assess reproductive parameters and it did not include measurements of thyroid hormone levels, endpoints that were identified at a dose of 75 mg/kg bw/day in the 2-generation reproduction study with spinetoram. The NOAEL for these effects was 10 mg/kg bw/day. Facial/perineal soiling and increased pigmentation in the kidneys were used as an indication of toxicity at the same dose level at which incidences of dystocia occurred. In addition, the results of the 90-day rat study revealed that histopathological alterations in thyroid (vacuolation) were occurring at doses (32/40 mg/kg bw/day) well below those at which any changes in thyroid hormones were reported (128/159 mg/kg bw/day). None of these effects (clinical signs, kidney and thyroid pathology) were observed in the 28-day dermal study, providing assurance that selection of the NOAEL from the dermal study affords protection to the reproductive and thyroid hormone endpoints. The target margin of exposure (MOE) is 100. Ten-fold uncertainty factors were applied each for interspecies extrapolation and intraspecies variability. The selection of this study and MOE is considered to be protective of all populations including nursing infants and the unborn children of exposed women. For the residential risk assessment (short-term), the *Pest Control Products Act* factor was reduced to 1-fold for the reasons discussed in the *Pest Control Products Act* Hazard Characterization section.

**Short-term Inhalation**

No repeat-dose inhalation studies were available for consideration, and therefore it was considered appropriate to default to an oral study for endpoint selection. The NOAEL of 4.9 mg/kg bw/day from the spinosad 90-day dog dietary study was chosen for the short-term inhalation risk assessment. Although a NOAEL for vacuolation of tissues was not determined for males in the 90-day dog dietary study with spinetoram (LOAEL of 5.7 mg/kg bw/day), the combined results of the spinetoram and spinosad dog studies were considered for determination of an overall NOAEL for this endpoint. The 90-day study duration was relevant, and in addition to general signs of toxicity, the predominant finding in the database of vacuolation in several tissues was observed. The target MOE is 300, which includes the standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, along with an additional 3-fold database uncertainty factor to address the potential increased susceptibility of lung alveolar macrophages following repeat inhalation exposure. The selection of this MOE is considered to be protective of all populations including the unborn children and nursing infants of exposed women. For the residential risk assessment, the *Pest Control Products Act* factor was reduced to 1-fold for the reasons discussed in the *Pest Control Products Act* Hazard Characterization section.

**Intermediate- and Long-term Inhalation**

No repeat-dose inhalation studies were available for consideration, and therefore it was considered appropriate to default to an oral study for endpoint selection. The NOAEL of 2.49 mg/kg bw/day from the spinetoram 1-year dog dietary study was chosen for the intermediate- and long-term inhalation risk assessments. Arteritis accompanied by necrosis of the arterial wall was observed at the LOAEL of 5.63 mg/kg bw/day. Although no pronounced durational effect was observed, the 1-year dog dietary study was considered of relevant duration and provided the lowest NOAEL in the database. The target MOE is 300, which includes the standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, along with an additional 3-fold database uncertainty factor to address the potential increased susceptibility of lung alveolar macrophages following repeat inhalation exposure. The selection of this MOE is considered to be protective of all populations including the unborn children and nursing infants of exposed women.

## 3.5 Food Residues Exposure Assessment

### 3.5.1 Residues in Plant and Animal Foodstuffs

Refer to Evaluation Report ERC2008-01, *Spinetoram (XDE-175)* for a summary of data reviewed and the rationale for the regulatory decision. The information captured herein relates to new information provided to the Agency in support of a conversion from conditional to full registration.

The orange and grape processing field trial data requirement identified in the Evaluation Report ERC2008-01, *Spinetoram (XDE-175)* were submitted and deemed to be adequate. The processing data confirm that residues of spinetoram in citrus oil, resulting from oranges treated according to approved label directions, will exceed the MRL of 3 ppm as listed in EMRL2008-28, *Spinetoram*. From the grape processing study, it was determined that the MRL for grape juice (1.0 ppm) and raisins (0.70 ppm) will no longer be required since residues of spinetoram in juice and raisins will be covered by the MRL for crop subgroup 13-07F (except gooseberry), which will be revised from 0.4 ppm to 0.5 ppm.

### 3.5.2 Dietary Risk Assessment

A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.14), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

#### 3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following assumptions were made in a refined chronic analysis: median residues of spinetoram, % crop treated, anticipated residue values for all animal commodities. The refined chronic aggregate exposure from food and water from all supported spinetoram food uses for the total population, including infants and children, and all representative population subgroups is considered acceptable. The PMRA estimates that chronic dietary exposure to spinetoram from food and water is 5.5% (0.001366 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 1-2 yrs old at 11.3% (0.001137 mg/kg bw/day) of the ADI.

#### 3.5.2.2 Acute Dietary Exposure Results and Characterization

No appropriate endpoint attributable to a single dose for the general population (including children and infants) was identified. Therefore, no acute dietary exposure assessment was conducted.

### 3.5.3 Aggregate Exposure and Risk

The aggregate risk for spinetoram consists of exposure from food and drinking water sources only; there are no residential uses. Aggregate risks were calculated based on a chronic endpoint. There was no acute endpoint identified for the general population, including infants and children.

### 3.5.4 Maximum Residue Limits

**Table 3.5.1 Proposed Revisions to Maximum Residue Limits**

| MRL (ppm) | Commodity |
|---|---|
| 9.0[1] | Citrus oil |
| 0.5[2] | Small fruit vine climbing subgroup except fuzzy kiwifruit [crop subgroup 13-07F (except gooseberry): Amur river grape; grape; kiwifruit, hardy; maypop; schisandra berry; cultivars, varieties, and/or hybrids of these.] |

[1] Based on newly submitted data.The MRL/US Tolerance for citrus oil is currently established at 3.0 ppm, whereas Codex has no MRL estabished on citrus oil.

[2] MRLs previously established on raisins (0.70 ppm), and grape juice (1.0 ppm) will now be covered by the raw agricultural commodity (RAC) MRL (0.4 ppm). Please note that the current MRL of 0.4 ppm is proposed to be revised to 0.5 ppm in order to facilitate international trade.

## 4.0 Impact on the Environment

Refer to the PMRA Evaluation Report ERC2008-01, *Spinetoram (XDE-175)* for a detailed assessment of the environmental impacts of spinetoram and its end-use products, Delegate WG Insecticide and Radiant SC Insecticide.

## 4.1 Fate and Behaviour in the Environment

The properties and environmental fate characterization of spinetoram have been previously reviewed and reported in Evaluation Report ERC2008-01, *Spinetoram (XDE-175)*.

## 4.2 Environmental Risk Characterization

### 4.2.1 Risks to Terrestrial Organisms

The potential environmental impacts of spinetoram on terrestrial organisms have been previously reviewed and reported in Evaluation Report ERC2008-01, *Spinetoram (XDE-175)*.

### 4.2.2 Risks to Aquatic Organisms

The potential impacts of spinetoram on aquatic organisms have been previously reviewed and reported in Evaluation Report ERC2008-01, *Spinetoram (XDE-175)*.

Two acute toxicity studies of spinetoram to the freshwater invertebrate, *Daphnia magna*, and the rainbow trout, *Oncorhynchus mykiss*, were submitted to address data gaps identified in Evaluation Report ERC2008-01, *Spinetoram (XDE-175)*. A revised risk assessment was conducted for aquatic organisms.

When Delegate WG Insecticide and Radiant SC Insecticide are applied at the maximum rate of 105 g a.i./ha, three times at 7-day intervals, spinetoram is not expected to pose an acute risks to aquatic organisms.

The risk quotients for chronic exposure of freshwater invertebrates (daphnids and benthic organisms) to spinetoram exceeded the level of concern at the screening level (see Appendix I, Table 6 and Evaluation Report ERC2008-01, *Spinetoram (XDE-175)*). The risk was further characterized by assessing the potential risks from spray drift and runoff separately. The outcome of the risk assessment for runoff is unchanged from the original assessment. Spinetoram may pose a risk to freshwater invertebrates from chronic exposure through runoff into water bodies (see Evaluation Report ERC2008-01, *Spinetoram (XDE-175)*). A statement to inform users of the potential risks to the environment is required on the product labels.

The outcome of the risk assessment for exposure through spray drift has changed since the original risk assessment. In the absence of a full data package for acute effects on aquatic organisms, a chronic no observed effect concentration (NOEC) of 0.00006 mg a.i./L for the freshwater invertebrate, *Daphnia magna*, was used in the calculation of no-spray buffer zones to protect sensitive aquatic habitats.

Acceptable acute toxicity studies have since been submitted to address the data deficiency. Results indicate that acute exposure to spinetoram is not expected to pose a risk to aquatic organisms. Furthermore, chronic exposure to spinetoram from spray drift is not expected, based on the rapid dissipation of this compound under aquatic field conditions ($DT_{50}$ is less than 1 day). Based on these points, risks to aquatic organisms from spray drift of spinetoram are not expected. The no-spray buffer zones which were originally required in the absence of acute toxicity data for the protection of non-target aquatic organisms are no longer required on the product labels.

# 5.0 Value

Refer to the PMRA Evaluation Report ERC2008-01, *Spinetoram (XDE-175)* for a detailed value assessment of the end-use products, Delegate WG Insecticide and Radiant SC Insecticide. Subsequent to initial registration, additional value data were submitted to support the addition of uses to the label of Delegate WG Insecticide (Table 1.1.1).

# 6.0 Pest Control Product Policy Considerations

## 6.1 Toxic Substances Management Policy Considerations

Refer to Evaluation Report ERC2008-01, *Spinetoram (XDE-175)* for information on the Toxic Substances Management Policy considerations for spinetoram.

## 6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[5] The list is used as described in the PMRA Notice of Intent NOI2005-01[6] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[7] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade spinetoram does not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

---

5 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette,* Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

6 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act*.

7 DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

- The end-use product, Delegate WG Insecticide, does not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

- The end-use product, Radiant SC Insecticide, contains the preservative 1,2-benzisothiazoline-3-one which contains low levels of dioxins and furans. These are being managed as outlined in the PMRA Regulatory Directive DIR99-03 for the implementation of TSMP.

- The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

# 7.0 Summary

## 7.1 Human Health and Safety

The toxicology database submitted for spinetoram is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of carcinogenicity in rats or mice after longer-term dosing. Spinetoram was not neurotoxic or genotoxic. Fetal loss occurred in the presence of maternal toxicity (dystocia and animal sacrifice due to moribund condition). The most consistent finding following repeated dosing in rats, mice and dogs was vacuolation and/or aggregates of macrophages in a variety of tissues, including endocrine-sensitive tissues, but primarily those of the lymphoid system. The vacuolation appeared to be consistent with effects produced by CADs which induce phospholipidosis. Since lung alveolar macrophages may have a pronounced susceptibility to the effects of CADs, likely due to their continuous phagocytic uptake of phospholipid-rich surfactant material from the alveolar lining, there remains uncertainty as to the toxicity of spinetoram following repeat inhalation exposure. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

## 7.2 Environmental Risk

A detailed assessment of the environmental impact of spinetoram and its end-use products, Delegate WG Insecticide and Radiant SC Insecticide, is provided in Evaluation Report ERC2008-01, *Spinetoram (XDE-175)*. The use of these products may pose a risk to bees, predatory and parasitic arthropods, wild mammals and non-target terrestrial plants. Risks can be mitigated with no-spray buffer zones to protect sensitive terrestrial habitats from spray drift and through the use of label statements to inform users of potential risks to the environment.

The data submitted to address the deficiencies identified in Evaluation Report ERC2008-01, *Spinetoram (XDE-175)* indicate that spinetoram poses a negligible acute risk to aquatic organisms. Chronic exposure from runoff may pose a risk to aquatic invertebrates, as previous outlined in Evaluation Report ERC2008-01, *Spinetoram (XDE-175)*. Exposure from spray drift of spinetoram is not expected to result in risk to aquatic organisms. No-spray buffer zones which were originally required on the product labels in the absence of acute toxicity data are no longer required, based on newly submitted data.

### 7.3 Value

Spinetoram and the end-use products Radiant SC Insecticide and Delegate WG Insecticide have value in providing control or suppression of various insect pests on pome fruits, stone fruits, tree nuts, caneberries, bushberries, cranberry, strawberry, grape, asparagus (fern), bulb vegetables Brassica leafy vegetables, leaves of root and tubers, root vegetables, fruiting vegetables, leafy vegetables (non-Brassica), cereals and soybean. Spinetoram provides an alternative active ingredient for uses that have traditionally relied on older classes of chemistry as well as uses that have few other registered alternatives.

## 8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Spinetoram Technical Insecticide and Radiant SC Insecticide and Delegate WG Insecticide, containing the technical grade active ingredient spinetoram, to control or suppress a variety of foliage-feeding insect pests in orchard, vineyard, and field crops.

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.

# List of Abbreviations

| Acronym | Definition |
|---|---|
| a.i. | active ingredient |
| ADI | acceptable daily intake |
| bw | body weight |
| bwg | body weight gain |
| CAD | cationic amphiliphic drugs |
| CAF | composite assessment factor |
| cm | centimetre(s) |
| DACO | data code |
| DEEM | Dietary exposure evaluation model |
| $DT_{50}$ | dissipation time 50% (the time required to observe a 50% decline in concentration) |
| $EC_{50}$ | effective concentration on 50% of the population |
| EEC | estimated environmental concentration |
| EPA | Environmental Protection Agency |
| fc | food consumption |
| FDA | Food and Drugs Act |
| g | gram(s) |
| GAP | good agricultural practices |
| ha | hectare(s) |
| HPLC | High performance liquid chromatography |
| ID | idenfication |
| kg | Kilogram (s) |
| L | litre |
| $LC_{50}$ | lethal concentration 50% |
| LOAEL | lowest observed adverse effect level |
| LOD | limit of detection |
| LOQ | limit of quantitation |
| mg | milligram(s) |
| MOE | margin of exposure |
| MRL | maximum residue limit |
| MS | mass spectrometry |
| NOAEL | no observed adverse effect level |
| NOEC | no observed effect concentration |
| PHI | preharvest interval |
| PMRA | Pest Management Regulatory Agency |
| ppm | parts per million |
| RAC | raw agricultural commodity |
| rel | relative |

| Acronym | Definition |
|---|---|
| RQ | risk quotient |
| SC | soluble concentrate |
| TGAI | Technical grade active ingredient |
| TSMP | Toxic Substance Management Policy |
| US | United States |
| wt | weight |

# Appendix I Tables and Figures

## Table 1 Residue Analysis

| Matrix | Method ID | Analyte | Method Type | LOQ | Reference |
|---|---|---|---|---|---|
| Soil and Sediment | GRM 07.04 | XDE-175-J | HPLC-MS/MS 748.6, 142.2 m/z | 0.0077 ppm | 2026329 |
| | | XDE-175-L | HPLC-MS/MS 760.9, 142.2 m/z | 0.0074 ppm | 2026329 |
| | | N-Demethyl-175-J | HPLC-MS/MS 734.9, 128.2 m/z | 0.0024 ppm | 2026329 |
| | | N-Demethyl-175-L | HPLC-MS/MS 746.7, 128.2 m/z | 0.0054 ppm | 2026329 |
| | | N-demethyl-N-nitroso-175-J | HPLC-MS/MS 763.8, 157.2 m/z | 0.0064 ppm | 2026329 |
| | | N-demethyl-N-nitroso-175-L | HPLC-MS/MS 775.5, 157.3 m/z | 0.0063 ppm | 2026329 |
| | | O-demethyl-175-J | HPLC-MS/MS 734.8, 142.2 m/z | 0.0025 ppm | 2026329 |
| | | O-demethyl-175-L | HPLC-MS/MS 746.6, 142.2 m/z | 0.0062 ppm | 2026329 |
| | | 3'-O-deethyl-175-J | HPLC-MS/MS 720.5, 142.2 m/z | 0.0055 ppm | 2026329 |
| | | 3'-O-deethyl-175-L | HPLC-MS/MS 732.8, 142.2 m/z | 0.0068 ppm | 2026329 |
| | | N-succinyl-175-J | HPLC-MS/MS 834.5, 228.2 m/z | 0.0069 ppm | 2026329 |
| | | N-succinyl-175-L | HPLC-MS/MS 846.7, 228.2 m/z | 0.0046 ppm | 2026329 |

## Table 2 Toxicity Profile of Technical Spinetoram

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

| Study Type/Animal PMRA # | Study Results |
|---|---|
| 2-year dietary<br>(with neuropathology component)<br><br>Fischer rat<br><br>PMRA #1459537 | NOAEL = 10.8/13.2 mg/kg bw/day<br>LOAEL = 21.6/26.6 mg/kg bw/day; ↑ vacuolation of epithelial cells of the thyroid follicles; ↓ bw & bwg, ↑ rel heart wt (♂); ↑ incidence of aggregates of macrophages/histiocytes in mesenteric and mediastinal lymph nodes, white pulp of the spleen (↑multifocal aggregates), Peyer's patches of the ileum (↑ multifocal aggregates) (♀)<br><br>**No evidence of carcinogenicity**<br>**No neuropathological alterations observed** |
| 78-week dietary<br><br>CD-1 mouse<br><br>PMRA#1424875 | NOAEL = 18.8/23.9 mg/kg bw/day<br>LOAEL = 37.5/46.6 mg/kg bw/day; hyperplasia and/or chronic inflammation of glandular mucosa or submucosa of the stomach, ↑ incidence of aggregates of alveolar macrophages in the lungs; cytoplasmic vacuolation of epithelial cells of the epididymides (♂); ↓ bwg & fc (♀).<br><br>**No evidence of carcinogenicity** |

## Table 3 Toxicology Endpoints for Use in Health Risk Assessment for Spinetoram

| Exposure Scenario | Study | Point of Departure and Endpoint | CAF[1] or Target MOE |
|---|---|---|---|
| Acute dietary general population | Not established as no appropriate endpoint warranting the setting of an acute reference dose. | | |
| Repeated dietary | 1-year dog dietary study | NOAEL = 2.49 mg/kg bw/day<br>Increased liver weights, arteritis accompanied by necrosis of the arterial wall in various lymphoid tissues | 100 |
| | ADI = 0.03 mg/kg bw/day | | |
| Dermal – all durations | 28-day rat dermal study | NOAEL = 1000 mg/kg bw/day<br>No systemic effects observed. | 100 |
| Short-term inhalation[2] | 90-day dog dietary study (spinosad) | NOAEL = 4.9 mg/kg bw/day<br>Vacuolation in various lymphoid tissues; clinical signs of toxicity; decreased mean body weight and food consumption; evidence of anemia and possible liver damage | 300 |
| Intermediate- and long-term inhalation[2] | 1-year dog dietary study | NOAEL = 2.49 mg/kg bw/day<br>Increased liver weights, arteritis accompanied by necrosis of the arterial wall in various lymphoid tissues | 300 |
| Cancer | No evidence of carcinogenicity. | | |

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments;
MOE refers to a target MOE for occupational assessments

[2] Since an oral NOAEL was selected, an inhalation factor was used in route-to-route extrapolation.

## Table 4 Integrated Food Residue Chemistry Summary

| **Processing Studies in/on Oranges.** | **PMRA No. 1096667; 1947937** |
|---|---|

Spinetoram, 120 g/L, a water dispersible granule formulation (GF-1640 WG), was applied to Valencia oranges at 85 to 87 BBCH plant growth stage in EPA region 3. The samples were harvested at a PHI of 1 day. The approximate rate of application was 347 g a.i./ha, applied 3 times at intervals of 4 days for an approximate total of 1050 g a.i./ha/season (5-fold US GAP) with spray volumes of 365 to 739 L/ha. The orange samples were processed into peel, pulp, dried pulp, juice, and oil.

Total residues of XDE-175 (XDE-175-L, XDE-175-J, *N*-demethyl-175-J and *N*-formyl-175-J) were determined using analytical method GRM 05.04, involving HPLC-MS/MS. The limit of detection (LOD) and limit of quantitation (LOQ) for each analyte were 0.003 ppm and 0.01 ppm, respectively. The average recoveries were between 68 and 113% for each analyte at each spiking level in whole oranges and the processed fractions.

The samples from this study were stored at -20°C from 14 days to 29 days from the date of sample collection to analysis (including processing), well within the demonstrated storage time of the stability study (372 days) for RACs and processed commodities.

**Residue Data from Orange Processing Study with Spinetoram.**

| RAC | Processed Commodity | Total Rate (g a.i./ha) | PHI (days) | Residues[1] (ppm) | Processing Factor | Empirical Factor[2] |
|---|---|---|---|---|---|---|
| Oranges | Fresh oranges | 1050 | 1 | 0.280* | -- | -- |
| | Peel | | | 0.384 | 1.4 | 3.3 |
| | Pulp | | | 0.087 | 0.3 | -- |
| | Dried pulp | | | 0.632 | 2.3 | -- |
| | Juice | | | 0.003 | 0.01 | 2.0 |
| | Oil | | | 32.23 | 115 | 1000 |

A comparison of the residues in the RAC with those in each processed fraction resulted in processing factors of 1.4, 0.3, 2.3, 0.01, and 115 for orange peel, pulp, dried pulp, juice, and oil, respectively. These processing factors were less than the theoretical processing factors.

* represents the average from 2 trials.

[1] Residues represent the sum of XDE--175-L, XDE-175-J, *N*-demethyl-XDE-175-J and *N*-formyl-XDE-175-J)

[2] Dir98-02; Section 10-12 (Table 1)

| **Residue Data from Grape Processing Study with Spinetoram.** | **PMRA No. 1947935** |
|---|---|

The field residue trials for processing of table grapes were carried out in Southern France; whereas trials for wine grapes were conducted in Northern France. Spinetoram, 120 g/L suspension concentrate (GF-1587), was applied to table and wine grapes at 85 to 87 BBCH plant growth stage. The trial sites represent typical European crop growing areas. Four applications of 42 g a.i./ha were applied to grapes, with water volumes of approximately 500-900 L/ha, for a total of 168 g a.i./ha/season. Samples of grapes were harvested 7 days after the last application. Table grapes were processed into raisins. Wine grapes were processed into juice, dry pomace, young wine and bottle wine.

Total residues of XDE-175 (XDE-175-L, XDE-175-J, *N*-demethyl-175-J and *N*-formyl-175-J) were determined using analytical method GRM 05.04, involving HPLC-MS/MS. The limit of detection (LOD) and limit of quantitation (LOQ) for each analyte were 0.003 ppm and 0.01 ppm, respectively. The recovery data shows the method performed well over the course of the study with recoveries within guideline levels (70 to 120%) for each analyte at each spiking level in grapes and the processed fractions.

| Matrix | Total Rate (g a.i.ha) | PHI (days) | Residues[1] (ppm) | Processing Factor | Empirical Factor[2] |
|---|---|---|---|---|---|
| **Table Grapes (Southern France)** | | | | | |
| RAC | 168 | 7 | 0.057 | -- | -- |
| Raisins | | | 0.092 | 1.6 | 4.3 |
| **Wine Grapes (Northern France)** | | | | | |
| RAC | 168 | 7 | 0.067 | -- | -- |
| Juice | | | 0.067 | 1.0 | 1.2 |
| Dry pomace | | | 0.243 | 3.6 | -- |
| Young wine | | | <0.01 | -- | -- |
| Bottled wine | | | <0.01 | -- | -- |

A comparison of the residues in the RAC with those in each processed fraction resulted in processing factors of 1.6 (raisins), and 3.6 (grape dry pomace). There was no concentration of residues of spinetoram in wine, and juice. These processing factors were less than the theoretical processing factors.

[1] Residues represent the sum of XDE--175-L, XDE-175-J, *N*-demethyl-XDE-175-J and *N*-formyl-XDE-175-J)

[2] Dir98-02; Section 10-12 (Table 1)

## Table 5 Toxicity of Spinetoram (XDE-175) to Aquatic Organisms

| **Organism** | **Exposure** | **Test substance** | **Endpoint value [1] (mg a.i./L)** | **Degree of toxicity [3]** |
|---|---|---|---|---|
| **Freshwater species** | | | | |
| *Daphnia magna* | acute | XDE-175 | $EC_{50}$: 3.4[2]<br>NOEC: <0.094 [2] | moderately toxic |
| | chronic | XDE-175 | $EC_{50}$: >0.000261<br>NOEC: 0.000062 | |
| *Chironomus sp* (midge) | chronic | XDE-175 | sediment mg a.i./kg:<br>$EC_{50}$: 0.24; NOEC: 0.0957<br>pore water:<br>$EC_{50}$: 0.0028; NOEC: 0.0016 | adverse effects at >0.0016 mg a.i./L pore water |
| Bluegill sunfish | acute | XDE-175 | $EC_{50}$: 2.69<br>NOEC: <0.988 | moderately toxic |
| Rainbow trout | acute | XDE-175 | $LC_{50}$: 3.48 [2]<br>NOEC: 1.19 [2] | moderately toxic |
| Fathead minnow | chronic | XDE-175 | NOEC: >0.186 | |
| Freshwater alga blue-green | acute | XDE-175 | $EC_{50}$: >15.2<br>NOEC: 15.2 | |
| Freshwater alga green alga | acute | XDE-175 | $EC_{50}$: 0.620<br>NOEC: 0.152 | |
| Freshwater diatom | acute | XDE-175 | $EC_{50}$: 0.13<br>NOEC: 0.013 | |

| Organism | Exposure | Test substance | Endpoint value [1] (mg a.i./L) | Degree of toxicity [3] |
|---|---|---|---|---|
| Vascular plant | acute | XDE-175 | $EC_{50}$: >14.2<br>NOEC: 6.63 | |
| **Marine species** | | | | |
| Crustacean (mysid shrimp) | acute | XDE-175 | $EC_{50}$: 0.355<br>NOEC: 0.076 | highly toxic |
| | chronic | XDE-175 | NOEC: <0.0194 | |
| Mollusk (Eastern oyster) | acute (shell deposition) | XDE-175 | $EC_{50}$: 0.393<br>NOEC: 0.084 | highly toxicity |
| Sheepshead minnow | acute | XDE-175 | $LC_{50}$: 7.87<br>NOEC: 1.8 | moderately toxic |
| | early life stages | XDE-175 | NOEC: 1.73 | |
| Marine diatom | acute | XDE-175 | $EC_{50}$: 0.086<br>NOEC: 0.014 | very highly toxic |

1 All data are from the original review of spinetoram (ERC2008-01, *Spinetoram (XDE-175)*), unless otherwise noted.
2 Data submitted to address the deficiencies identified in ERC2008-01, *Spinetoram (XDE-175)*.
3 USEPA classification, where applicable.

## Table 6 Screening Level Risk Assessment for Aquatic Organisms

| Organism | Exposure | Endpoint value mg a.i./L | EEC (mg a.i./L)[2] | RQ[3] | Level of Concern Exceeded? |
|---|---|---|---|---|---|
| **Freshwater species** | | | | | |
| *Daphnia magna* | acute | $EC_{50}$: 3.4 | 0.013 | 0.008 | No |
| | chronic | NOEC:0.00006 | 0.013 | 217 | Yes[4] |
| Bluegill sunfish | acute | $LC_{50}$: 2.69[1] | 0.013 | 0.05 | No |
| Rainbow trout | acute | $LC_{50}$: 3.48 | 0.013 | 0.04 | No |
| Fathead minnow | chronic | NOEC: 0.186 | 0.013 | 0.07 | No |
| Amphibians | acute | $LC_{50}$: 2.69[1] | 0.07 | 0.26 | No |
| | chronic | NOEC: 0.186[1] | 0.07[1] | 0.38[1] | No |
| Benthic organisms (midge) | chronic | water NOEC:0.0016 | 0.013 | 8.13 | Yes[4] |
| Freshwater diatom | acute | $EC_{50}$: 0.13 | 0.013 | 0.2[1] | No |
| Vascular plant | acute | $EC_{50}$: 14.2 | 0.013 | 0.002 | No |
| **Marine species** | | | | | |
| Crustacean (mysid shrimp) | acute | $LC_{50}$: 0.355 | 0.013 | 0.07 | No |
| | chronic | NOEC: 0.0194 | 0.013 | 0.67 | No |
| Mollusk (Eastern oyster) | acute | $LC_{50}$: 0.393 | 0.013 | 0.066[1] | No |
| Sheepshead minnow | acute | $LC_{50}$: 7.87 | 0.013 | 0.02 | No |
| | chronic | NOEC: 1.73 | 0.013 | 0.01 | No |
| Marine diatom | acute | $EC_{50}$: 0.086 | 0.013 | 0.30[1] | No |

1 Values corrected from original risk assessment described in ERC2008-01, *Spinetoram (XDE-175)*
2 Screening level EEC in 15 cm water depth for amphibians and 80 cm depth for other aquatic organisms
3 Aquatic invertebrates, algae and plants (acute): RQ = EEC/($EC_{50}$÷2); Fish and amphibians (acute): EEC/($LC_{50}$÷10); chronic (all organisms): RQ = EEC/NOEC.
4 Risks from spray drift and from runoff were further characterized separately in ERC2008-01, *Spinetoram (XDE-175)*. It is noted that since the original review and the submission of acute toxicity data to address deficiencies, chronic risks from spray drift of spinetoram are not expected.

# References

## A. List of Studies/Information Submitted by Registrant

### 1.0 Chemistry

| PMRA Document Number | Reference |
|---|---|
| 1481689 | 2007, Packaging Stability Study to Assess the Compatibility of GF-1640 with Commercial Containers (Foil Laminate Overpack Bag), DACO: 3.5.10 CBI |
| 1483968 | 2007, Storage Stability and Package Corrosion Characteristics of GF1587; Two Year Ambient Study, DACO: 3.5.10,3.5.14 CBI |
| 1528289 | 2007, Group A: Product Identity and Composition, Discussion of Formation of Impurities, and Certified Limits for Spinetoram Technical -- Addendum to MRID No. 46695001, DACO: 2.11.4 |
| 1528290 | 2007, Analytical Method Validation for the Determination for XDE-175 (Spinetoram) in GF-1587, GF-1629 and GF-1640 Formulations and in XDE-175 Technical Grade Active Ingredient, DACO: 2.13.1 |
| 1528291 | 2007, Analytical Method and Validation for the Determination of Residual Solvent in Spinetoram (XDE-175) Technical by Gas Chromatography, DACO: 2.13.1 |
| 1528292 | 2007, Analytical Method and Validation for the Determination of Impurities in Spinetoram (XDE-175) Technical, DACO: 2.13.1 |
| 1528293 | 2007, Analysis of Product Samples for Impurities in Spinetoram (XDE-175) Technical Grade Active Ingredient, DACO: 2.13.2 |
| 1528294 | 2007, Analysis of Product Samples for Active Ingredient, Residual Solvents, and Water in Spinetoram (XDE-175) Technical Grade Active Ingredient, DACO: 2.13.3 |
| 2026321 | 2007, Group A: Product Identity and Composition, Discussion of Formation of Impurities, and Certified Limits for Spinetoram Tech, DACO: 2.11.4 CBI |
| 2026322 | 2007, Analytical Method and Validation for the Determination of XDE-175 (Spinetoram) in GF-1587, GF-1629 and GF-1640 Formulations and in XDE-175 TGAI, DACO: 2.13.1 CBI |
| 2026324 | 2007, Analytical Method and Validation for the Determination of Residual Solvent in Spinetoram (XDE-175) Technical by Gas Chromatography, DACO: 2.13.1 CBI |
| 2026326 | 2007, Analytical Method and Validation for the Determination of Impurities in Spinetoram (XDE-175) Tech, DACO: 2.13.1 CBI |

2026327 2007, Analysis of Product Samples for Impurities in Spinetoram (XDE-175) TGAI, DACO: 2.13.2 CBI

2026328 2007, Analysis of Product Samples for AI, Residual Solvents and Water in Spinetoram (XDE-175) TGAI, DACO: 2.13.3 CBI

2139029 2011, Group A - Product Identity and Composition, Description of Materials Used to Produce the Product, Description of Production Process, Discussion of Formation of Impurities, Preliminary Analysis, Certified Limits, and Enforcement Analytical Method for Spinetoram Technical, DACO: 2.11.3,2.11.4,2.12.1, 2.13.1,2.13.2,2.13.3 CBI

2026329 2007, Method Validation Report for the Determination of Residues of XDE-175 and its Metabolites in Soil using DAS method GRM 07.04, DACO: 8.2.2


## 2.0 Human and Animal Health

| PMRA Document Number | Reference |
|---|---|


1459537 2007, XDE- 175: Two-Year Chronic Toxicity / Oncogenicity and Chronic Neurotoxicity Study in F344/DuCrl Rat, DACO: 4.4.1

1943983 2008, Short Term Inhalation - Waiver, DACO: 4.3.6,4.8

1424875 2007, XDE-175: 18-Month Dietary Oncogenicity Study in Crl: CD1(ICR) Mice, DACO: 4.4.4


## 3.0 Environment

| PMRA Document Number | Reference |
|---|---|


1943988 2010, XDE-175 (Spinetoram)- Acute Toxicity to Water Fleas, (*Daphnia magna*) Under Static-Renewal Conditions. [CBI Removed], DACO 9.3.2.

1943989 2009, Spinetoram: Acute Toxicity Test with the Rainbow Trout, *Oncorhynchus mykiss*, Determined Under Flow-Through Conditions. [CBI Removed]. Laboratory Study No. 64878. Study report date: 17-September-2009. Sponsor Project No. 090153. pp. 64. DACO 9.5.2.1.

1947935 2007, Magnitude of the Residue of XDE-175 in Apples, Table Grapes and Wine Grapes from Europe - 2006, DACO: 7.4.5

1947937 2008, Magnitude of the Residues of Spinetoram in Apples, Leaf Lettuce, Tomatoes, sugar Beet Tops and Roots and Oranges and Orange Processing Fractions, DACO: 7.4.5

## B. Additional Information

### 1.0 Human Health


| PMRA Document Number | Reference |
|---|---|
| 1459073 | Lullmann, H., Lullmann-Rauch, R. and Wassermann, O, 1975, Drug-Induced Phospholipidoses, CRC Critical Review in Toxicology:185-218, DACO: 11.1, 4.8 |
| 1459077 | Reasor, M.J., 1988, A Review of the Biology and Toxicologic Implications of the Induction of Lysosomal Lamellar Bodies by Drugs, Toxicology and Applied Pharmacology, 97:47-56, DACO: 11.1, 4.8 |
| 1459080 | Halliwell, W.H., 1997, Cationic Amphiphilic Drug-Induced Phospholipidosis, Toxicologic Pathology, 25:53-60, DACO: 11.1, 4.8 |
| 1459083 | Lullmann, H., Lullmann-Rauch, R., Wassermann, O., 1978. Commentary - Lipidosis Induced by Amphiphilic Cationic Drugs, Biochemical Pharmacology, 27:1103-1108, DACO: 11.1, 4.8 |
| 1459084 | Schneider, P., 1992. Drug-induced lysosomal disorders in laboratory animals: new substances acting on lysosomes, Arch. Toxicol. 66:23-33, DACO: 11.1, 4.8 |
| 1459085 | Reasor, M.J. et al., 2001. Minireview - Drug-Induced Phospholipidosis: Are There Functional Consequences?, Society for Experimental Biology and Medicine, 226:825-830, DACO: 11.1, 4.8 |
| 2233990 | Pauluhn, J., 2004, Inhaled cationic amphiphilic drug-induced pulmonary phospholipidosis in rats and dogs: time-course and dose-response of biomarkers of exposure and effect., J. Pauluhn, Toxicology 207 (2005) 59-72, DACO: 4.8 |
| 2233995 | Shayman, J.A. and Abe, A., 2012, Drug induced phospholipidosis: An acquired lysosomal storage disorder., J.A. Shayman, A.Abe/Biochimica et Biophysica Acta 30(2012) 1388-1981, DACO: 4.8 |