Proposed Registration Decision PRD2015-05

Spinosad

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Overview

Proposed Registration Decision for Spinosad

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 Spinosad Technical Insecticide and Ortho Home Defense Max Ant Bait Stations, containing the technical grade active ingredient spinosad, to be used in a bait station to control ants and ant colonies.

Spinosad Technical Insecticide (Registration Number 26833) is registered in Canada for use in a variety of end-use products, which are used on greenhouse food and ornamental crops, outdoor food and ornamental crops and turf against a wide variety of insect pests. The detailed review for spinosad can be found in Regulatory Note REG2001-10, *Spinosad (XDE-175)*. Spinosad is considered toxicologically equivalent to a similar compound, spinetoram, and as such, the databases can be used in combination. The detailed review for spinetoram can be found in Evaluation Report ERC2008-01, *Spinetoram*. The current applications were submitted to add a major new use in and around structures.

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 Spinosad Technical Insecticide and Ortho Home Defense Max Ant Bait Stations.

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.

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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.

Before making a final registration decision on spinosad, 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 spinosad, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA 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 Spinosad?

Spinosad is a fermentation product of the bacterium *Saccharopolyspora spinosa* that must be eaten by the pest to be effective. It acts on insect nerves, causing paralysis and death. Products containing spinosad are also registered for use on greenhouse food and ornamental crops, outdoor food and ornamental crops, and turf against a wide variety of insect pests.

Health Considerations

Can Approved Uses of Spinosad Affect Human Health?

Ortho Home Defense Max Ant Bait Stations, containing spinosad, is unlikely to affect your health when used according to label directions.

Potential exposure to spinosad may occur when handling and applying the product. 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.

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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 pesticide-containing products are used according to label directions.

In laboratory animals, technical spinosad was of low acute toxicity via the oral, dermal and inhalation routes of exposure. It was minimally irritating to the eye and non-irritating to the skin, and did not cause an allergic skin reaction.

The end-use product, Ortho Home Defense Max Ant Bait Stations, was of low acute toxicity via the oral, dermal and inhalation routes of exposure. It was minimally irritating to the eye and non-irritating to the skin, but did cause an allergic skin reaction. Consequently, the statement, "Potential Dermal Sensitizer" is required on the label.

Spinosad did not cause cancer in laboratory animals and was non-genotoxic. There was no indication that spinosad caused damage to the nervous system. Health effects in animals given repeated doses of spinosad included effects on the thyroid gland, lymphoid tissues, kidneys, spleen and blood system. Spinosad did not cause birth defects in laboratory animals. When spinosad was given to pregnant animals, fetal death was observed at doses that produced significant toxicity in the mothers. There is uncertainty regarding the susceptibility of lungs following repeated inhalation exposure, necessitating the application of extra protective factors for inhalation risk assessment to further reduce the allowable level of human exposure to spinosad.

The risk assessment protects against the effects of spinosad by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests. In the case of Ortho Home Defense Max Ant Bait Stations, potential exposure is considered to be negligible as the product is an impregnated material bait that is enclosed in a ready-to-use bait station.

Risks in Residential and Other Non-Occupational Environments

Residential risks are not of concern when Ortho Home Defense Max Ant Bait Stations is used according to label directions and instructions.

Residential exposures to spinosad are considered negligible when adults place, replace and dispose of Ortho Home Defense Max Ant Bait Stations ready-to-use ant bait stations. Adults, youth, and children are not expected to be exposed by direct skin contact with spinosad residues since the bait is contained inside a sealed bait station. In addition, the label states to keep bait stations out of reach of children.

Residential exposures (application and post-application) to the end-use product are not expected to result in unacceptable risk when this product is used according to label directions. Precautionary and hygiene statements on the label are considered adequate to protect individuals from unnecessary risks due to placement or post-placement exposures.

Therefore, health risks to residents and bystanders are not of concern.

Occupational Risks From Handling Ortho Home Defense Max Ant Bait Stations

No occupational scenarios were proposed for this domestic product.

Environmental Considerations

What Happens When Spinosad Is Introduced Into the Environment?

When spinosad is used as ant bait in enclosed bait stations, for use indoors or outdoors around the perimeter of homes, there is very limited potential for release of spinosad to terrestrial or aquatic environments.

Wild birds and mammals, honeybees, earthworms and beneficial insects will not be exposed to spinosad in the bait stations and, therefore, the risk is expected to be negligible. Similarly, spinosad is not likely to enter surface waters from this use and, as such, risks to fish and other aquatic life are also negligible.

Value Considerations

What Is the Value of Ortho Home Defense Max Ant Bait Stations?

Ortho Home Defense Max Ant Bait Stations contain ant bait that kills ants and ant colonies. It is a domestic class product for use indoors and outdoors around the perimeter of homes.

Spinosad, formulated as bait in Ortho Home Defense Max Ant Bait Stations, kills ants and ant colonies. This product is not intended for use against carpenter ants. Spinosad is a new mode of action for use against ants in Canada.

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 Ortho Home Defense Max Ant Bait Stations to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

The primary label includes the phrase “KEEP OUT OF REACH OF CHILDREN” and in the Precautions section, statements include, “Keep away from food and drinks…” and “Do not eat, drink and smoke during use.”

Environment

The presence of petroleum distillate in the product warrants environmental hazard statements on the Ortho Home Defense Max Ant Bait Stations label. A label statement regarding the disposal of used product is also required to prevent contamination of ponds, waterways and ditches.

Next Steps

Before making a final registration decision on spinosad, 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 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 spinosad (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 Reading Room (located in Ottawa).

Science Evaluation

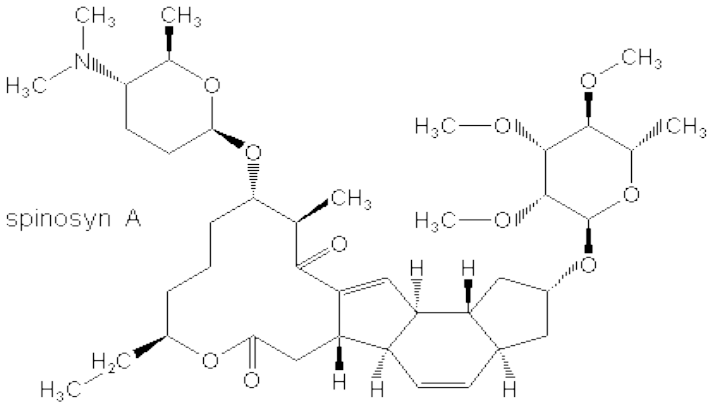
Spinosad

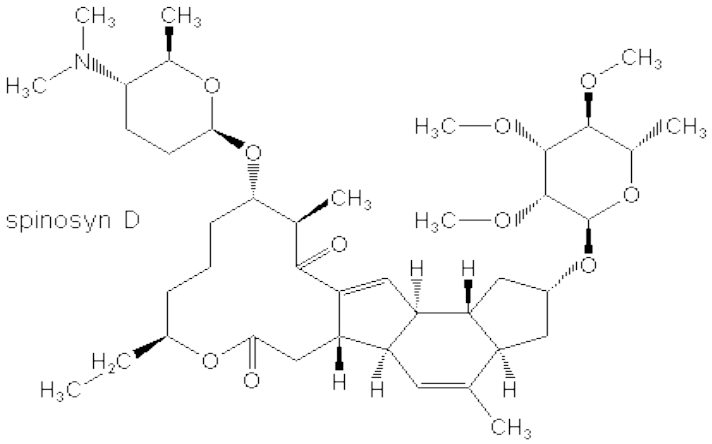
1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active Substance	Spinosad, a combination of Spinosyn A and Spinosyn D
Function	Insecticide
Chemical Name	
1. International Union of Pure and Applied Chemistry (IUPAC)	Mixture of 50-95% (2R,3aS,5aR,5bS,9S,13S,14R,16aS,16bR)-2-(6-deoxy-2,3,4-tri-O-methyl-α-L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13, 14,15,16a,16b-hexadecahydro-14-methyl-1H-as-indaceno[3,2-d]oxacyclododecine-7,15-dione *(= Spinosyn A)* and 50-5%(2S,3aR,5aS,5bS,9S,13S,14R,16aS,16bS)-2-(6-deoxy-2,3,4-tri-O-methyl-α-L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-4,14-dimethyl-1H-8-as-indaceno-[3,2-d]oxacyclododecine-7,15-dione (=*Spinosyn D)*
2. Chemical Abstracts Service (CAS)	(2R,3aS,5aR,5bS,9S,13S,14R,16aS,16bR)-2-[(6-deoxy-2,3,4-tri-O-methyl-α-L-mannopyranosyl)oxy]-13-[[(2R,5S,6R)-5-(dimethylamino)tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-14-methyl-1H-as-indaceno[3,2-d]oxacyclododecin-7,15-dione *(= Spinosyn A)* Mixture with (2S,3aR,5aS,5bS,9S,13S,14R,16aS,16bS)-2-[(6-deoxy-2,3,4-tri-O-methyl-α-L-mannopyranosyl)oxy]-13-[[(2R,5S,6R)-5-(dimethylamino)tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-dimethyl-1H-as-indaceno[3,2-d]oxacyclododecin-7,15-dione *(= Spinosyn D)*
CAS Number	Spinosad: 168316-95-8 Spinosyn A: 131929-60-7 Spinosyn D: 131929-63-0

Molecular Formula





Molecular Weight	Spinosyn A:	731.45
	Spinosyn D:	745.45
Structural Formula	Spinosyn A:	$C_{41}H_{65}NO_{10}$
	Spinosyn D:	$C_{42}H_{67}NO_{10}$
Purity of the Active Ingredient	Spinosad at 90.4% nominal	

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product—Spinosad Technical Insecticide

Property	Result		
Colour and physical state	Light grey-white solid		
Odour	Stale water		
Melting range	Spinosyn A: 84-99.5°C Spinosyn D: 161.5-170°C		
Boiling point or range	Solid at room temperature		
Density at 20°C	0.512 g/mL		
Vapour pressure at 25°C	Spinosyn A: 3.0×10^{-9} Pa Spinosyn D: 2.0×10^{-9} Pa		
Ultraviolet (UV) – visible spectrum		λ_{max}	**ε ($mol^{-1}cm^{-1}$)**
	Spinosyn A		
	Methanol	243.2	1.10×10^5
		201.0	6.77×10^4
	Basic	244.0	1.09×10^5
	Acidic	244.2	1.08×10^5
		200.2	5.73×10^4
	Spinosyn D		
	Methanol	242.6	1.10×10^5
		203.0	1.08×10^5
	Basic	243.6	1.10×10^5
	Acidic	243.8	1.10×10^5
		202.8	9.88×10^4
Solubility in water at 20°C (ppm)		**Spinosyn A**	**Spinosyn D**
	Distilled water	89.4	0.495
	pH 5 buffer	290	28.7
	pH 7 buffer	235	0.332
	pH 9 buffer	16	0.053
Solubility in organic solvents at 20°C (g/100 mL)		**Spinosyn A**	**Spinosyn D**
	Acetone	16.8	1.01
	Acetonitrile	13.4	0.255
	Dichloromethane	52.5	44.8
	Amyl acetate	3.69	2.30
	Hexane	0.448	0.0743
	Methanol	19.0	0.252
	Isopropanol	3.98	0.129
	1-octanol	0.926	0.127
	Toluene	45.7	15.2

Property	Result		
n-Octanol-water partition coefficient (K_{ow})	**pH**	**Spinosyn A**	**Spinosyn D**
	5	2.8	3.2
	7	4.0	4.5
	9	5.2	5.2
	Distilled water	3.9	4.4
Dissociation constant (pK_a)	Spinosyn A: pK_a = 8.10 Spinosyn D: pK_a = 7.87		
Stability (temperature, metal)	Stable to metals and heat		

End-Use Product—Ortho Home Defense Max Ant Bait Stations

Property	Result
Colour	Dark yellow
Odour	Weak musty smell
Physical state	Turbid, slightly viscous liquid
Formulation type	Impregnated fabric (IF)
Guarantee	Spinosad at 0.08% nominal
Container material and description	Polystyrene bait box × 2
Density at 20°C	1.24 g/mL
pH of 1% dispersion in water	7.6
Oxidizing or reducing action	The product does not have any oxidizing properties.
Storage stability	The product was shown to be stable when stored in commercial packaging (polystyrene bait box) at 54°C for 14 days.
Corrosion characteristics	The product was shown not to be corrosive to its commercial packaging (polystyrene bait box) when stored at 54°C for 14 days.
Explodability	The product does not have any explosive properties.

1.3 Directions for Use

Use two Ortho Home Defense Max Ant Bait Stations per 15 m^2. When ant infestations are heavy, use up to four bait stations per 15 m^2. It is recommended that the bait stations be replaced after three to four weeks. To kill ant colonies, the bait stations should remain in place for three months.

1.4 Mode of Action

Spinosad acts on insect nerves, specifically as a nicotinic acetylcholine receptor allosteric activator, causing paralysis and death.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Spinosad Technical Insecticide have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Spinosad is derived from the same soil bacteria as another currently registered active ingredient, spinetoram. The two compounds are almost structurally identical. On the strength of information contained in both databases, they are considered to be toxicologically equivalent and the databases can be used in combination when establishing endpoints for human-health risk assessment. Summaries of the toxicology databases for spinosad and spinetoram are available in Regulatory Note REG2001-10, *Spinosad* and Evaluation Report ERC2008-01, *Spinetoram*. Accordingly, the current assessment takes into account knowledge of both toxicology databases and provides updates where necessary.

Spinosad, as well as 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. These included thyroid gland, kidneys, spleen, lungs and the hematopoietic system, but primarily those of the lymphoid system. The vacuolation appeared to be consistent with effects produced by cationic amphiphilic drugs (CADs) which induce phospholipidosis characterized by lamellar bodies within the vacuoles. Scientific literature on CADs indicates that lung macrophages may be more susceptible to the effects of spinosad due to the high phagocytic activity towards phospholipid-rich surfactant material in the alveolar lining (Pauluhn 2004; Halliwell 1997; Reasor 1989; Lüllmann et al. 1975). The potential for increased sensitivity of the lungs following repeated inhalation exposure necessitated the application of a database uncertainty factor in the inhalation risk assessment.

Ortho Home Defense Max Ant Bait Stations is considered to be of low acute toxicity to rats via the oral and inhalation routes, and of low acute toxicity to rabbits via the dermal route of exposure. It is considered to be minimally irritating to the eye and non-irritating to the skin of rabbits, and is a dermal sensitizer.

Results of the toxicology studies conducted on laboratory animals with Ortho Home Defense Max Ant Bait Stations are summarized in Appendix I, Table 1. Although a quantitative risk assessment was not required for Ortho Home Defense Max Ant Bait Stations, the toxicology endpoints for spinosad (also applicable to spinetoram) have been updated and are summarized in Appendix I, Table 2.

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 Pest Management Regulatory Agency (PMRA). Information on the reporting of incidents can be found on the PMRA website. Incidents were searched and reviewed for the active ingredient spinosad. As of 16 October 2014, one human incident involving the active ingredient spinosad has been reported to the PMRA. Eye irritation was reported to have occurred during application; this incident was considered to be possibly related to spinosad. This finding does not impact the risk assessment.

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 combined toxicity databases for spinosad and spinetoram as it pertains to the toxicity to infants and children, extensive data were available for both chemicals. Both databases contain the full complement of required studies including gavage developmental toxicity studies in rats and rabbits, and a dietary two-generation reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, no evidence of sensitivity of the young was observed in the reproductive toxicity study with spinosad. Both parents and offspring demonstrated a decrease in bodyweight at the same dose levels. In addition, decreased litter size and pup survival were evident at a dose that caused dystocia, post-partum bleeding and deaths in dams. In the rabbit developmental toxicity study, there were no effects observed in fetuses at any dose level, whereas maternal animals exhibited effects on body weight and food consumption at the high dose. In the rat developmental toxicity study, delayed ossification of fetal sternebrae occurred in the absence of maternal toxicity. These findings were considered equivocal since concurrent control values exceeded historical controls, only one ossification site was affected, and the effect is considered transitory in nature. Consequently, there was a low level of concern for these findings.

With respect to spinetoram, the findings in the rat reproduction and rabbit developmental toxicity studies were similar to those for spinosad. There was no evidence of fetal toxicity in the spinetoram rat developmental toxicity study at the highest dose level tested; this dose level produced decreases in bodyweight gain and food consumption in the dams.
Overall, the combined databases are adequate for determining sensitivity of the young for spinosad and spinetoram. There is a low level of concern for sensitivity of the young and effects on the young are well characterized. Although the fetal effects observed in the reproductive toxicity study were considered serious endpoints, the concern was tempered by the presence of maternal toxicity suggesting that a three-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 for both spinosad and spinetoram has been reduced to one-fold.

3.2 Acute Reference Dose

One is not required as there was no endpoint of concern warranting the establishment of an acute reference dose (ARfD).

3.3 Acceptable Daily Intake

To estimate the risk of repeated dietary exposure, the one-year dietary study in the dog conducted with spinetoram with a no observed adverse effect level (NOAEL) of 2.49 mg/kg bw/day was selected. At the lowest observed adverse effect level (LOAEL) of 5.63 mg/kg bw/day, increased liver weights and arteritis accompanied by necrosis of the arterial wall in various lymphoid tissues were 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 one-fold. **The composite assessment factor (CAF) is thus 100.**

The acceptable daily intake (ADI) was calculated according to the following formula:

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

3.4 Occupational and Residential Risk Assessment

The proposed impregnated material product is contained in ready-to-use, single-use bait stations. Exposure to spinosad is expected to be primarily via the dermal route for homeowners placing and removing bait stations. Residential exposures are expected to be acute-term in duration from setting and replacing the bait stations.

3.4.1 Toxicological Endpoints

Although not all toxicology endpoints were required for the current risk assessment, as stated previously in Section 3.1, the toxicology endpoints for spinosad have been updated and are presented below.

Short- , Intermediate- and Long-term Dermal

A 28-day dermal study in rats with spinetoram and a 21-day dermal study in rabbits with spinosad were available for consideration. The study with spinetoram was more robust than the one with spinosad as it had a more extensive histopathology examination. For this reason, it was selected for dermal risk assessment. The study was well conducted and included histopathological examination of the target tissues of toxicity, including thyroid and lymphoid tissues. No treatment-related effects were observed in this study up to the limit dose of 1000 mg/kg bw/day. The study was considered appropriate for all durations as there did not appear to be any significant increase in toxicity with increasing duration of exposure in either the spinosad or spinetoram databases. However, this study was not designed to assess reproductive parameters and it did not include measurements of thyroid hormone levels, effects that were identified at a dose of 75 mg/kg bw/day in the two-generation reproduction study with spinetoram. The NOAEL for these effects was 10 mg/kg bw/day. In the reproduction study, other indications of toxicity, namely facial/perineal soiling and increased pigmentation in the kidneys, were observed at the same dose level at which dystocia occurred. In addition, the results of the 90-day rat study with spinetoram 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) in the study. 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 endpoints. Ten-fold uncertainty factors were applied each for interspecies extrapolation and intraspecies variability, resulting in a target margin of exposure (MOE) of 100. 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, the *Pest Control Products Act* factor was reduced to one-fold for the reasons discussed in the *Pest Control Products Act* Hazard Characterization section.

Short- and Intermediate-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 90-day dietary study in the dog with spinosad was chosen for short- and intermediate-term inhalation risk assessments. The 90-day study duration was relevant and the predominant finding in the database of vacuolation in lymphoid tissues was observed at the LOAEL of 9.7 mg/kg bw/day. 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 for 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 one-fold for the reasons discussed in the *Pest Control Products Act* Hazard Characterization section.

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 one-year dog dietary study was chosen for long-term inhalation risk assessment. Increased liver weights and arteritis accompanied by necrosis of the arterial wall in various lymphoid tissues were 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 combined databases. 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 for 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 one-fold for the reasons discussed in the *Pest Control Products Act* Hazard Characterization section.

Incidental (Non-Dietary) Oral Ingestion (Short-term)

For short-term non-dietary incidental oral exposure in children, the NOAEL of 4.9 mg/kg bw/day from the 90-day dietary study in the dog with spinosad was selected for risk assessment. The NOAEL of the 90-day study was of relevant duration and the predominant finding in the database of vacuolation in lymphoid tissues was observed at the LOAEL of 9.7 mg/kg bw/day. Ten-fold uncertainty factors were applied each for interspecies extrapolation and intraspecies variability, resulting in a target MOE of 100. 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 one-fold for the reasons discussed in the *Pest Control Products Act* Hazard Characterization section.

Short- and Intermediate-term Aggregate Assessment

For aggregate risk assessment for the general population (including pregnant women, infants and children) for short- to intermediate-term duration, the selected toxicological endpoint is vacuolation in lymphoid tissues. For oral and inhalation exposure, the NOAEL of 4.9 mg/kg bw/day from the 90-day dietary study in the dog with spinosad was selected. The LOAEL for this effect was 9.7 mg/kg bw/day. It was not considered necessary to include the dermal route in the aggregate risk assessment as vacuolation was not evident following dermal dosing in rats.

For the oral route of exposure, a target MOE of 100 was selected. This target MOE includes a 10-fold uncertainty factor for interspecies extrapolation and a 10-fold uncertainty factor for intraspecies variability. For the inhalation route of exposure, a target MOE of 300 was selected. This target MOE includes a 10-fold uncertainty factor for interspecies extrapolation, a 10-fold uncertainty factor for intraspecies variability and a 3-fold database uncertainty factor to address the potential for increased susceptibility of lung alveolar macrophages following repeat inhalation exposure. The *Pest Control Products Act* factor was reduced to one-fold as discussed in the *Pest Control Products Act* Hazard Characterization section.

Cancer Assessment

A cancer risk assessment was not necessary as there was no evidence of carcinogenicity in the combined databases.

3.4.2 Occupational Exposure and Risk

An occupational exposure risk assessment was not required for the application to register Ortho Home Defense Max Ant Bait Stations as no occupational exposure is anticipated with this domestic product.

3.4.3 Residential Exposure and Risk Assessment

The United States Environmental Protection Agency (USEPA) 2012 Residential Standard Operating Procedures for Residential Exposure Assessment (Indoor Environments) is being used to assess this product. For ready-to-use baits in/around residential areas, the Residential Standard Operating Procedure states that "… exposure is considered negligible."

The vapour pressure of spinosad is very low (2 to 3×10^{-11} kPa at 25°C) and the product is an impregnated material formulation (in other words, more solid than liquid), which is contained in a bait station. Therefore, inhalation exposures from vapours are considered negligible.

3.4.3.1 Handler Exposure and Risk

Limited exposure to a homeowner setting to the Ortho Home Defense Max Ant Bait Stations is expected. Homeowners must wear rubber gloves while setting, collecting and disposing of bait stations. In addition, Ortho Home Defense Max Ant Bait Stations has an impregnated material formulation which is contained in a bait station, and spinosad has a low vapour pressure. Therefore, dermal and inhalation exposures are considered negligible.

3.4.3.2 Postapplication Exposure and Risk

The label states to keep the product out of reach of children. Children are unlikely to ingest the product since the bait station holes are not accessible using fingers, and a bittering agent is intended to deter children from ingesting the bait. Therefore, children's exposures to the ant bait stations are considered negligible.

3.4.3.3 Bystander Exposure and Risk

Bystander exposure is expected to be much less than adults who place, replace and dispose of the ant bait stations, and is considered negligible. Therefore, health risks to bystanders are not of concern.

3.5 Food Residues Exposure Assessment

A food residue exposure assessment was not required for the application to register Ortho Home Defense Max Ant Bait Stations as no dietary exposure is anticipated with this use pattern.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

The fate and behaviour of spinosad in the terrestrial and aquatic environment is summarized in Regulatory Note REG2001-10, *Spinosad*.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. As spinosad is enclosed in bait stations and used indoors or outdoors around the perimeter of homes, there is very limited exposure to the terrestrial and aquatic environment. As a result, any quantity or concentration of spinosad released to the environment would be negligible.

4.2.1 Risks to Terrestrial Organisms

The formulated end-use product is enclosed in a bait station with small slits; hence, birds and mammals are unlikely to be exposed to any quantities of spinosad. Exposure is negligible compared to uses of spinosad in agricultural applications. Similarly, for honeybees, earthworms and beneficial arthropods, access to the formulated product inside the bait station is not likely and thus, the risk from exposure to spinosad is considered to be negligible.

4.2.2 Risks to Aquatic Organisms

Given the proposed use indoors and outdoors around the perimeter of residences using enclosed bait stations with small openings, spinosad is not expected to enter the aquatic environment and the risks to aquatic organisms are expected to be negligible.

5.0 Value

5.1 Effectiveness Against Pests

Seven laboratory and three field trials against three ant genera (*Lasius, Tetramonium* and *Tapinoma*) showed that Ortho Home Defense Max Ant Bait Stations, at a rate of 2-4 bait stations per 15 m^2, killed foraging ants in 10-21 days. Foraging ants brought the bait back to the colony where it was spread to other ants. Ant colonies were killed in 2-12 weeks.

5.1.1 Acceptable Efficacy Claims

The submitted efficacy data supported the use of Ortho Home Defense Max Ant Bait Stations to kill foraging ants and to kill ant colonies within three months at 2-4 bait stations per 15 m^2. Up to four bait stations per 15 m^2 should be used when ant infestations are heavy.

5.2 Sustainability

5.2.1 Survey of Alternatives

Appendix 1, Table 3 lists alternative active ingredients registered in Canada for the same uses as for Ortho Home Defense Max Ant Bait Stations. Active ingredients include older conventional chemistries such as carbamates, organophosphates and pyrethroids and newer conventional active ingredients such as chlorfenapyr. Non-conventional active ingredients include insecticidal soap, diatomaceous earth, thyme oil and wintergreen oil.

5.2.2 Compatibility with Current Management Practices Including Integrated Pest Management

Ortho Home Defense Max Ant Bait Stations compatible with current ant management practices inside and around homes (for example, sanitation).

5.2.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

There is no known resistance to spinosad by any ant species.

5.2.4 Contribution to Risk Reduction and Sustainability

Spinosad represents a new mode of action for use against ants in Canada. Therefore, it will be useful in preventing the development of insecticide resistance in ants.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances (those that meet all four criteria outlined in the policy, in other words, persistent [in air, soil, water and/or sediment], bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*).

During the previous review process, spinosad and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA determined that spinosad does not meet the criteria for a TSMP Track-1 substance (see Regulatory Note REG2001-10, *Spinosad*).

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical grade active ingredient and formulants and contaminants in the end-use product are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[8] 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:

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5 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*.

6 *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*.

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

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

The end-use product contains List 2 aromatic petroleum distillates carried through from the technical grade active ingredient at a maximum level of 9 ppm. Other formulants and impurities of human health or environmental concern as identified in the PMRA formulants database, Section 2.13.4 of DIR98-04 and Appendix II of DIR99-03 (excluding those identified in the *Canada Gazette*) are not expected to be present in the end-use product or carried through from the technical grade active ingredient.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for spinosad, which also draws upon the toxicology database of 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. Spinosad 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, 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 the continuous phagocytic uptake of phospholipid-rich surfactant material from the alveolar lining, there remains uncertainty as to the toxicity of spinosad 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.

Residential applicator and post-application exposures (including children) to spinosad in Ortho Home Defense Max Ant Bait Stations for indoor and outdoor perimeter uses are not expected to result in unacceptable risks when used according to label directions.

7.2 Environmental Risk

Negligible risk to terrestrial and aquatic organisms is anticipated as a result of very limited environmental exposure to spinosad as the formulated product is enclosed in a bait station.

7.3 Value

The mode of action of the active ingredient in Ortho Home Defense Max Ant Bait Stations is new in Canada for use against ants. Used indoors and outdoors around the perimeter of homes, it kills ants and ant colonies at a rate of 2-4 bait stations per 15 m^2.

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 Spinosad Technical Insecticide and Ortho Home Defense Max Ant Bait Stations, containing the technical grade active ingredient spinosad, to be used as bait in a trap to control ants and ant colonies.

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

λ	wavelength
ε	emittance
◦C	degrees of Celsius
ADI	acceptable daily intake
bw	body weight
CAD	cationic amphiphilic drug
CAF	composite assessment factor
CAS	Chemical Abstracts Service
cm	centimetre(s)
g	gram(s)
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{ow}	*n*–octanol-water partition coefficient
kPa	kilopascal(s)
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
m^2	square metre(s)
MAS	maximum average score for 24, 48 and 72 hours
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre(s)
MOE	margin of exposure
mol-	mole
NOAEL	no observed adverse effect level
NZW	New Zealand white
Pa	Pascal
pKa	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
REG	regulatory note
RTU	ready-to-use
SOP	Standard Operating Procedure
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
UV	ultraviolet

Appendix I Tables and Figures

Table 1 Toxicity Profile of Ortho Home Defense Max Ant Bait Stations Containing Spinosad

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Fischer rat PMRA #2310454, 2310456	$LD_{50} \geq 2000$ mg/kg bw Low toxicity
Acute dermal toxicity NZW rabbit PMRA #2310454, 2310457	$LD_{50} \geq 2000$ mg/kg bw Low toxicity
Acute inhalation toxicity (nose-only) Fischer rat PMRA #2310454, 2310458	$LC_{50} > 5.18$ mg/L Low toxicity
Dermal irritation NZW rabbit PMRA #2310454, 2310460	MAS = 0, MIS = 0 Non-irritating
Eye irritation NZW rabbit PMRA #2310454, 2310459	At 24 hours, slight conjunctival redness was observed. Eyes were normal at 48 hours. MAS = 0.11, MIS = 6 (at 1 hour) Minimally irritating
Dermal sensitization PMRA #2310454, 2310461	Potential skin sensitizer due to the presence of a known sensitizer.

Table 2 Toxicology Endpoints for Spinosad (also applicable to Spinetoram)

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary All populations	Not required as there was no endpoint of concern warranting the establishment of an acute reference dose.		
Chronic dietary All populations	1-year dog dietary study (spinetoram)	NOAEL = 2.49 mg/kg bw/day 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 (spinetoram)	NOAEL = 1000 mg/kg bw/day No systemic effects observed.	100

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Short- and intermediate-term inhalation[2]	90-day dog dietary study (spinosad)	NOAEL = 4.9 mg/kg bw/day Vacuolation in various lymphoid tissues.	300
Long-term inhalation[2]	1-year dog dietary study (spinetoram)	NOAEL = 2.49 mg/kg bw/day Increased liver weights, arteritis accompanied by necrosis of the arterial wall in various lymphoid tissues.	300
Incidental (non-dietary) oral (short-term)	90-day dog dietary study (spinosad)	NOAEL = 4.9 mg/kg bw/day Vacuolation in various lymphoid tissues.	100
Aggregate Risk Assessment – Based on Vacuolation in Lymphoid Tissues			
Short- , intermediate-term aggregate risk assessment	Oral: 90-day dog dietary study (spinosad) Inhalation: 90-day dog dietary study (spinosad) Dermal: not required (no effects noted)	Oral: NOAEL = 4.9 mg/kg bw/day Vacuolation in various lymphoid tissues. Inhalation: NOAEL = 4.9 mg/kg bw/day Vacuolation in various lymphoid tissues. Dermal: not required (No effects noted.)	100 300
Cancer	Not required		

[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 and residential assessments.
[2] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 3 Alternative Active Ingredients Registered for Supported Ortho Home Defense Max Ant Bait Stations Uses (Search Was Conducted in October 2014)

Site	**Mode of Action Group:** Active Ingredient(s)
Inside homes	**Unclassified:** boric acid, borax, disodium octaborate tetrahydrate, diatomaceous earth, soybean oil, thyme oil, wintergreen oil **1A - Carbamates:** propoxur **1B - Organophosphates:** chlorpyrifos **3A - Pyrethroids:** cyfluthrin, D-cis/trans allethrin, D-phenothrin, D-trans allethrin, imiprothrin, lambda-cyhalothrin, permethrin, prallethrin, pyrethrins, tetramethrin **4A - Neonicotinoids:** imidacloprid, thiamethoxam **6:** abamectin **20A:** hydramethylnon
Around homes	**Unclassified:** boric acid, borax, insecticidal soap, silicon dioxide, thyme oil, wintergreen oil **1A - Carbamates:** propoxur **1B - Organophosphates:** dichlorvos, malathion **3A - Pyrethroids:** D-cis/trans allethrin, D-phenothrin, D-trans allethrin, lambda-cyhalothrin,permethrin, pyrethrins, tetramethrin **4A - Neonicotinoids:** imidacloprid, thiamethoxam **6:** abamectin **13:** chlorfenapyr

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2310442	2012, Analytical Methods for Detection and Identification, DACO: 3.4.1 CBI
2310444	2010, Spinosad Gel UKS 171K- Physical Chemical Analysis, 0 C, 54 C & 5a RT Storage Stability, DACO: 3.5.1, 3.5.10, 3.5.11, 3.5.12, 3.5.2, 3.5.3, 3.5.4, 3.5.5, 3.5.6, 3.5.7, 3.5.8, 3.5.9 CBI
2310445	2012, Physical and Chemical Properties of Biocidal Product, DACO: 3.5.1, 3.5.10, 3.5.11, 3.5.12, 3.5.2, 3.5.3, 3.5.4, 3.5.5, 3.5.6, 3.5.7, 3.5.8, 3.5.9 CBI
2310446	2010, Oxidizing and Explosive Properties of the Formulation UKS 171K, DACO: 3.5.12, 3.5.8 CBI
2310449	2013, Miscibility for Scotts Ecosense Ant-B-Gon, DACO: 3.5.13 CBI
2310451	2013, Corrosion Characteristics for Scotts Ecosense Ant-B-Gon, DACO: 3.5.14 CBI
2310452	2013, Waiver for Not Submitting Dielectric Breakdown Voltage Data for Scotts Ecosense Ant-B-Gon, DACO: 3.5.15 CBI
2310476	2010, 14 day 54 C Accelerated Storage Stability and Pack Compatibility Study for the Product Stored in Polystyrene Packs, DACO: 3.5.10 CBI

2.0 Human and Animal Health

PMRA Document Number	Reference
2310454	2013, Waiver for Toxicology Summaries for Scotts EcoSense Ant-B-Gon, DACO: 4.1
2310465	2013, Use Description/Scenario for Scotts Ecosense Ant-B-Gon, DACO: 5.2

3.0 Environment

PMRA Document Number	Reference
2310467	2013, Environmental Chemistry and Fate Summaries, DACO: 8.1
2310468	2013, Laboratory Studies of Transformation Summary for Scotts Ecosense Ant-B-Gon, DACO: 8.2.3.1
2310469	2013, Storage, Disposal and Decontamination Summary for Scotts Ecosense Ant-B-Gon (submitted in support of DACO 8.4.1), DACO: 8.4.1
2310470	2013, Effects on Earthworms and Other Soil Non-Target Macro-organisms, Believed to be at Risk, DACO: 9.9
2310471	2013, Effects on Beneficial Arthropods Other Than Bees, DACO: 9.9
2310472	2013, Acute Toxicity to Honeybees, DACO: 9.9

4.0 Value

PMRA Document Number	Reference
2310412	2013, Value Summaries, DACO: 10.1
2310413	2013, Identity of Biocidal Product, DACO: 10.1
2310416	2013, Mode of Action, DACO: 10.2.1
2310417	2013, Description of Pest Problem, DACO: 10.2.2
2310420	2013, Efficacy Trials Summary, DACO: 10.2.3.1
2310421	2008, Efficacy UKS 171B Bait Station, DACO: 10.2.3.2(C),10.2.3.3(C)
2310422	2012, Intended Uses and Efficacy, DACO: 10.2.3.2(C),10.2.3.3(C)
2310423	2012, Field Assessment of the Efficacy of a Bait Station Against Garden Ants, DACO: 10.2.3.3
2310424	2010, Field Assessment of the Efficacy of a Bait Station Against Garden Ants, DACO: 10.2.3.3
2310425	2010, Field Assessment of the Efficacy of a Bait Station Against Garden Ants, DACO: 10.2.3.3
2310426	2013, Waiver for Local Efficacy: Small-Scale Trials (field, greenhouse) for Scotts Ecosense Ant-B-Gon, DACO: 10.2.3.3
2310427	2013, Summary & Non-Safety Adverse Effects for Scotts Ecosense Ant-B-Gon, DACO: 10.3.1,10.3.2

B. Additional Information Considered

i) Published Information

1.0 Human and Animal 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. and Kacew, S., 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. Toxicology 207 (2005) 59-72, DACO: 4.8
2233995	Shayman, J.A. and Abe, A., 2012. Drug Induced Phospholipidosis: An Acquired Lysosomal Storage Disorder. Biochimica et Biophysica Acta xx(2012) xxx-xxx, DACO: 4.8
	USEPA (October 2012). The Standard Operating Procedures for Residential Pesticide Exposure Assessment. Health Effects Division, Office of Pesticide Programs, Office of Chemical Safety and Pollution Prevention, http://www.epa.gov/opp00001/science/residential-exposure-sop.html

2.0 Value

2014 Insecticide Resistance Action Committee Mode of Action Classification Scheme. http://www.irac-online.org/documents/moa-classification/?ext=pdf. Website was accessed on October 21, 2014.

2014 Arthropod Pesticide Resistance Database, Michigan State University. Website was accessed on October 21, 2014.