Proposed Registration Decision PRD2019-01

Dinotefuran and Related End-Use Products

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Overview

Proposed Registration Decision for Dinotefuran

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

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

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 dinotefuran and Vectra 3D for Dogs Weighing 25.1 to 43 kg, Vectra 3D for Dogs and Puppies Over 7 Weeks of Age Weighing 9.1 to 25 kg, Vectra 3D for Dogs and Puppies Over 7 Weeks of Age Weighing 4.6 to 9 kg (the three end-use products hereinafter referred to as Vectra 3D products) and Prescription Treatment Brand Alpine Pressurized Insecticide, Prescription Treatment Brand Alpine Dust Insecticide, Prescription Treatment Brand Alpine Cockroach Gel Bait Reservoir (the three end-use products hereinafter referred to as Prescription Treatment Brand Alpine products).

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.

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

The *Pest Control Products 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.

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. 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 Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides section of Canada.ca.

Before making a final registration decision on dinotefuran, Vectra 3D products and Prescription Treatment Brand Alpine products, Health Canada's PMRA will consider any comments received from the public in response to this consultation document.[3] Health Canada will then publish a Registration Decision[4] on Dinotefuran and Related End-Use Products, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada'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 Dinotefuran?

Dinotefuran is an insecticide which kills insects by contact or ingestion. It is one of the active ingredients in the Vectra 3D domestic class products, which repel and/or kill ticks, specific insect and mite pests on dogs and puppies. It is also the active ingredient or one of the active ingredients in the Prescription Treatment Brand Alpine commercial class products used to kill several structural pests found inside and/or on the exterior surfaces of commercial, industrial and residential structures and inside transportation vehicles.

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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."

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*.

Health Considerations

Can Approved Uses of Dinotefuran Affect Human Health?

Products containing dinotefuran are unlikely to affect your health when used according to label directions.

Potential exposure to products containing dinotefuran may occur when handling and applying the end-use products, or when coming in contact with treated surfaces or pets. 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). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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 products are used according to label directions.

In laboratory animals, the technical grade active ingredient dinotefuran was of low acute toxicity by the oral, dermal and inhalation routes of exposure. Dinotefuran was minimally irritating to the eyes and skin, and did not cause an allergic skin reaction.

The Vectra 3D products, which are intended for use on dogs of various weight ranges, were of low acute toxicity via the oral and dermal routes of exposure, moderately irritating to the eyes and mildly irritating to the skin, and did not cause an allergic skin reaction.

The Prescription Treatment Brand Alpine products were of low acute toxicity via the oral, dermal and inhalation routes of exposure. Prescription Treatment Brand Alpine Pressurized Insecticide and Prescription Treatment Brand Alpine Cockroach Gel Bait Reservoir were minimally to non-irritating to the eyes. However, Prescription Treatment Brand Alpine Dust Insecticide was mildly irritating to the eyes, and consequently the signal word and hazard statement “CAUTION POISON” are required on the label. All three of the products were minimally to non- irritating to the skin, and did not cause an allergic skin reaction.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of dinotefuran to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were effects on the nervous system and body weight. There was no evidence of sensitivity of the young. There was no evidence to suggest that dinotefuran damaged genetic material. Dinotefuran did, however, cause benign thyroid tumours in rats at very high-dose levels. The risk assessment protects against the effects noted above and other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from dinotefuran on food and water are not a concern.

The end-use products are not intended for application to food. In addition, the Prescription Treatment Brand Alpine product labels instruct not to contaminate food and water with the end-use products; therefore, exposure to dinotefuran through food from the end-use product uses is anticipated to be negligible.

Risks in Residential and Other Non-Occupational Environments

Residential risks are not of concern when Vectra 3D products are used according to label directions and instructions.

Exposure to dinotefuran can occur when adults handle these end-use products, and come in direct contact with dinotefuran residue on the skin. Adults, youth, and children can come in direct contact with dinotefuran residue on the skin when contacting treated pets. In addition, children may ingest residues by hand-to-mouth activity after contacting treated dogs. Inhalation exposure was considered negligible.

Residential exposures (application and postapplication) to the Vectra 3D products are not expected to result in unacceptable risks when used according to label directions. No concern was identified for adults, youth, and children who dermally contacted treated dogs, and for young children who engage in hand-to-mouth activity after touching dogs treated with the end-use products.

For bystanders, exposures are considered to be addressed by the residential postapplication exposure assessments. Therefore, health risks to bystanders are not of concern.

Estimated risks from residential exposure are not of concern provided that directions specified on the Prescription Treatment Brand Alpine products labels are followed.

Residential exposure to individuals contacting treated indoor and outdoor surfaces is not expected to result in risks of concern when dinotefuran is used according to label directions.

Occupational Risks from Handling Vectra 3D products

Vectra 3D products are domestic products; therefore, no quantitative occupational assessments were conducted.

No quantitative occupational assessments were conducted. However, commercial workers (for example, veterinary, kennel, and pet care) may wear personal protective equipment (PPE) including gloves and laboratory coat/apron, when applying pet products. Applying pet products is only one of many tasks that workers would do. There is sufficient evidence to indicate that their exposures will not result in risks of concern.

Occupational risks are not of concern when the Prescription Treatment Brand Alpine products are used according to the label directions, which include protective measures.

Applicators loading and applying Prescription Treatment Brand Alpine products can come into direct contact with dinotefuran on the skin or through inhalation. Therefore, the labels will specify that anyone loading and/or applying an end-use product containing dinotefuran must wear a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks. A respirator is required when Prescription Treatment Brand Alpine Dust Insecticide is loaded and applied.

Environmental Considerations

What Happens When Dinotefuran Is Introduced Into the Environment?

When Prescription Treatment Brand Alpine products are used according to label directions, dinotefuran is not expected to pose risks of concern to the environment.

Prescription Treatment Brand Alpine products containing dinotefuran are proposed to be used as a crack and crevice, void, spot, and perimeter treatment for flying and crawling insects indoors. Other proposed uses include the localized treatment of the exterior surface of structures and direct treatment of the nests of stinging insects, such as bees, hornets and wasps (including paper wasps and yellow jackets). For outdoor treatment of stinging insect nests, dinotefuran is to be applied directly into voids (above- and below-ground) where nests are located. As such, environmental releases are expected to be minimal and a quantitative risk assessment was not conducted. The Prescription Treatment Brand Alpine products, containing dinotefuran, are not expected to pose risks of concern to the environment.

It should be noted that an environmental risk assessment for the registration of Vectra 3D Domestic class products is not required. These proposed Domestic class products are spot-on products for use on companion animals. Because of the use pattern, dinotefuran is not expected to result in environmental exposure.

Value Considerations

What Is the Value of the Vectra 3D Products?

They are spot-on products which combine dinotefuran (4.95%) with two other active ingredients, permethrin (36.08%) and pyriproxyfen (0.44%), for use against fleas, ticks, stable flies, mosquitoes, dog biting lice and walking dandruff mites on dogs and puppies weighing 4.6–43 kg and over seven weeks of age.

These products are new tools for use on dogs against labelled pests. They are the first pesticide product registered for use against walking dandruff mites on dogs, and have acceptable value.

What Is the Value of:

Prescription Treatment Brand Alpine Pressurized Insecticide (0.5% dinotefuran), Prescription Treatment Brand Alpine Dust Insecticide (0.25 % dinotefuran and 77.4% silicon dioxide present as diatomaceous earth), and Prescription Treatment Brand Alpine Cockroach Gel Bait Reservoir (0.5% dinotefuran)?

They are pressurized, dust and gel products, respectively, that are registered to kill a variety of structural pests (for example, ants, bed bugs, cockroaches, stored product pests, wasps) inside and/or on the exterior surfaces of structures and inside transport vehicles.

These products are new tools that kill labelled structural pests and have acceptable value. Some of these pests, such as cockroaches and bed bugs, impact the health and well-being of people. The Prescription Treatment Brand Alpine Dust Insecticide kills nests of stinging insects and can be applied in locations where a spray cannot be applied, such as around electrical fittings.

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 labels of the technical grade active ingredient and end-use products to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

To avoid direct contact with dinotefuran, bystanders and residents must not be present during loading and/or application of the Prescription Treatment Brand Alpine products and cannot re-enter treated areas until residues have dried or dusts have settled.

Applicators loading and applying Prescription Treatment Brand Alpine products can come into direct contact with dinotefuran on the skin or through inhalation. Therefore, the labels will specify that anyone loading and/or applying an end-use product containing dinotefuran must wear a long-sleeved shirt, long pants, chemical-resistant gloves, and shoes plus socks. A respirator is required when Prescription Treatment Brand Alpine Dust Insecticide is loaded and applied.

Environment

Label statements are required to limit the outdoor use of Prescription Treatment Brand Alpine dinotefuran-containing products to crack and crevice, void or spot treatments, and to indicate that direct application of dinotefuran to water is not allowed.

Next Steps

Before making a final registration decision on dinotefuran, Vectra 3D products and Prescription Treatment Brand Alpine products, Health Canada's PMRA will consider any comments received from the public in response to this consultation document. Health Canada 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). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada's response to these comments.

Other Information

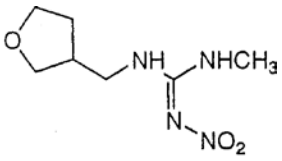
When Health Canada makes its registration decision, it will publish a Registration Decision on Dinotefuran and Related End-Use Products (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection,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

Science Evaluation

Dinotefuran, Vectra 3D Products and Prescription Treatment Brand Alpine Products

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Dinotefuran
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	(*EZ*)-(*RS*)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine
2. Chemical Abstracts Service (CAS)	*N*-methyl-*N′*-nitro-*N″*-[(tetrahydro-3-furanyl)methyl]guanidine
CAS number	165252-70-0
Molecular formula	$C_7H_{14}N_4O_3$
Molecular weight	202.2
Structural formula	
Purity of the active ingredient	99.6%

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

Technical Product—Dinotefuran Technical

Property	Result
Colour and physical state	White crystalline solid
Odour	Odourless
Melting range	107.5°C
Boiling point or range	N/A
Density at 20°C	1.40 g/mL
Vapour pressure at 30°C	< 1.7×10^{-6} Pa

Property	Result
Henry's law constant	8.63×10^{-14} atm-m^3/mol
Ultraviolet (UV)-visible spectrum	λ_{max} = 268 nm, ε = 12400 M^{-1} cm^{-1} No absorbance at λ > 350 nm
Solubility in water at 20°C	39.83×10^3 mg/L (pH=6.98)
Solubility in organic solvents at 20°C	**Solvent** — **Solubility (mg/L)** Hexane — 0.0090 Heptane — 0.0105 Xylene — 72 Toluene — 149 Dichloromethane — 60.9×10^3 Acetone — 57.8×10^3 Methanol — 57.2×10^3 Ethanol — 19.4×10^3 Ethyl acetate — 5200
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = -0.549 (25°C)
Dissociation constant (pK_a)	12.6
Stability (temperature, metal)	Thermally stable; chemically stable when exposed to iron or aluminum powder but physical changes were observed when exposed to iron or aluminum ions.

End-Use Product—Vectra 3D for Dogs and Puppies Over 7 Weeks of Age Weighing 4.6 to 9 kg

Property	Result
Colour	Amber yellow
Odour	Characteristic solvent odour
Physical state	Liquid
Formulation type	Solution (SN)
Guarantee	Dinotefuran 4.95% Permethrin 36.08% Pyriproxyfen 0.44%
Container material and description	Aluminum polymer composite tube with applicator tip (1.6 mL/tube, 1–144 tubes/package).
Density at 20°C	1.10 g/mL
pH of 1% dispersion in water	5.8
Oxidizing or reducing action	Not an oxidizing or reducing agent.
Storage stability	The product is stable for 1 year when stored at ambient conditions in aluminum polymer composite.

Property	Result
Corrosion characteristics	The product is non-corrosive to the packaging material.
Explodability	The product does not contain any flammable or explosive components.

End-Use Product—Vectra 3D for Dogs and Puppies Over 7 Weeks of Age Weighing 9.1 to 25 kg

Property	Result
Colour	Amber yellow
Odour	Characteristic solvent odour
Physical state	Liquid
Formulation type	Solution (SN)
Guarantee	Dinotefuran 4.95% Permethrin 36.08% Pyriproxyfen 0.44%
Container material and description	Aluminum polymer composite tube with applicator tip (3.6 mL/tube, 1–144 tubes/package).
Density at 20°C	1.10 g/mL
pH of 1% dispersion in water	5.8
Oxidizing or reducing action	Not an oxidizing or reducing agent.
Storage stability	The product is stable for 1 year when stored at ambient conditions in aluminum polymer composite.
Corrosion characteristics	The product is non-corrosive to the packaging material.
Explodability	The product does not contain any flammable or explosive components.

End-Use Product—Vectra 3D for Dogs Weighing 25.1 to 43 kg

Property	Result
Colour	Amber yellow
Odour	Characteristic solvent odour
Physical state	Liquid
Formulation type	Solution (SN)
Guarantee	Dinotefuran 4.95% Permethrin 36.08% Pyriproxyfen 0.44%
Container material and description	Aluminum polymer composite tube with applicator tip (4.7 mL/tube, 1–144 tubes/package).

Property	Result
Density at 20°C	1.10 g/mL
pH of 1% dispersion in water	5.8
Oxidizing or reducing action	Not an oxidizing or reducing agent.
Storage stability	The product is stable for 1 year when stored at ambient conditions in aluminum polymer composite.
Corrosion characteristics	The product is non-corrosive to the packaging material.
Explodability	The product does not contain any flammable or explosive components.

End-Use Product—Prescription Treatment Brand Alpine Pressurized Insecticide

Property	Result
Colour	Colourless
Odour	Acetone-like odour
Physical state	Liquid
Formulation type	Pressurized product (PP)
Guarantee	Dinotefuran 0.5%
Container material and description	Tin-lined steel can, 517.54 g
Density	0.946 g/cm^3
pH of 1% dispersion in water	8.587 (23.2°C)
Oxidizing or reducing action	The product does not contain oxidizing or reducing agents.
Storage stability	The product is stable for 1 year when stored at room temperature (22°C) in a can similar to the commercial packaging.
Corrosion characteristics	The product is non-corrosive to the packaging material.
Explodability	Explosive (pressurized product)

End-Use Product— Prescription Treatment Brand Alpine Dust Insecticide

Property	Result
Colour	Off-white
Odour	No distinct odour
Physical state	Solid
Formulation type	Dust or powder (DU)
Guarantee	Dinotefuran 0.25% Silicon dioxide, present as diatomaceous earth 77.4%

Property	Result
Container material and description	Plastic bucket and bottle; 0.01 kg to 5 kg; 0.232 kg, 4.54 kg
Density	Bulk density 0.182 g/cm^3; tap density: 0.215 g/cm^3
pH of 1% dispersion in water	7.419 (22.5°C)
Oxidizing or reducing action	The product does not contain any oxidizing or reducing agents.
Storage stability	The product is stable for 1 year when stored at room temperature in a Nalgene (plastic) jar.
Corrosion characteristics	The product is non-corrosive to the packaging material.
Explodability	The product does not contain potentially explosive components.

End-Use Product— Prescription Treatment Brand Alpine Cockroach Gel Bait Reservoir

Property	Result
Colour	Dark tan to brown
Odour	Bone-meal like odour
Physical state	Gel (liquid)
Formulation type	Paste (PA)
Guarantee	Dinotefuran 0.50%
Container material and description	Plastic reservoir, 30 g
Density	1.17 g/cm^3
pH of 1% dispersion in water	6.76
Oxidizing or reducing action	The product does not contain oxidizing or reducing agents.
Storage stability	The product is stable for 1 year when stored at room temperature (22°C) in a plastic reservoir.
Corrosion characteristics	The product is non-corrosive to the packaging material.
Explodability	The product does not contain explosive components.

1.3 Directions for Use

Vectra 3D Products

Vectra 3D products are domestic class insecticides packaged in single-dose tubes for application to a dog's back. Each product has tubes of a specific volume that depends on the weight class of the dogs being treated: 1.6, 3.6 and 4.7 mL for dogs weighing 4.6–9.0 kg, 9.1–25.0 kg and 25.1–43.0 kg, respectively. The products are applied once a month and are for use against fleas (all life stages), ticks, stable flies, mosquitoes, dog biting lice and walking dandruff mites. For full details refer to the product labels.

Prescription Treatment Brand Alpine Pressurized Insecticide

Prescription Treatment Brand Alpine Pressurized Insecticide is a commercial class product that is applied inside and on the exterior surfaces of commercial, industrial and residential buildings and inside transportation vehicles. It kills structural pests such as ants, bed bugs, boxelder bugs, clover mites and cockroaches (German and oriental). It is applied as a crack and crevice or interior perimeter treatment, a void treatment or a spot treatment. The product may be reapplied after 10 days if pests continue to be a problem. For full details, refer to the product label.

Prescription Treatment Brand Alpine Dust Insecticide

Prescription Treatment Brand Alpine Dust Insecticide is a commercial class product that kills a wide variety of structural pests such as ants, bed bugs, boxelder bugs, cockroaches, stored product pests and wasps. It also kills the nests of bees, hornets and wasps. Application is made to the inside and exterior surfaces of commercial, industrial and residential structures and inside transportation vehicles. It is applied as a crack and crevice, spot, interior perimeter or void treatment at a maximum application rate of 10 g/m^2. The product may be reapplied as necessary, if pests continue to be a problem. For full details, refer to the product label.

Prescription Treatment Brand Cockroach Gel Bait Reservoir

Prescription Treatment Brand Alpine Cockroach Gel Bait Reservoir is a commercial class product which controls German and oriental cockroaches. It is for indoor use in commercial, industrial and residential buildings and inside transportation vehicles. It is applied as interior perimeter, spot, crack and crevice and void treatments. The application rate is 1–12 g/10 m^2, depending on the level of infestation. Bait applications should not be made more than once a month, unless bait is consumed or no longer palatable. For full details, refer to the product label.

1.4 Mode of Action

Dinotefuran is an insecticide in the Insecticide Resistance Action Committee's Mode of Action Group 4A. It acts on the insect nervous system as a nicotinic acetylcholine receptor agonist. Insects which ingest or contact dinotefuran become paralysed and die.

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 impurities in Dinotefuran Technical have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The methods provided for the analysis of the active ingredients in the formulations have been validated and assessed to be acceptable for use as enforcement analytical methods.

2.3 Methods for Residue Analysis

High-performance liquid chromatography methods with mass spectrometry (HPLC-MS), with tandem mass spectrometry (HPLC-MS/MS) and with UV detection (HPLC-UV) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Dinotefuran belongs to the nitroguanidine sub-class of the neonicotinoid class of insecticides and acts by interfering with the acetylcholine receptors of the insect's nervous system. Dinotefuran has a lower affinity for vertebrate nicotinic receptors than those of insects. A detailed review of the dinotefuran toxicology database was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to dinotefuran.

The absorption, distribution, metabolism and excretion of dinotefuran, ^{14}C-radiolabelled in the guanidine and tetrahydrofuran groups (1:1 ratio of radiolabels), were investigated in rats following administration of either single or repeated low oral (gavage) doses, a single high oral (gavage) dose, or a single low intravenous dose. In addition, single low oral (gavage) doses of ^{14}C-radiolabelled dinotefuran were administered to pregnant and lactating rat dams to assess placental and lactational transfer, and to postnatal day (PND) 12 rats to investigate toxicokinetic parameters. Lactating rats were also administered repeated low or high-dose levels of ^{14}C-radiolabelled dinotefuran by gavage to assess concentrations in milk.

Dinotefuran was rapidly and almost completely absorbed, regardless of dosing regimen, with maximum plasma concentrations achieved by two hours post-dose. Elimination was also rapid following single or repeat low-dose administration, and slightly longer following single high-dose administration. Dinotefuran was eliminated primarily through the urine; elimination was mostly complete within 24 hours of dosing. Fecal radioactivity was low, and limited amounts of radioactivity were recovered in the bile and expired air. Route and rate of elimination were not significantly influenced by sex, dose level or dosing regimen.

Radiolabelled dinotefuran was widely distributed in all tissues. Within four hours following administration of a single low dose, concentrations were highest in the kidneys, stomach, urinary bladder, intestinal tract, prostate, testes and bone (females only). Brain concentrations were relatively low. Concentrations in all tissues quickly declined, with levels below the limit of detection (LOD) in most tissues at 168 hours post-dosing.

Plasma and tissue levels were also low at 168 hours following repeat low- or single high-dose administration, with highest concentrations noted in mammary gland (female) and skin. Repeat-dose administration did not increase tissue concentrations or prolong clearance. Disposition of radioactivity was similar following single- and multiple-dosing regimens and after administration of low and high doses.

Unchanged dinotefuran was the major component in urine and in plasma, milk, bile, feces, and most tissues, regardless of dose level. Less than 10% of the administered dose was metabolized. There were no apparent differences in metabolism related to treatment regimen, dose level, or sex. The main urinary metabolites were PHP (6-hydroxy-5-(2-hydroxyethyl)-1-methyl-1,3-diazinane-2-ylidene-N-nitroamine) and PHP isomers. These metabolites were formed via enzymatic hydroxylation on the tetrahydrofuran ring, after which further oxidation, reduction and acetylation of PHP occurred to form multiple minor metabolites.

In the placental transfer study in which pregnant rats were administered dinotefuran by gavage on gestation day 18, radioactivity was rapidly transferred from maternal blood to fetuses, and distributed to fetal tissues. Maximum concentrations in fetal tissue, except for brain, occurred within 0.5 hours of maternal dosing. Fetal brain concentrations reached a maximum at 1.5 hours. Thereafter, radioactivity in all tissues declined rapidly to low levels four hours following dose administration. Similar concentrations of radioactivity were noted in maternal and fetal blood, suggesting a rapid equilibrium and similar tissue distribution in fetal and maternal tissues.

In rat dams administered dinotefuran by gavage on lactation day 12, radioactivity was rapidly transferred from maternal blood to milk. Maximum concentrations for plasma and milk occurred at 0.5 hours post-dosing. Concentrations in milk declined rapidly over the 4-hour post-dosing observation period. The $T_{½}$ for milk indicated that radioactivity levels would be below detection limits at 24 hours post-dosing. Concentrations of dinotefuran in milk were approximately twofold higher than in plasma, with each decreasing at a similar rate. The results of the repeat-dose study which investigated transfer of dinotefuran into the milk of lactating dams indicated that despite a 10-fold difference between the low- and high-dose levels, only a fourfold difference was present in dinotefuran concentrations in plasma and milk, thus indicating that saturation may be occurring.

In neonatal rats administered dinotefuran by gavage on PND 12, absorption and urinary elimination were noted to be slower when compared to adult animals. Tissue distribution and metabolism in neonates were similar to adults.

Dinotefuran was of low acute toxicity via the oral route in rats and mice. Clinical signs of toxicity following acute oral exposure of dinotefuran included hypoactivity, staggered gait, tonic convulsions, tremors and death. Surviving animals appeared normal within three days of dosing. Dinotefuran was of low acute toxicity via the dermal and inhalation routes in rats. It was minimally irritating to the eyes and skin of rabbits, and was not a skin sensitizer in guinea pigs via the Maximization method of testing.

The Prescription Treatment Brand Alpine products were of low acute toxicity to rats via the oral, dermal and inhalation routes of exposure. Prescription Treatment Brand Alpine Pressurized Insecticide and Prescription Treatment Brand Alpine Cockroach Gel Bait Reservoir were minimally to non-irritating to the eyes of rabbits; however, Prescription Treatment Brand Alpine Dust Insecticide was mildly irritating to rabbit eyes. The products were minimally to non-irritating to the skin of rabbits, and negative for skin sensitization in guinea pigs using the Buehler method of testing. The Vectra 3D products, which are intended for use on dogs of various weight ranges, were of low acute toxicity to rats via the oral and dermal routes of exposure. They were moderately irritating to the eyes and mildly irritating to the skin of rabbits, and were not a skin sensitizer in guinea pigs when tested using the Buehler method.

Following repeat dietary dosing with dinotefuran in rats, mice and dogs, the most sensitive effects were decreases in body weight and body weight gain, which were also frequently the first effects observed. Decreases in body weight occurred earlier at higher dose levels, often within the first week of dosing, along with decreased food consumption and food efficiency. At the highest dose levels tested in rodents, dietary concentrations of dinotefuran often approached or exceeded the limit dose. Consequently, decreased diet palatability at the high-dose levels may have contributed to the reductions in body weight. Diet palatability was also an issue in the 90-day dog toxicity study, where the highest dose level tested was lowered twice during the study due to inappetence. However, the decreases in food consumption observed overall in the toxicology database were not of a significant magnitude to account for the observed body weight effects, since food efficiency was affected in multiple studies.

Adrenal gland effects were noted in the dinotefuran toxicology database. In the rat 90-day dietary toxicity study, vacuolation of the adrenal cortex was observed in both sexes at a dose level that exceeded the limit dose of testing. No adverse adrenal findings were noted at a similarly high-dose level when dosing was extended to two years. In the mouse dietary oncogenicity study, an increase in the incidence of adrenal cortical cell hypertrophy was noted at terminal sacrifice in males.

A decrease in thymus weights was noted in both the rat and dog following extended duration of dietary dosing; however, there were no corresponding histopathological findings in rodents. In the 1-year dog study, an increased incidence in ultimobranchial cysts was noted in the thymus of male dogs at the mid- and high-dose levels. This finding was not noted in females or in either sex after 90 days of dietary dosing.

Several other organ/tissues were affected in the dog following repeated dietary dosing. In the 90-day study, decreased pituitary weights were noted in both sexes at the mid-dose and high-dose levels, with pituitary cysts observed in high-dose animals. Degeneration of individual acinar cells in the pancreas, and hemorrhage in mesenteric and mandibular lymph nodes were also noted in both sexes at the high-dose level. Decreased spleen weights were recorded in high dose females. Pituitary, pancreatic and lymph node effects were not evident in the dietary 1-year dog study; however, doses in the 1-year study were substantially lower in comparison to the 90-day study. Red blood cell (RBC) parameters were increased in females following a year of dietary administration. Decreased testes weights were also noted in males.

Kidney and uterine effects were evident in male and female rats, respectively, at the highest dose level following long-term dietary dosing. Increased incidences of lymphohisticytic infiltrate, as well as ulceration and mineralization of the kidney pelvis were noted in males. In females, there was an increase in uterine weights.

Following short-term dermal exposure in rats up to the limit dose of testing, there was no evidence of systemic toxicity, clinical signs of toxicity, or adverse effects on motor activity or the functional observational battery. With respect to dermal irritation, an increase in incidence and severity of acanthosis/hyperkeratosis in the treated skin of high-dose females was the only finding noted.

Effects noted in a 28-day inhalation toxicity study in rats were similar to those noted following repeated dietary administration, with decreases in body weight, body weight gain and food consumption noted in males at the lowest dose level tested. Thinning fur and/or hair loss was noted in both sexes at the next higher dose level. Decreased thymus weights were recorded in males at the highest dose level tested along with alterations in white blood cell populations.

Dinotefuran was not genotoxic in a battery of tests which included bacterial reverse mutation assays with *Salmonella typhimurium* and E. coli, bacterial DNA damage and repair with *Bacillus subtilis*, in vitro mammalian forward cell mutation and chromosome aberration assays, and an in vivo mouse micronucleus assay.

Following long-term exposure in rats, an increased incidence of thyroid C-cell adenomas was noted in males at a dose level approximating the limit dose of testing. There was no corresponding increase in the incidence of thyroid C-cell carcinoma. Due to the high-dose level at which this effect was noted, the endpoints selected for the non-cancer risk assessment are considered protective of these findings. Dinotefuran was not oncogenic in the mouse or in female rats.

In a dietary multigeneration reproductive toxicity study in rats, effects were noted at the highest dose level only. In parental animals, decreased body weight, bodyweight gain and food consumption, as well as decreased spleen weights were observed. In offspring, decreased body weight, bodyweight gain, and spleen weights were observed in both generations. In addition, decreased grip strength was noted in F_1 offspring of both sexes and decreased absolute thymus and brain weights were noted in F_2 offspring. Reproductive toxicity was noted in both generations. An increased incidence of testicular tubular degeneration, as well as decreases in sperm motility, specifically an increase in the percentage of stationary sperm, was noted in F_1 males. In F_1 ovary follicle staging, there was a decrease in the number of primordial follicles and a corresponding increase in the number of antral follicles. The number of corpora lutea was also increased for these animals. In the P generation, decreased relative uterine weights, along with uterine atrophy and atrophy and/or vacuolar degeneration of the vaginal mucosa were noted. Although ovarian follicle staging and reproductive histopathology were not assessed at lower-dose levels, the high-dose level in this study approached the limit dose of testing and toxicology reference values selected for risk assessment provide adequate margins to these effects. There was no evidence of sensitivity of the young in this study.

Developmental toxicity was examined following gavage dosing to pregnant rats and rabbits. In rats, there was a delay in fetal ossification of metatarsals 2–5 at the highest dose level. Maternal toxicity in the form of decreased body weight, food consumption and water consumption, was also noted at this dose level. There were no adverse developmental effects noted in rabbit fetuses, despite overt maternal toxicity in the form of clinical signs (for example, hypoactivity, prone position, panting, and tremors), decreased body weight and bodyweight gain, and stomach and liver findings. At a higher dose level in the dose range-finding study, clinical signs of toxicity were more pronounced, and abortions, occurring after gestation day 20, were noted. There was no evidence of increased sensitivity of the young in either the rat or rabbit study.

The potential for dinotefuran to produce neurotoxic effects was investigated in rats following acute gavage and short-term dietary dosing, as well as in a dietary developmental neurotoxicity (DNT) study. Dinotefuran produced effects indicative of neurotoxicity in these studies. Decreased rearing, as well as decreased motor activity was noted in females on the day of dosing in the acute neurotoxicity study. At the next higher dose level, decreased motor activity was evident in males and decreased body temperatures were noted in both sexes. Similar effects were noted following repeat dietary dosing, with the decreases in motor activity in high-dose females being most pronounced at study week two. Other findings at this dose level included decreased body weight and body temperature in both sexes. At the next lower-dose level, motor activity was inversely affected, with increased counts noted in later sub-sessions for both sexes, indicating a possible lack of habituation. In the DNT study, an increase in motor activity was noted in high-dose female offspring on PND 21. At the mid-dose level, motor activity was also increased, but the data were more variable. The spread in the data points at this dose level, when considered within the context of the overall pattern of response across the dose groups, suggested that the mid-dose level in this study likely represented a transition point for the effects on motor activity. For these reasons, the mid-dose findings were considered equivocal. It is acknowledged that this may represent a conservative interpretation. There was no evidence of maternal toxicity at the mid-dose level; maternal toxicity was limited to decreased body weight gain at the highest dose level only. Motor activity was not assessed in maternal animals in the DNT study, whereas it was assessed in the short-term neurotoxicity study. In the latter study, adult females exhibited increased motor activity at a dose level similar to that which produced the equivocal findings in the DNT study. Thus, it was concluded that the DNT findings did not suggest sensitivity of the young.

In 28-day immunotoxicity studies in mice and rats, in which dinotefuran was administered in the diet, there were no indications of perturbation or dysregulation of the immune response. In a non-guideline developmental immunotoxicity (DIT) study, there were no immunologically-adverse effects on antibody-forming cell response or Natural Killer cell activity in offspring exposed in utero, via maternal milk, or for five weeks following weaning. Although decreased body weights were observed in offspring in the absence of any evidence of overt toxicity in maternal animals, the offspring finding occurred at a dose level that slightly exceeded the limit dose of testing.

Several studies/investigations to assess safety to treated dogs and puppies following topical treatment with two test formulations representative of Vectra 3D products were available. These studies were conducted in puppies as young as seven weeks of age (three studies in total) and in

adult dogs. There were no adverse effects noted in adult dogs. Cosmetic hair coat effects such as matting, spiking, clumping, and greasy appearance, were noted at the treated site for all adult dogs, including the control animals. These cosmetic hair coat findings were also observed in all three puppy studies. In addition, tremors, ataxia, lethargy and loose feces were noted in the first puppy study following application of 5-times the proposed application rate. In that same study, ataxia was noted at two hours post-dosing in one puppy administered the proposed application rate. These findings were not observed, however, in the subsequent studies in which puppies received equivalent or higher doses of the product, or in a supplemental veterinarian field study with Vectra 3D products. In this veterinarian field study, the dogs of homeowners were examined by a veterinarian, and then treated at home with either the product or an alternative registered topical treatment by the owner. Animals were observed for adverse effects by the owner at home. The veterinarian followed up with the owners via telephone on study days 1 and 30, recording any observations they reported. The incidence of reported effects was minimal, occurring at the same rate as that of the registered topical treatment, and were limited to changes in activity, abnormal behaviour and loose feces, and possible signs related to one of the other active ingredients in Vectra 3D products. Cosmetic hair coat findings as noted above were also reported.

Results of the toxicology studies conducted on laboratory animals with dinotefuran and its associated end-use products, as well as the safety to treated animals studies, are summarized in Appendix I, Tables 2 and 3. The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 4.

3.1.1 Incident Reports Related to Human and Animal Health

Dinotefuran is a new active ingredient pending registration for use in Canada. As of 22 May 2018, no human incidents involving dinotefuran were submitted to the PMRA. There were three American domestic animal death incidents in the PMRA database involving dinotefuran. These incidents occurred with other active ingredients (Z-9 tricosene, prallethrin or pyriproxyfen), and the use patterns were not relevant to the proposed end-use products.

Concerns were previously identified by the PMRA for flea and tick spot-on products. Therefore, human and domestic animal incident data were requested from the registrant to inform the PMRA's registration decision of the proposed companion animal spot-on Vectra 3D products. In the United States, Vectra 3D products have been registered since 2007.

The PMRA evaluation of United States human incident data for Vectra 3D products indicated that the adverse effects were mainly minor in severity and included signs such as skin irritation or hives, which resolved rapidly. The USEPA (United States Environmental Protection Agency) review of human incident data involving all registered uses of dinotefuran concluded that there were no concerns, based on the low severity of the incidents.

The American animal incident data with Vectra 3D products involved both cats and dogs. Incidents involving cats were associated with product misuse; therefore, the Vectra 3D products will require mitigation measures as outlined in the Regulatory Directive DIR2010-02, *Label Improvements for Spot-on Pesticides Used for Flea and Tick Control on Companion Animals*, to

prevent the use of permethrin-containing spot-on dog products on cats. The incidents in dogs generally occurred after the product was used as per label directions. The reported signs in dogs were mainly minor in nature and involved effects such as discomfort, skin irritation, and lack of appetite or lethargy. In a few cases, serious signs such as gait disturbances or seizures were reported. Reports of death were very rare. Incidents were more frequent in smaller dogs compared to larger-sized dogs. Therefore, a precautionary statement will appear on the Vectra 3D product labels indicating that smaller animals are more likely to experience an adverse reaction and for owners to observe their pets carefully, consistent with DIR2010-02.

The reported effects in the dog incidents involving Vectra 3D products were consistent with the effects seen with other spot-on products. Based on the examined American incident data, which showed that dogs can develop adverse health effects after treatment with Vectra 3D products, it is proposed that the product labels include the listing of possible side effects, to inform consumers. This labelling approach is similar to that taken by the USEPA for all spot-on products.

3.1.2 *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, the standard complement of required studies including developmental toxicity studies in rats and rabbits and a multigeneration reproductive toxicity study in rats, was available. In addition, a DNT study, a non-guideline DIT study, and a lactational transfer study, all conducted in rats, were available for dinotefuran.

With respect to potential prenatal and postnatal toxicity, toxicokinetic investigations in pregnant and lactating rat dams demonstrated placental and lactational transfer of dinotefuran following gavage administration. Neonatal rats receiving dinotefuran by gavage on PND 12 demonstrated slower absorption and urinary elimination, but similar tissue distribution and metabolism, when compared to adult animals. In the reproductive and prenatal developmental toxicity studies, there was no indication of increased susceptibility of fetuses or offspring compared to parental animals. There were no adverse developmental effects noted in rabbit fetuses, despite overt maternal toxicity including clinical signs and effects on body weight. Delayed ossification was observed in rat fetuses in the presence of maternal toxicity which included effects on body weight and food consumption. In the DIT study, effects in offspring were limited to decreases in body weight occurring at a dose that slightly exceeded the limit dose of testing. In the rat reproductive toxicity study, sperm and testes effects, altered ovarian follicle counts, uterine and vaginal effects, decreased grip-strength and decreased spleen, thymus and brain weights were noted in the offspring at the highest dose level; these effects occurred in the presence of maternal toxicity (decreased body weight and bodyweight gain). In the DNT study, there was an equivocal increase in motor activity counts in PND 21 female offspring at a dose level that did not result in

overt toxicity in the dams. It was acknowledged that the interpretation of motor activity data in offspring at this dose level may be conservative. Although motor activity was not assessed in maternal animals, adult females exhibited an increase in motor activity at a similar dose level in the short-term neurotoxicity study. In view of this, it was concluded that there did not appear to be evidence of sensitivity of the young in the DNT study.

Overall, there was no evidence in the dinotefuran database of sensitivity of the young and the toxicology reference values selected provide adequate margins to the effects noted above. The *Pest Control Products Act* factor was thus reduced to onefold.

3.2 Acute Reference Dose

Establishment of an acute reference dose is not required as there are no proposed food uses and contamination of drinking water sources is not expected.

3.3 Acceptable Daily Intake

Establishment of an acceptable daily intake is not required as there are no proposed food uses and contamination of drinking water sources is not expected.

3.4 Occupational and Residential Risk Assessment

Fleas, ticks, mosquitoes, mites, lice, and flies are seasonal in most parts of Canada. The proposed domestic-class spot-on products are expected to be used on a monthly basis. However, it is unlikely that high pest pressure is prevalent throughout the year. Year-round and long-term infestation would be cause for concern and indicate that more stringent mitigation measures be conducted.

Dermal exposures to homeowners applying Vectra 3D products are characterized as short-term (1–30 days per year) and postapplication dermal contact with treated dogs is considered intermediate-term (1 month to 6 months) in duration. Child (1<2 years old) incidental oral exposure from hand-to-mouth activity is considered to be of short-term duration. Inhalation exposure is considered to be negligible.

Occupational exposure to dinotefuran is characterized as intermediate-term and is predominantly by the dermal and inhalation routes during loading and application of the Prescription Treatment Brand Alpine products.

For people re-entering treated areas, exposure is expected to be through the dermal route for adults (16+ years) and through the dermal and incidental oral routes for children (1< 2 years). Children 2 years old to < 16 years old are not assessed separately because their exposure is expected to be less than that of 1 < 2 year olds. Children (1<2 years) are expected to have greater exposure because of additional routes of exposure (incidental oral) as well as a greater body surface area (cm^2) to body weight (kg) ratio. Also, the duration of exposure for occupants of a treated building is expected to be short-term for all pests as well as also long-term for bed bugs.

3.4.1 Toxicology Reference Values

Dermal Exposure (all durations)

For dermal risk assessments of all durations, the 1-year dog dietary study with a no observed adverse effects level (NOAEL) of 20 mg/kg bw/day was selected. At the lowest observed adverse effect level (LOAEL) of 108 mg/kg bw/day, decreased thymus weights were observed in both sexes, and decreased body weight and bodyweight gain, as well as changes in RBC parameters, were observed in females. Although a rat 28-day dermal toxicity study was available, this study was not selected for the dermal risk assessment. When taking into account endpoints of concern in the toxicology database and dermal absorption estimates, the dermal study did not provide adequate margins to the reproductive effects noted in the rat offspring (testes effects, altered ovarian follicle counts, uterine and vaginal effects) for which lower-dose levels were not assessed. For residential and occupational scenarios, the target Margin of Exposure (MOE) is 100. 10-fold factors were applied each for interspecies extrapolation and intraspecies variability. For residential scenarios, the *Pest Control Products Act* factor was reduced to onefold as discussed in the *Pest Control Products Act* Hazard Characterization section.

Inhalation Exposure (intermediate- to long-term)

For intermediate- to long-term inhalation risk assessments, the NOAEL of 20 mg/kg bw/day from the 1-year dog dietary study was selected. At the LOAEL of 108 mg/kg bw/day, decreased thymus weights were observed in both sexes, and decreased body weight and bodyweight gain, as well as changes in RBC parameters, were observed in females. The available rat 28-day inhalation toxicity study was not selected since it was not of the appropriate duration given the evidence of increased toxicity with increased duration of dosing in the dinotefuran toxicology database. The target MOE for these scenarios is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. For residential exposures, the *Pest Control Products Act* factor was reduced to onefold as discussed in the *Pest Control Products Act* Hazard Characterization section.

Non-Dietary (Incidental) Oral Exposure

For assessment of acute incidental oral exposure, the rabbit gavage developmental toxicity study was chosen. A point of departure of 125 mg/kg bw/day was selected on the basis of clinical signs of toxicity (hypoactivity, tremors) observed after administration of a single dose at the next higher dose level of 300 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied, resulting in a target MOE of 100. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to onefold.

For assessment of short- to intermediate-term incidental oral exposure, the 90-day and 1-year dietary studies in the dog were selected and considered to be co-critical studies. The NOAEL of 22 mg/kg bw/day was selected from the 1-year dog study based on decreases in body weight in females that were recorded at 58 and 108 mg/kg bw/day, in the 90-day and 1-year dog studies,

respectively. In the 90-day dog study, 58 mg/kg bw/day represented the lowest dose level tested. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied, resulting in a target MOE of 100. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to onefold.

Cancer Assessment

The incidence of thyroid C-cell adenomas in male rats was increased at a dose level that approached the limit dose of testing; there was no corresponding increase in the incidence of carcinoma. The toxicology reference values selected for the repeat-dose non-cancer risk assessment provide a margin of 500 to the NOAEL for thyroid C-cell adenomas in male rats, and thus are protective of this finding.

Aggregate Assessment

For short-term aggregate risk assessment for the general population (including pregnant women, infants and children), the selected toxicological endpoint common for the oral and inhalation routes of exposure was decreased body weight/bodyweight gain. For oral exposure, the NOAEL of 22 mg/kg bw/day for females from the 1-year dietary study in dogs was selected on the basis of decreased body weight/bodyweight gain in females at 108 mg/kg bw/day. For inhalation exposure, the LOAEC of 0.22 mg/L (approximately 60 mg/kg bw/day) in the rat 28-day inhalation toxicity study was selected on the basis of decreased body weight/bodyweight gain in males at this dose level. As there was no effect on body weight at the limit dose of testing in the 28-day rat dermal toxicity study, it was not necessary to include the dermal route in the aggregate risk assessment. A target MOE of 100 was selected for the oral route of exposure based on standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. For the inhalation route of exposure, the target MOE was 300, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as an additional threefold factor due to lack of a NOAEC in the 28-day inhalation toxicity study. For residential scenarios, the *Pest Control Products Act* factor was reduced to onefold as discussed in the *Pest Control Products Act* Hazard Characterization section.

For intermediate- to long-term aggregate risk assessment for the general population (including pregnant women, infants and children), the selected toxicological endpoint common to all routes of exposure was decreased body weight/bodyweight gain. The NOAEL of 22 mg/kg bw/day from the 1-year dietary study in dogs was selected on the basis of decreased body weight/bodyweight gain in females at 108 mg/kg bw/day. This study was selected for the dermal and inhalation exposure routes since there was evidence in the repeat-dose oral studies of increased toxicity with increased duration of dosing and the available dermal and inhalation toxicity studies were of only short-term duration. For all routes of exposure, a target MOE of 100 was selected, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. For residential scenarios, the *Pest Control Products Act* factor was reduced to onefold as discussed in the *Pest Control Products Act* Hazard Characterization section.

Cumulative Assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Dinotefuran belongs to a group of insecticides commonly known as the neonicotinoids. Currently, other chemicals within this group are undergoing re-evaluation. Upon completion of the re-evaluation of the individual chemicals in this group, it will be determined whether a cumulative health risk assessment is necessary, and if so, this will be performed with all relevant chemicals of the common mechanism group.

3.4.1.1 Dermal Absorption

In support of the registration of the Vectra 3D products, an in vivo dermal absorption study in rats was submitted. Seventy-two male Sprague-Dawley rats were administered actual doses (4 rats per treatment) of 3.2, 30, and 302 µg/cm^2 of dinotefuran in Milli-Q water to 10 cm^2 of skin area on the back, and monitored up to 24 hours post-dosing. The high-dose represents the active concentration in the undiluted product, and the two dilutions representing field spray application concentrations. For each dosing concentration, samples were collected after 0.5, 1, 2, 4, 10, and 24 hours of exposure. The skin wash was conducted after the exposure duration.

The systemically absorbed dose was calculated by the addition of mean recoveries of treated skin, non-treated skin, urine, faeces, cage wash, whole blood, carcass, and GI tract. For the potentially absorbed dose, the tape strips (*stratum corneum*) were added to the systemically absorbed dose.

Very low systemic absorption in all doses (≤2.3%) suggests that dinotefuran is not well absorbed with water as the carrier. However, since the study only monitored the rats up to 24 hours postapplication, there is uncertainty regarding the fate of skin-bound residues. The maximum potential absorption (systemic + application site (including skin-bound residues)) at the low dose of 3.2µg/cm^2 was 36.47% (10 hrs exposure); at 30 µg/cm^2 was 26.50% (24 hrs exposure); and at 302 µg/cm^2 was 10.27% (24 hrs exposure). In the low dose, skin-bound residue in the *stratum corneum* was approximately 36% for both 10-hr and 24-hr exposures, suggesting that dermal penetration reached saturation; however, monitoring beyond 24 hours would be required to confirm this.

Using the potentially absorbed dose of 36% may be a conservative estimate of dermal absorption; however, the blank product formulation was not used as the vehicle in the study. In turn, the dermal absorption (Table 3.4.1) value of 36% is considered appropriate to use for end-use products with a solid formulation type, for liquid end-use products where the main diluent/carrier/solvent is water, and for all postapplication scenarios. Liquid and aerosol end-use products may contain solvents known to enhance dermal absorption relative to water. Therefore, for liquid and aerosol end-use products, which do not have water as the main diluent/carrier/solvent, a dermal absorption value of 100% was applied for mixer/loader/applicator risk assessments.

Table 3.4.1 Dermal absorption values (% of total dose applied) from the in vivo rat study, after 10 hours of exposure

Product type	Applicator dermal absorption value	Postapplication dermal absorption value
Pet spot-on	100%, based on likely increase of dermal absorption due to amount of solvents in the proposed products relative to water used as the vehicle in the study.	36%, based on the solvents being volatile, such that the vehicle contributes less to dermal absorption.
Aerosol	100%, based on content of solvents in the product are likely to increase dermal absorption relative to water used as the vehicle in the study.	36%, as the vehicle contributes less to dermal absorption as the solvents are volatile and people are not to contact treated surfaces until they are dry.
Dust	36% for loader, applicator, and postapplication exposures. Dust typically is not well absorbed relative to a liquid.	

3.4.2 Occupational Exposure and Risk

Vectra 3D products are domestic-class products. There are no commercial scenario-specific exposure data available at this time; therefore, no quantitative occupational assessments were conducted. However, commercial workers (for example, veterinary, kennel, and pet care) may wear PPE including gloves and laboratory coat/apron, when applying pet products. The number of animals they would treat with Vectra 3D products in a typical day is unknown, but applying pet products is only one of many tasks that workers would do. There is sufficient evidence to indicate that their exposures will not result in risks of concern.

3.4.2.1 Loader/applicator Exposure and Risk Assessment

There is potential for exposure to applicators loading and/or applying dinotefuran. Dermal and inhalation exposure estimates for applicators making structural applications (spot, crack and crevice, void and perimeter treatment) of aerosol, dust and gel formulations were generated using PHED unit exposure values (version 1.1) and amount handled per day data from the Canadian Pest Management Association (CPMA). Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted.

The exposure estimates are based on applicators wearing a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks.

Dermal exposure was estimated by combining the unit exposure values with the amount of product handled per day and the dermal absorption value. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the intermediate-term toxicological reference values to obtain the MOE. All calculated MOEs exceeded the target MOE of 100 (Appendix I, Table 5).

3.4.2.2 Postapplication Worker Exposure and Risk

There is potential for exposure to workers re-entering areas treated with dinotefuran. However, it is expected to be less than that to an applicator from loading and/or applying for which the target MOE was exceeded. Also, it is expected that workers re-entering treated areas will be wearing long sleeves, long pants, shoes and socks.

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Handler Exposure and Risk

Adults (16<80 years of age) have potential for exposure to the Vectra 3D products during application. Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted. Therefore, dermal exposure estimates were generated for adults applying Vectra 3D products, using the USEPA Residential Exposure Assessment Standard Operating Procedures (2012) (known as Residential Standard Operating Procedure (SOP)), *Treated Pets.* This SOP considers inhalation exposure to be negligible.

Exposures to adults applying Vectra 3D products are expected to be short-term in duration and to occur primarily by the dermal route. Exposure estimates were derived for adults applying the products to dogs and puppies using ready-to-use squeeze tubes containing pre-measured volumes of the product. The exposure scenario is based on an adult, wearing no PPE and applying one tube of a product to the lowest weight dog in the range. Dermal exposure is estimated by coupling the amount of active handled per dog, the dermal unit exposure, the dermal absorption value, and treating two dogs per day. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates (Table 3.4.2) were compared to the short-term dermal reference value to obtain the MOE; the target MOE is 100.

Table 3.4.2 Homeowner applicator exposure and risk assessment of Vectra 3D products containing dinotefuran.

Dog size for each product	Application Rate[a] (kg a.i./tube/dog)	Dermal Unit Exposure (mg/kg a.i.)	Dermal Exposure (mg/day)	Dermal Absorbed Dose[b] (mg/kg/day)	Dermal MOE[c]
4.6 kg–9 kg	0.000087	264.55	0.0460	0.0005754	35000
9.1 kg–25 kg	0.000196	264.55	0.1037	0.001296	15000
25.1 kg–43 kg	0.000256	264.55	0.1354	0.001693	12000

a. Total amount of active ingredient contained in each spot-on product tube = spot-on volume × guarantee (%) of active ingredient × specific gravity × 0.001 kg/g;

b. Dermal Absorbed Dose = Dermal unit exposure (µg/kg ai) × 2 dogs per day × dermal absorption/adult body weight (USEPA Residential SOP, October 2012, *Treated Pets*)

Default number of two pets treated in a day (USEPA Residential SOP, 2012, *Treated Pets*); one spot-on tube per pet;
Dermal absorption value: dinotefuran, 100%;
Adult body weight of 80kg;

c. NOAEL = 20 mg/kg bw/day, the target MOE is 100.

Dermal MOEs were greater than the target of 100. Therefore, risks to applicators (adults) applying the product to dogs and puppies are not of concern.

3.4.3.2 Postapplication Exposure and Risk

There is potential for exposure to adults, youth, and children when petting, playing, and grooming dogs treated with Vectra 3D products. The primary route of postapplication exposure is through the dermal route for adults, youth, and children. Quantitative dermal risk assessments were based on the highest volume of product that can be applied to the smallest dog in the weight range covered by the product. Inhalation is not considered to be of concern for postapplication exposure to spot-on pet products. Non-dietary, hand-to-mouth oral exposure for children (1<2 years old) may also occur. The duration of exposure is considered to be short- to intermediate-term. No dissipation of the product is taken into account, as residents can contact a treated dog as soon as the treatment has dried.

Two chemical-specific dislodgeable residue stroking studies were submitted to estimate postapplication exposures following contact with treated dogs. Both studies were designed to estimate the residue transferred when petting a dog treated with a spot-on product.

One study used a product containing guarantees of 22.0% dinotefuran and 3.00% pyriproxyfen. Fifteen beagles (older than 8 weeks of age) weighing from 9.7 kg to 13.2 kg were divided into 3 groups of 5 dogs each. The spot-on product (one-4 mL tube/dog) was applied topically. On day 3 (pre-treatment; as background residue measurement and at 24 hours postapplication, a stroking event was performed by stroking in the direction of the fur with 3 strokes (left flank, centre line from head to tail, and right flank) using a mannequin hand covered by a nitrile glove under three cotton gloves. The stroking event was performed a total of 10, 20, or 30 times. The dinotefuran was extracted from the individual (inner, middle, and outer) cotton gloves before analysis by high-performance liquid chromatography (HPLC).

The mean transferred residue (mean ± standard deviation) did not increase linearly with the number of stroking events: 3.27% ± 1.28% at 10 times; 5.42% ± 2.22% at 20 times; and 4.75% ± 1.42% at 30 times). The trend of transferable residues and the significant variability among the means indicates that the most appropriate stroking scenario to use for postapplication exposure assessment is the maximum mean residue of 5.42% or 20 replicates of a 3-stroke event to maximize residue transfer.

The second study was designed to calculate the amount of residue transferred when petting dogs treated with a spot-on product containing guarantees of 0.443% pyriproxyfen, 4.93% dinotefuran, and 36.59% permethrin.

The spot-on product was applied topically to dogs (0.4 mL/kg bw) along the dorsal midline of twenty (10 male and 10 female) adult beagles (mean of 8.9 ± 0.8 kg bw). Mean applied doses were 22.2 ± 0.4 mg dinotefuran/kg bw, 164.8 ± 3 mg permethrin/kg dog, and 2.0 ± 0.04 mg pyriproxyfen/kg bw. The dogs were stroked on day 0 (pre-treatment) and randomly placed into one of 3 stroking frequency groups: 1) At 4 hours, 8 hours after treatment, and then on days 1, 3, 7, 14, 21, and 30 (Group 1); 2) only on day 3 after treatment (Group 2); or 3) only on day 30

after treatment (Group 3). Five strokes were performed along the body (ventral and flank on each side plus along the dorsal midline), with the lay of the haircoat, using an adult hand wearing a disposable glove covered by a single cotton glove for each dog sampled. The active ingredients were extracted from the cotton gloves and analyzed by HPLC with tandem mass spectrometric detection.

The mean peak transferable residue concentration (1.65 mg dinotefuran; 12.42 mg permethrin; 0.151 mg pyriproxyfen/glove) at 4 hours after treatment was the most appropriate residue for use in the risk assessments. Groups 2 and 3 only had 4 animals/group, and indicated that the trend of residue dissipation in group 1 was not underestimating residues. The dose concentration was relevant to the proposed product use on 9 kg dogs.

Postapplication exposure assessments for use in residential areas are considered to be representative of those in some non-residential (office buildings, public spaces, commercial areas, etc.) and outdoor areas. This assumption is based on the duration of contact with treated surfaces, which is assumed to be greater in indoor residential areas. Also, when the end-use products are used outdoors, they are limited in application to the surfaces of structures where contact is expected to be minimal.

All exposures are considered short-term in duration. Use of the end-use products to control bed bugs can potentially result in long-term exposure; however, unless there is 1) a substantial difference between the short- and long-term reference values and 2) different routes of exposure in the toxicological studies from which the reference values were derived (i.e., dermal versus oral routes), the short-term risk assessments will be representative of the long-term risk. For dinotefuran, the dermal reference value is the same for all durations, the incidental oral reference value is the same for all durations and the inhalation reference values are the same once the target MOEs are taken into consideration. Exposure parameter defaults for long-term assessments use more conservative values, such as the 50^{th} percentile, in comparison to short-term assessments, which use the arithmetic mean or 90^{th} percentile. As such, the endpoints must differ by orders of magnitude to compensate for the change in the default parameter values. Therefore, a separate long-term risk assessment is not required and risks from all exposure durations are represented by the short-term exposure assessment.

Exposure estimates were generated using default values from the 2012 USEPA Residential SOP for Indoor Environments (Section 7) combined with the application rates from the label and the approved use pattern. Only exposure estimates from use of the aerosol product are presented as exposure covers that of the dust product because of the higher guarantee and application rate.

The USEPA 2012 Residential SOP states that postapplication risk assessments for dermal, inhalation or oral exposure are not required for paste/gel products used as baits. Repetitive dermal and incidental oral exposures (i.e., over the entire exposure time to an indoor treated surface) are not expected to occur because of label statements limiting application to areas inaccessible to children.

Inhalation exposure was not calculated for any of the proposed end-use products as the vapour pressure of dinotefuran is less than 1.7×10^{-9} kPa at 30°C. This meets the NAFTA waiver criteria for being non-volatile indoors[5], therefore, people entering treated rooms are not expected to be exposed to dinotefuran vapours from the aerosol, dust or bait end-use products.

Exposure estimates were compared to the short-term reference value to obtain the MOE. The MOEs for all individual routes of exposure exceeded the target MOE (Appendix I, Tables 6, 7, 8).

3.4.3.2.1 Dermal Exposure Assessment

The mean peak transferable residue concentration (1.65 mg/glove) from the stroking study using a 5-stroke event is considered to be appropriate for conducting the postapplication exposure assessments for the Vectra 3D products, as the product used in the study is representative of the proposed formulations.

A 5-stroke event is considered to underestimate the residue transferred during contact with treated dogs in a day. Therefore, a 60-stroke event was used in the risk assessments because it is considered more reflective of daily contact with treated dogs. The submitted stroking study that measured residue transfer with different numbers of 3-stroke events at 24 hours postapplication lends additional support to this assumption. Therefore, the peak transferable residue per glove in the 5-stroke study was multiplied by 12 to estimate the equivalent residue transferred from 60 strokes after one hour of contact with treated pets per day. This amount, while not reflecting the typical contact with a pet, is not expected to underestimate daily dermal exposures resulting from contact with treated dogs.

It is also assumed that individuals come in contact with treated dogs on the day the product is applied, that 100% of the product is on the dog, and the product is evenly distributed over the entire surface area of the dog.

Postapplication estimates of dermal exposures and risks to homeowners, including children, who contact treated dogs, are presented in Table 3.4.3. The transferable residue is estimated using the adjusted peak residue transferred to an adult hand in one hour and the dog size being contacted. The transferable residue is then adjusted by age-specific hand surface area and daily exposure time, and normalized by age-specific body weight.

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[5] Non-volatile products are defined as those having vapor pressures less than 1×10^{-5} kPa for indoor uses, and less than 1×10^{-4} kPa for outdoor uses at 20–30ºC. NAFTA (1999). International Harmonisation Position Paper on Methodology Issues, Appendices. 18 January 1999.

Table 3.4.3 Dinotefuran risk estimates for postapplication dermal contact with dogs treated with a spot-on product.

Product Dog Size	Dog Surface Area[a] (lowest weight in range) (cm^2)	Index Lifestage (years-old)	Transferable Residue[b] (mg a.i./day)	Hand Surface Area Ratio	Exposure time (hours/day)	Dermal Absorbed Dose[c] (mg/kg/day)	Dermal MOE[d]
4.6–9 kg	2956	Adult (16–80)	13.66	1	0.77	0.0467	430
		Youth (11<16)		0.81	0.92	0.0633	320
		Child (1<2)		0.34	1	0.1485	130
9.1–25 kg	4606	Adult (16–80)	19.72	1	0.77	0.0674	300
		Youth (11<16)		0.81	0.92	0.0914	220
		Child (1<2)		0.34	1	0.2145	**93**
25.1–43 kg	8906	Adult (16–80)	13.31	1	0.77	0.0455	440
		Youth (11<16)		0.81	0.92	0.0617	320
		Child (1<2)		0.34	1	0.1448	140

Note: **Bolded** MOE values indicate that calculated MOEs do not meet the target value

a. Dog surface area calculated from weight using USEPA Exposure Factors Handbook (2011) equation.

b. Transferable Residue = Transferred Residue (mg a.i./stroking event) × stroking event adjustment (unitless) × ((amount a.i. to be applied/SA_{dog})/(amount a.i. applied in study/mean SA_{dog} in study))

Where, Transferred Residue in study = 1.65mg dinotefuran
Stroking event adjustment = 12; (60 /5 strokes per event)
Amount a.i. to be applied = tube volume (mL) × density × guarantee × 1000mg/g = mg dinotefuran
Amount applied in study = average mL applied from study × density × guarantee = 198mg
SA_{dog} in study = 4573 cm^2 for a 9 kg dog

c. Exposure (mg/kg bw/day) = Transferable Residue × Hand Surface Area Ratio × Exposure Time × Dermal Absorption/Body Weight

Where,
Exposure = Absorbed dermal dose normalized to human body weight (mg/kg bw/day)
Transferable Residue; from b)
Hand surface area ratio (unitless) = SA_{adult} (cm^2)/$SA_{adult,\ youth,\ or\ child}$ (cm^2)
Exposure Time (h); amount of time a human dermally contacts a pet in a day = 0.77, adult; 0.92, youth; and 1.0, child
Dermal Absorption; 36% for dinotefuran;
bw = adult body weight (kg) = adult, 80 kg; youth, 57 kg; and child, 11 kg

d. Margin of Exposure (MOE) = NOAEL/Exposure

Where, NOAEL = 20 mg/kg bw/day, the target MOE is 100.

The MOE for children (1<2 yrs old),who are expected to pet and play with treated dogs weighing between 9.1 kg and 25 kg, does not meet the target MOE of 100. However, considering the conservatisms in the risk assessment, dermal risks to children are not considered to be of concern.

3.4.3.2.2 Toddler Hand-to-mouth Exposure Assessment

There is potential oral exposure for younger children (1<2 yrs old) from incidental ingestion of product residue that is transferred to a child's hands from handling/touching treated pets, as a result of hand-to-mouth transfer. Therefore, a non-dietary oral exposure assessment is conducted for young children to take into account their behavioural pattern. The intermediate-term endpoint is used to address oral exposures that occur when the product is used for several months.

Hand-to-mouth non-dietary oral exposure estimates of dinotefuran are calculated based on the USEPA Residential SOP (2012, *Treated Pets*) and presented in Table 3.4.4.

Table 3.4.4 Risk estimates for child (1<2 years of age) hand-to-mouth exposure to dinotefuran from VECTRA 3D spot-on products.

Product Dog Size	Dermal Exposure[a] (mg/hour)	Hand residue loading[b] (mg/cm^2)	Oral Dose[c] (mg/kg/day)	Hand-to-Mouth MOE[d]
4.6-9 kg	4.54	4.54	0.05160	430
9.1-25 kg	6.55	6.55	0.07451	300
25.1-43 kg	4.43	4.43	0.05031	440

a. Dermal Exposure (mg/hour) = Transferred Residue (from dog stroking study) × Hand Surface Area Ratio × Exposure Time (from postapplication dermal exposures)
b. Hand residue loading = Dermal Exposure (mg/hour) × 1.0 (Fraction available on hands for oral exposure)
c. Hand-to-Mouth algorithm (adapted 2017) from USEPA Residential SOP, Treated Pets; Postapplication Non-Dietary Ingestion Exposure Assessment:
d. Margin of Exposure (MOE); incidental oral (short-term) reference value for dinotefuran NOAEL is 22 mg/kg bw/day (target MOE = 100).

The target MOEs are met for toddler incidental oral risks from hand-to-mouth activity from contacting dogs treated with Vectra 3D products; therefore, risks are not of concern.

3.4.3.3 Bystander Exposure and Risk

The Prescription Treatment Brand Alpine product labels specifically state that no one is to be present during application. Therefore, bystander exposure is expected to be negligible.

3.4.3.4 Aggregate Exposure and Risk Assessment

Homeowners (adults, 16<80 years of age) can treat dogs and come in contact with the treated pets immediately after applying the spot-on product. Therefore, application and postapplication exposures for these individuals should be aggregated. Youth (11<16 years of age) are only considered to have postapplication dermal contact with pets. Since there is no dietary intake of dinotefuran, no aggregate assessment is required for the youth sub-population. A young child may, in addition to postapplication dermal contact, engage in incidental oral ingestion from hand-to-mouth activity. No short-term aggregate risks are calculated since the only relevant endpoint for the spot-on products is oral exposure. However, intermediate-term aggregate risks are relevant to this scenario and presented in Table 3.4.5.

Table 3.4.5 Residential aggregated exposures to dinotefuran from dogs treated with VECTRA 3D products.

Product Dog Size	Sub-population	Applicator Dermal Exposure[a] (mg/kg bw/day)	Postapplication Dermal Exposure[b] (mg/kg bw/day)	Hand-to-Mouth Exposure[c] (mg/kg bw/day)	Intermediate-term Aggregate MOE[d]
4.6–9 kg	Adults (16<80)	0.00058	0.0467	N/A	420
	Child (1<2)	N/A	0.1485	0.05160	110

9.1–25 kg	Adults (16<80)	0.0013	0.0674	N/A	290
	Child (1<2)	N/A	0.2145	0.07451	**76**
25.1–43 kg	Adults (16<80)	0.00169	0.0455	N/A	420
	Child (1<2)	N/A	0.1448	0.05031	110

Note: **Bolded** MOE values indicate scenarios that do not meet the target aggregate MOE of 100
a. From Table 3.4.2
b. From Table 3.4.3
c. From Table 3.4.4
d. Aggregate determined according to SPN2003-04; NOAEL of 22 mg/kg bw/day; target MOE = 100.

While the MOE for children does not meet the target MOE of 100, given the conservatisms of the individual risk assessments, the aggregate risks to adults, youth, and children are not considered to be of concern from the use of Vectra 3D spot-on products.

3.5 Food Residues Exposure Assessment

A food residue exposure assessment was not required for the application to register the end-use products as no dietary exposure is anticipated with these use patterns.

4.0 Impact on the Environment

Prescription Treatment Brand Alpine products containing dinotefuran are proposed to be used as a crack and crevice, void, spot or perimeter treatment for flying and crawling insects indoors. Other proposed uses include the localized treatment of the exterior surface of structures and direct treatment of the nests of stinging insects including bees, hornets and wasps (including paper wasps and yellow jackets). For outdoor treatment of stinging insect nests, dinotefuran is to be applied directly into voids (above- and below-ground) where nests are located. As such, environmental releases are expected to be minimal and a quantitative risk assessment was not conducted. The proposed Prescription Treatment Brand Alpine products containing dinotefuran are not expected to pose risks of concern to the environment.

It should be noted that an environmental risk assessment for the registration of Vectra 3D Domestic class products is not required. These proposed Domestic class products are spot-on products for use on companion animals. Because of the use pattern, dinotefuran is not expected to result in environmental exposure.

4.1 Incident Reports Related to the Environment

No environmental incidents involving dinotefuran and/or silicon dioxide were located in the PMRA database. According to the United States Ecological Incident Information System database there were four environment incidents in the United States involving dinotefuran and none for silicon dioxide. All four dinotefuran incidents involved dead bees and were considered at least possibly related to the reported pesticide. Limited exposure details were provided in the available American reports, but incidents were related to product misuse or spray application to bees. Unlike the proposed spot treatment uses on or around structures in Canada, dinotefuran is registered for various broadcast foliar applications in the United States Overall, the assessment of incident reports involving dinotefuran did not identify any significant environmental effects.

After reviewing the available information, the environmental risks associated with the proposed uses of dinotefuran and related Prescription Treatment Brand Alpine end-use products are acceptable when used according to the proposed label directions.

5.0 Value

Vectra 3D Products

Vectra 3D products combine dinotefuran with permethrin and pyriproxyfen. Dinotefuran kills flea adults; permethrin repels mosquitoes and stable flies, and kills stable flies, walking dandruff mites, dog biting lice, ticks and flea adults; and pyriproxyfen is an insect growth regulator that affects the development of fleas. These pesticide products are the only ones registered for use on dogs to kill walking dandruff mite, which is a minor pest. Other active ingredients are registered against all other labelled pests.

Vectra 3D products label claims were supported based on 21 trials. Results of 17 trials (16 laboratory and one operational) demonstrated that the Vectra 3D products kill ticks and adult fleas on dogs and prevent the development of fleas. These trials showed that the products remain effective against ticks and flea adults for up to 30 days, including after swimming (once per week) or after up to two bathings. Results of two laboratory trials, one for each pest, demonstrated that Vectra 3D products repel mosquitoes for up to one month, and repel and kill stable flies for up to one month. Results from two published trials, one for each pest, demonstrated that permethrin doses similar to those in the Vectra 3D products kill dog biting lice and walking dandruff mites on dogs.

A report was provided that showed the coat of one dog (0.3% of dogs in the operational trial) changed colour at the site of the application at 12 days after application of the Vectra 3D products. This discolouration was not of concern because it disappeared after five days.

Prescription Treatment Brand Alpine Products

Many of the structural pests listed on the labels of the three Prescription Treatment Brand Alpine products are nuisance pests in commercial, industrial and residential structures. Several of these pests impact the health and well-being of Canadians including wasps, hornets, cockroaches and bed bugs. These products may be used with other pest control practices (for example, inspection, sanitation, structural repairs) to manage labelled pests.

Alternative products are registered against all pests on the Prescription Treatment Brand Alpine products labels for some of the pests. However, dinotefuran represents a new mode of action for use against webbing clothes moth, several stored products pests (for example, grain beetles) and several nuisance pests (for example, multi-coloured Asian lady beetles, and boxelder bugs) in or on structures. Few active ingredients are registered for use on nests of stinging insects or as dust formulations for use against structural pests. This is important because dust formulations are often used in locations where the moisture from a spray may cause damage or pose a hazard (for example, around electrical outlets).

Prescription Treatment Brand Alpine Pressurized Insecticide label claims were supported based on the results of 20 trials. Trials were conducted in the laboratory except for two field studies, one each on bed bugs and German cockroaches. Prescription Treatment Brand Alpine Dust Insecticide label claims were supported based on extrapolation from precedent products containing only silicon dioxide, 18 laboratory trials and a field trial. Prescription Treatment Brand Alpine Cockroach Gel Bait Reservoir label claims were supported based on four laboratory and four field trials.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The Toxic Substances Management Policy 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), bioaccumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, dinotefuran was assessed in accordance with the PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy,* and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Bioaccumulation: The log octanol-water partition coefficient factor (log K_{ow}) of -0.549 for dinotefuran at 25°C was reported. Given that Toxic Substances Management Policy Track 1 criterion is ≥5.0 for the log K_{ow}, it is concluded that dinotefuran does not meet the criterion for bioaccumulation.

- Dinotefuran does not meet all Track 1 criteria and, therefore, is not considered a Track 1 substance.

6.2 Formulants and Contaminants of Health or Environmental Concern

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

During the environmental review process, contaminants in the technical grade active ingredient (Dinotefuran Technical) as well as formulants and contaminants in the end-use products were compared against the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern maintained in the Canada Gazette. The list is used as described in the PMRA Notice of Intent NOI2005-01 and is based on existing policies and regulations including DIR99-03 and DIR2006-02, 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 conclusion:

- Technical grade dinotefuran and the related end-use products do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for dinotefuran is adequate to define the majority of toxic effects that may result from exposure. In short-term and chronic studies on laboratory animals, decreases in body weight and body weight gain were the primary treatment-related findings. Dinotefuran was neurotoxic in adult and developing animals. There was no evidence of carcinogenicity in mice or female rats after longer-term dosing; however, an increase in the incidence of benign thyroid tumours was noted at a very high-dose level in male rats. There was no evidence of increased susceptibility of the young in the reproduction, DNT, DIT, or developmental toxicity studies. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose level at which these effects occurred in animal tests.

Quantitative risk assessments for dinotefuran were conducted for ready-to-use, spot-on pet care products for dogs. Residential exposures to individuals handling and contacting treated dogs, including toddlers, are not expected to result in risks of concern when Vectra 3D products are used according to label directions.

Applicators handling Prescription Treatment Brand Alpine products are not expected to be exposed to levels of dinotefuran that will result in unacceptable risks when the end-use products are used according to label directions. The personal protective equipment of a long-sleeved shirt, long pants, chemical resistant gloves and shoes plus socks on the product label is adequate to protect workers. In additional, a respirator will be added to the label during loading and application of the dust product.

Residential exposure to individuals contacting treated areas is not expected to result in unacceptable risks when Prescription Treatment Brand Alpine products are used according to label directions where residents cannot re-enter treated areas until residues have dried or have settled.

7.2 Environmental Risk

The proposed uses of Prescription Treatment Brand Alpine products containing dinotefuran are for indoor and limited outdoor uses. When used according to the label directions of the proposed end-use products, environmental releases of dinotefuran are expected to be minimal. Label statements will be required on the proposed Prescription Treatment Brand Alpine products labels to limit the outdoor use of these dinotefuran-containing products to crack and crevice or spot treatments, as well as localized treatment of the exterior surface of structures and direct treatment of the nests of stinging insects, such as bees, hornets and wasps. In addition, labels must indicate that direct application of these dinotefuran containing end-use products to water is not allowed.

It should be noted that that an environmental risk assessment for the registration of Vectra 3D Domestic class products is not required. These proposed Domestic class products are spot-on products for use on companion animals. Because of the use pattern, dinotefuran is not expected to result in environmental exposure.

7.3 Value

Vectra 3D Products

Vectra 3D products, containing dinotefuran as well as permethrin and pyriproxyfen, are new tools to kill and/or repel labelled pests on dogs and puppies over 4.5 kg and over seven weeks of age. They are the only pesticide products registered for use on dogs to kill walking dandruff mite, which is a minor pest.

Prescription Treatment Brand Alpine Products

Prescription Treatment Brand Alpine products are new tools that can be used with other control practices against labelled structural pests indoors and/or on the exterior surfaces of structures and inside transportation vehicles. Some of the labelled pests (for example, bed bugs, cockroaches, wasps) impact the health and well-being of people. Dinotefuran represents a new mode of action for several of the labelled pests. The dust product combines dinotefuran with silicon dioxide to kill various structural pests, kill nests of stinging insects and can be used in locations where the use of sprays is not possible. The spray product kills many structural pests on contact and provides residual control of ants. The bait product controls German and oriental cockroaches.

8.0 Proposed Regulatory Decision

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

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

List of Abbreviations

µg	micrograms
µg/kg a.i.	Micrograms per kilogram of active ingredient
a.i.	active ingredient
AD	administered dose
AUC	area under the curve
BCDN	N-methyl-1,4,4a,5,6,7a-hexahydrofuro[2,3-d]pyrimidin-2-amine
bw	body weight
bwg	bodyweight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CBI	Confidential Business Information
cm	centimetres
C_{max}	maximum plasma concentration
CPMA	Canadian Pest Management Association
DACO	data code
DIT	developmental immunotoxicity
DN	1-methyl-3-(tetrahydro-3-furylmethyl)guanidine
DN-3-OH	1-(3-hydroxytetrahydro-3-furylmethyl)-3-methylguanidine
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity
EP	end-use product
F_1	first generation
F_2	second generation
fc	food consumption
fe	food efficiency
g	gram
GD	gestation day
GI	gastrointestinal
Hct	hematocrit
Hgb	hemoglobin
HPLC	High-performance liquid chromatography
HPLC-MS	High-performance liquid chromatography with mass spectrometry
HPLC-MS/MS	High-performance liquid chromatography with tandem mass spectrometry
HPLC-UV	High-performance liquid chromatography with UV detection
hr(s)	hour(s)
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{ow}	*n*–octanol-water partition coefficient
kPa	kilopascal
L	litre
LC_{50}	lethal concentration 50%
LD	lactation day
LD_{50}	lethal dose 50%
LOAEC	lowest observed adverse effect concentration
LOAEL	lowest observed adverse effect level

LOD	limit of detection
LOQ	limit of quantitation
MAS	maximum average score
mg	milligram
mg/kg bw/day	Milligrams per kilogram of body weight per day
MG	1-methylguanidine
MIS	maximum irritation score
mL	millilitre
MNG	1-methyl-2-nitroguanidine
MOE	margin of exposure
MRID	United States Master Record Identification Number
MS	mass spectrometry
m/z	mass-to-charge ratio
N/A	not applicable
NAFTA	North American Free Trade Agreement
nm	nanometre
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NZW	New Zealand white
p	statistical probability
P	parental generation
PCPA	Pest Control Product Act
PHED	Pesticide Handlers Exposure Database
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	personal protective equipment
ppm	parts per million
RBC	red blood cell
rel	relative
SA	surface area
SPN	Science Policy Note
T_{max}	time to maximum plasma concentration
$T_{1/2}$	half-life
UF	1-methyl-3-(tetrahydro-3-furylmethyl)urea
USEPA	United States Environmental Protection Agency
UV	ultraviolet
wc	water consumption
wk	week
wt	weight
X	times
♂	male
♀	female
↓	decrease
↑	increase

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type		LOD/LOQ	Reference
Hive	N/A	Dinotefuran	HPLC-MS/MS	*m/z* 203→129	0.010 mg/kg	1917861, 1917865, 1917863
Plant	N/A	Dinotefuran	HPLC-MS/MS	*m/z* 203→129	0.008 mg/kg	1917437
		DN	HPLC-MS/MS	*m/z* 158→102	0.008 mg/kg	
		UF	HPLC-MS/MS	*m/z* 159→102	0.008 mg/kg	
Animal	N/A	Dinotefuran	HPLC-MS/MS	*m/z* 203→129	0.01 mg/kg	1917426, 1917427
		DN	HPLC-MS/MS	*m/z* 158→102	0.01 mg/kg	
		UF	HPLC-MS/MS	*m/z* 159→102	0.01 mg/kg	
Soil	N/A	Dinotefuran	HPLC-UV	270 nm	0.010 mg/kg	1917679, 1917682, 1917688, 1917692
		MNG	HPLC-MS/MS	*m/z* 119→73	0.010 mg/kg	1917683, 1917685
Sediment	The soil methods may be extended to sediment					
Water (fresh)	N/A	Dinotefuran	HPLC-UV	270 nm	0.05 µg/mL	1917767
		MG	HPLC-MS	*m/z* 74.2	0.05 µg/mL	
		UF	HPLC-MS	*m/z* 159.0	0.01 µg/mL	
		DN-3-OH	HPLC-MS	*m/z* 174.1	0.01 µg/mL	
		BCDN	HPLC-MS	*m/z* 156.1	0.01 µg/mL	
		DN	HPLC-MS	*m/z* 158.0	0.01 µg/mL	
Water (salt)	N/A	Dinotefuran	HPLC-UV	286 nm	0.05 µg/mL	1917952, 1917955

Table 2a Toxicity Profile of Prescription Treatment Brand Alpine Pressurized Insecticide, Containing Dinotefuran

(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 (Up-down procedure) Sprague Dawley rat PMRA# 1918782	LD_{50} (♀) > 5000 mg/kg bw **Low Toxicity** No clinical signs of toxicity.
Acute dermal Sprague Dawley rat PMRA# 1918784	LD_{50} (♂/♀) > 5000 mg/kg bw **Low Toxicity** No clinical signs of toxicity. No signs of dermal irritation.

Study Type/Animal/PMRA#	Study Results
Acute inhalation Sprague Dawley rat PMRA# 1918786	LC_{50} (♂/♀) > 2.05 mg/L **Low Toxicity** Nasal discharge, hunched posture and hypoactivity were noted in all animals during exposure. Animals appeared normal upon removal from the test chamber and throughout the remainder of the study.
Eye irritation New Zealand White (NZW) rabbit PMRA# 1918788	MAS = 0.9 MIS = 8.7 (1 hr) **Minimally irritating**
Dermal irritation NZW rabbit PMRA# 1918190	MAS = 0.2 MIS = 1.0 (1 hr) **Minimally irritating**
Dermal sensitization (Buehler) Hartley albino guinea pig PMRA# 1918792	**Negative**

Table 2b Toxicity Profile of Prescription Treatment Brand Alpine Dust Insecticide, Containing Dinotefuran

(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 (Up-down procedure) Sprague Dawley rat PMRA# 1918842	LD_{50} (♀) > 5000 mg/kg bw **Low Toxicity** No clinical signs of toxicity.
Acute dermal Sprague Dawley rat PMRA# 1918844	LD_{50} (♂/♀) > 5000 mg/kg bw **Low Toxicity** No clinical signs of toxicity. No signs of dermal irritation.
Acute inhalation Sprague Dawley rat PMRA# 1918846	LC_{50} (♂/♀) > 2.05 mg/L **Low Toxicity** Hunched posture and hypoactivity were noted during the first 30 minutes, visibility poor thereafter. Animals appeared normal upon removal and throughout the remainder of the study.

Study Type/Animal/PMRA#	Study Results
Eye irritation NZW rabbit PMRA# 1918848	MAS = 5.7 MIS = 15 (1 hr) All scores not zero at 72 hours **Mildly irritating**
Dermal irritation NZW rabbit PMRA# 1918850	MAS = 0 MIS = 1.0 (1 hr) **Non-irritating**
Dermal sensitization (Buehler) Hartley albino guinea pig PMRA# 1918852	**Negative**

Table 2c Toxicity Profile of Prescription Treatment Brand Alpine Cockroach Gel Bait Reservoir, Containing Dinotefuran

(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 Sprague Dawley rat PMRA# 1918909	LD_{50} (♂/♀) > 2000 mg/kg bw **Low Toxicity** No clinical signs of toxicity.
Acute dermal Sprague Dawley rat PMRA# 1918911	LD_{50} (♂/♀) > 5000 mg/kg bw **Low Toxicity** No clinical signs of toxicity. No signs of dermal irritation.
Acute inhalation	The end-use product is a gel in an enclosed bait station; as such, inhalation is not a likely route of exposure.
Eye irritation NZW rabbit PMRA# 1918915	MAS = 0 MIS = 0 (1 hr) **Non irritating**
Dermal irritation NZW rabbit PMRA# 1918915	MAS = 0.1 MIS = 0.7 (1 hr) **Minimally irritating**
Dermal sensitization (Buehler) Hartley albino guinea pig PMRA# 1918918	No evidence of sensitization; however, study considered supplemental as only half of the required amount of test material was used.

Table 2d Toxicity Profile of Vectra 3D Products, Containing Permethrin, Dinotefuran and Pyriproxyfen

(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 Sprague Dawley rat PMRA# 1918025	LD_{50} (♂/♀) > 5000 mg/kg bw **Low Toxicity** Hypoactivity was evident on the day of dosing only. Red facial staining and soft feces were recorded on study day 1, but resolved by study day 2. Anogenital staining was recorded in 1♀ throughout the study. Body weight loss was observed in one animal during week 2.
Acute dermal Sprague Dawley rat PMRA# 1918031	LD_{50} (♂/♀) > 5000 mg/kg bw **Low Toxicity** Clinical signs were limited to anogenital staining. No signs of dermal irritation.
Acute inhalation Waiver request PMRA# 1918037	Waiver request granted. The product is a liquid applied directly, via an applicator, to the skin of the animal; thus application will not likely generate respirable particles.
Eye irritation NZW rabbit PMRA# 1918044	MAS = 35.2 MIS = 37 (24 hrs) **Moderately irritating** Soft feces were noted in 1♀ on day 2 only.
Dermal irritation NZW rabbit PMRA# 1918049	MAS = 2.6 MIS = 3.3 (24 hrs) **Mildly irritating**
Dermal sensitization (Buehler) Hartley albino guinea pig PMRA# 1918057	**Negative**

Table 2e Safety to treated animals of Vectra 3D for Dogs and Puppies Over 7 Weeks of Age, Containing Permethrin, Dinotefuran and Pyriproxyfen

Study Type/Animal/PMRA#	Study Results
Safety to treated animals – adult dogs Beagle dog PMRA# 1918063	Six animals/sex/group were administered the test substance as 1 application of the proposed dose (1X), 3 applications, each an hour apart (3X), 5 applications, each an hour apart (5X) or vehicle control (formulants only, active ingredients omitted) on study day 0, then observed for 14 days. There were no clinical signs attributed to treatment. Cosmetic effects in hair coat noted at ≥ 1 hr post-administration in all animals included matting, greasy

Study Type/Animal/PMRA#	Study Results
	appearance, clumping, spiking, discoloration and deposits. These effects resolved by study day 5. There were no treatment-related hematological or clinical chemistry findings. ↓ fc on day 1 in all animals; however, most pronounced in control and 5X animals, suggesting that it was possibly due to formulant(s) and/or stress of handling during 5 applications. Estimated exposure levels/application (1X) Permethrin = 1230 mg Dinotefuran = 167 mg Pyriproxyfen = 17 mg Total dose received **1X group:** Permethrin: 66–122 mg/kg bw Dinotefuran: 9.0–17 mg/kg bw Pyriproxyfen: 0.9–1.7 mg/kg bw **3X group:** Permethrin: 168–362 mg/kg bw Dinotefuran: 23–49 mg/kg bw Pyriproxifen: 2.3–5.0 mg/kg bw **5X group:** Permethrin: 320–615 mg/kg bw Dinotefuran: 43–84 mg/kg bw Pyriproxifen: 4.4–8.5 mg/kg bw
Study Type/Animal/PMRA#	**Study Results**
Safety to treated animals – 7-week old puppies Beagle dog PMRA# 1918080	Six animals/sex/group were administered the test substance as 1 application of the proposed dose (1X), 3 applications, each an hour apart (3X), 5 applications, each an hour apart (5X) or vehicle control (formulants only, active ingredients omitted) on study day 0, then observed for 14 days. Cosmetic effects in hair coat noted at ≥ 1 hr post-administration in all animals included matting, spiking, clumping, greasy appearance, discoloration and deposits. These effects resolved by study day 5 for all groups. 1X Ataxia was noted in 1 puppy at 2 hrs post-exposure only. Pruritus was also noted in this animal at 1 and 5 hrs post-dosing. 5X Tremors were observed in 2 puppies at 4 hrs postapplication, resolving within 2 hrs. Ataxia was also present in one of these puppies at 5 hrs only. Ataxia was observed in 1 other puppy, along with lethargy on study days 1 and 2. Lethargy was also recorded in this animal on the morning of study day 5. This animal had an abnormal appearance at the site of application that was observed between study days 1 and 6, but not on a consistent basis. In addition, pruritus was noted in this animal at 3 hrs, and on study days 3–6. An increased incidence of abnormal feces (not specified but could include loose feces with blood/mucous, diarrhea (watery/runny) or dry hard feces) was observed in these animals beginning immediately after dosing, and continuing throughout treatment.

Study Type/Animal/PMRA#	Study Results
	Estimated exposure levels/application (1X) Permethrin = 343 mg Dinotefuran = 47 mg Pyriproxyfen = 5 mg Total dose received **1X group:** Permethrin: 137–229 mg/kg bw Dinotefuran: 19–31 mg/kg bw Pyriproxyfen: 2.0-3.3 mg/kg bw **3X group:** Permethrin: 368–792 mg/kg bw Dinotefuran: 50–108 mg/kg bw Pyriproxyfen: 5.4–11.5 mg/kg bw **5X group:** Permethrin: 591–1429 mg/kg bw Dinotefuran: 81–196 mg/kg bw Pyriproxyfen 8.6–20.8 mg/kg bw
Safety to treated animals – 7-week old puppies (2 administrations) Beagle dog PMRA# 1918094	Six animals/sex/group were administered the test substance as 1 application of the proposed dose level (1X), 3 applications, each an hour apart (3X), 5 applications, each an hour apart (5X) or vehicle control (formulants only, active ingredients omitted) on study day 0. A second administration, of the same dose level/number of applications, was performed on study day 14. Puppies were observed for 28 days. There were no clinical signs attributed to treatment. Vomiting was noted in one 5X ♀ prior to treatment 2 on day 0 and 1 control ♀ at 2 hrs post administration on day 14, as well as sporadically in individual animals with no relation to treatment. Lethargy was noted in 1 control ♂ on day 17 and one 1X ♀ on day 24, with no relation to treatment. Ataxia and tremor were not observed in any animal. The incidence of loose feces was low and similar across all dose groups. On day 1, fc was ↓ in all dose groups. Cosmetic effects in hair coat noted at ≥ 1 hr post-administration in all animals included matting, spiking, clumping, greasy appearance, discoloration and deposits. These effects resolved by study days 5 and 17, after the first and second administration, respectively, for all groups. Estimated exposure levels/application (1X) Permethrin = 561 mg Dinotefuran = 83 mg Pyriproxyfen = 8.3 mg Total dose received **1X group:** Permethrin**:** 198–435 mg/kg bw Dinotefuran: 29–64 mg/kg bw Pyriproxyfen: 2.9–6.4 mg/kg bw **3X group:** Permethrin: 448–1476 mg/kg bw Dinotefuran: 66–218 mg/kg bw Pyriproxyfen: 6.6–21.8 mg/kg bw

Study Type/Animal/PMRA#	Study Results
	5X group: Permethrin: 845–2063 mg/kg bw Dinotefuran: 125–305 mg/kg bw Pyriproxyfen: 12.5–31 mg/kg bw
Safety to treated animals – 7-week old puppies (2008) Beagle dog PMRA# 2108524	Four/sex/group were administered the test substance as 5 applications, an hour apart (5X) or vehicle control (formulants only, active ingredients omitted) on study day 0, then observed for 14 days. Loose feces were noted in one 5X ♂ at pre-treatment and 1 hr post-administration and in 1 control ♂ in the morning on study day 1. There were no clinical signs attributed to treatment. ↓ fc was noted on day 1 in 2 control ♀ and 2 5X ♀, as well as at later time points, sporadically for these animals. This may have been possibly due to the formulant(s) and/or the stress of handling over 5 applications. Cosmetic effects in hair coat noted at ≥ 1 hr post-administration in all animals included greasy appearance, clumping, spiking, matting and deposits. These effects resolved by study day 2 for both groups. Estimated exposure levels/application (1X) Dinotefuran = 325 mg Pyriproxyfen = 46 mg Total dose received **5X group:** Dinotefuran: 540–772 mg/kg bw Pyriproxyfen: 76–108 mg/kg bw
Veterinarian field study Dog PMRA# 1918107	Dogs were examined by a veterinarian on study day 0 for general health and then treated at home by the owner with either the product or an alternative registered topical treatment (K9 Advantix). Animals were observed in the home by the owner for adverse effects. The veterinarian followed up via telephone on study days 1 and 30 and recorded any findings reported. Vectra 3D (204 dogs) Two dogs exhibited signs which may have been related to permethrin use (biting at treatment site, lethargy, staring, decreased appetite); however, study authors excluded these animals due to treatment with another flea product 3 weeks prior (deviation from the 4 week setback period specified in protocol) and poor health (overweight animal, with multiple visits to veterinarian for lethargy, infections and itching in 2 years prior). Loose feces were reported in a third animal. Abnormal behaviour was noted in a fourth dog (appeared depressed, decreased appetite) but was dismissed due to a pre-existing condition (gastritis) that was remedied with a change in diet. A fifth dog was reported to be “acting funny” with no clarification. At the 30-day follow-up, 5 dogs were reported with abnormal behaviour. Three dogs were noted to have increased activity, one dog was reported to wheeze 2-3 times/day, making a gasping sound and then sneezing and one dog was reported to have been less active, with vomiting and diarrhea for about a week. Cosmetic appearance findings were reported in 16 dogs and included: spiking of hair, sticky or clumpy hair, wet, oily appearance, greasy and flakey, appeared dirty, skin slightly red but not painful. Alopecia was reported in 1 animal. K9 Advantix (37 dogs) One dog was noted as less active and one dog was noted to be itchy at the

Study Type/Animal/PMRA#	Study Results
	treatment site Cosmetic appearance findings were reported in 4 dogs and included: sticky or clumpy hair, oil and itchy, and wet. Alopecia was reported in 1 animal.

Table 3 Toxicity Profile of Technical Dinotefuran (MTI-446)

[Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. NOAELs and LOAELs are expressed as ♂/♀, unless otherwise specified. Organ weight effects reflect both absolute organ weights and relative organ to body weights unless otherwise noted. Effects observed above the LOAEL(s) as well as non-adverse effects observed below the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.]

Study Type/Animal/PMRA#	Study Results
Toxicokinetics Sprague Dawley rat PMRA# 1917562	In a preliminary study, distribution was similar regardless of position of radiolabel; therefore, animals were administered MTI-446 (dinotefuran) in a 1:1 ratio of both ^{14}C-radiolabels (guanidine and tetrahydrofuran groups) for the principal investigations. Low dose = 50 mg/kg bw/day; high-dose = 1000 mg/kg bw/day In order to assess absorption, distribution, metabolism and excretion, animals were dosed via gavage with a single low-dose, repeat low-dose (7 days of ^{14}C labeled MTI-446), repeat low-dose (first 14 days unlabeled, final day with ^{14}C labeled MTI-446), or single high-dose. Enterohepatic recirculation was assessed using bile-cannulated animals (single gavage low- or high-dose). An additional group received a single low-dose intravenous administration. Pregnant ♀s were administered a single low-dose on GD18 via gavage to assess placental transfer and measure levels of MIT-446 in maternal and fetal tissues. Lactating ♀s were administered a single low-dose on LD12 via gavage to assess lactational transfer and measure levels of MIT-446 in milk. **Absorption/Elimination:** MTI-466 was rapidly and readily (92–98%) absorbed with maximum plasma concentrations (C_{max}) of 40.8–47.4 and 471–566 ppm noted at 0.25–0.63 and 2.0–2.1hrs (T_{max}) following single/repeated low dosing, or a single high-dose, respectively. Elimination was rapid for single/repeat low dose groups with elimination half-lives ($T_{½}$) ranging from 3.64–7.86 hrs, with the exception of the repeat-dose ♀ animals, which had a $T_{½}$ of 16.1 hrs. Animals administered a single high-dose had slightly longer $T_{½}$ (13.8/15.2 hrs for ♂/♀, respectively). AUC values were 69–110 and 2360–2660 (ppm/hr) for low and high-doses, respectively, indicating that the toxicokinetic characteristics of MTI-466 were considered to be linear within a dose range of 50 to 1000 mg/kg bw. Similar recoveries were recorded following oral and intravenous dosing, indicating almost complete absorption from the intestinal tract.

Study Type/Animal/PMRA#	Study Results
	Distribution: Radiolabels were widely distributed in all tissues. Following a single low dose, concentrations in the kidneys, stomach, urinary bladder, intestinal tract, prostate, testes and bone (♀ only) were noted to be higher than the plasma on at least one occasion between 0.5 and 4 hrs. Brain concentrations were relatively low. Concentrations in all tissues quickly declined, with levels below the LOD in most tissues at 168 hrs post-dosing. The only exceptions were skin (♂), kidney (♂) and mammary gland (♀). Plasma levels were low following repeat low or single high-dose administration, with highest concentrations noted in mammary gland (♀) and skin. Repeated administration did not increase tissue concentrations or prolong clearance. Disposition of radioactivity was similar following single and multiple regimens and after administration of low and high-doses. Whole-body autoradiography findings were consistent with these findings. **Excretion:** MTI-466 was eliminated mainly through the urine (88–99%) and was 84–99% complete within 24 hrs of treatment. Fecal recovery and cage wash accounted for 1.1–3.2% and 0.6–7.0%, respectively of the radioactivity. Limited amounts of radioactivity (≤0.88%) were recovered in the bile. Route and rate of elimination were not influenced by sex, dose level or dosing regimen. Expired air amounted to 0.01–0.05% of administered dose. **Metabolism:** Unchanged MTI-466 was the major component in urine (92–97%). It was also the primary component in the plasma, milk, bile, feces, and most tissues collected 4–8 hrs after treatment, regardless of dose level, with less than 10% of AD metabolized. There were no apparent differences in metabolism related to treatment regimen or dose. Urinary metabolites (2–6% of AD) formed via enzymatic hydroxylation on the tetrahydrofuran ring to generate PHP (6-hydroxy-5-(2-hydroxyethyl)-1-methyl-1,3-diazinane-2-ylidene-N-nitroamine) isomers (main metabolites), followed by further oxidation, reduction and acetylation. **Placental transfer:** Radioactivity was rapidly transferred from maternal blood to fetuses, and distributed to fetal tissues. Maximum concentrations occurred in all fetal tissue, with the exception of brain, within 0.5 hrs of maternal treatment. Maximum fetal brain concentrations were noted at 1.5 hrs. Thereafter, radioactivity in all tissues declined rapidly to low levels within 4 hrs. Similar concentrations of radioactivity were noted in maternal and fetal blood, suggesting a rapid equilibrium and similar tissue distribution in fetal and maternal tissues. **Lactational transfer:** Radioactivity was rapidly transferred from maternal blood to milk. Maximum concentrations for plasma and milk (29.3 and 34.8 ppm, respectively) occurred at 0.5 hours after maternal treatment. Concentrations in milk declined rapidly to 6.51 ppm at 4 hrs. $T_{½}$ for milk was calculated to be 1.39 hrs, indicating that radioactivity levels would be below detection limits at 24 hours post-treatment. For all parameters measured in this study, no sex-related or dose-related differences or label position effects were found.
Toxicokinetics Sprague Dawley rat – neonate (PND12) PMRA# 1917569	Neonatal rats were administered a single gavage dose of (50 mg/kg bw) ^{14}C MTI-446 radiolabelled on the guanidine group on PND 12. **Absorption:** Absorption from the GI tract was > 75% at 4 hrs, the last sampling time point. C_{max} of 21 ppm in both sexes was detected at 0.5 hrs, thereafter declining to 9 ppm at 4 hrs. The GI tract and contents contained 56–60% of AD at 0.5 hrs, substantially more than noted in the adult study at this time-point (10–15%), indicating reduced oral absorption (<50% in neonates versus 90% in adults).

Study Type/Animal/PMRA#	Study Results
	Distribution/Elimination: Concentrations in blood, plasma and liver were comparable at each time point; however, concentrations in the stomach and kidneys exceeded plasma concentrations. Whole-body autoradiography data indicated that radiolabelled MTI-466 was widely distributed throughout organs and tissues with most radioactivity contained in the stomach (and contents), kidneys, urinary bladder, and urine. Maximum tissue concentrations occurred at either 0.5 or 1.5 hrs post-dosing, mainly declining thereafter; however, concentrations in the kidney, urinary bladder and urine increased, indicating predominantly urinary elimination. Elimination from most tissues was incomplete at 4 hrs post-dosing. Low levels of radioactivity occurred in the brain. When compared to the adult study, radioactivity levels in plasma and kidneys of pups were lower at 0.5 hrs and higher at 4 hrs, indicating that urinary elimination may be slower in neonatal animals. This finding, along with the higher levels noted in the GI tract indicate that oral absorption and urinary elimination are slower in neonatal animals.
Lactational transfer Sprague Dawley rat PMRA# 2109023	Lactating rats were administered gavage doses of 50 or 500 mg/kg bw/day ^{14}C MTI-446 radiolabelled on the guanidine group on LD 2, 4, 8 and 12. Concentrations in maternal milk, whole blood and plasma were determined at 0.5 and 1.5 hrs, and at 2 and 4 hrs, post-dosing for low- and high-dose animals, respectively. No unusual appearance or behaviour in pups or dams. No effects on bw. 50 mg/kg bw At 0.5 hrs, concentrations of radioactivity in blood and plasma were similar (30.1–35.2 ppm), with concentrations in milk roughly twofold higher (55.2–62.9 ppm). Although concentrations declined by half at 1.5 hrs (blood/plasma 13.9–17.5 ppm; milk 26.4–36.9 ppm), concentrations in milk remained twofold higher. Concentrations in each respective matrix were similar across all sampling days (LD 2, 4, 8, 12). 500 mg/kg bw Concentrations of radioactivity in all matrices were highest on day LD 2, for the remaining sampling days levels were similar. At 2 hrs, concentrations in blood and plasma were similar (136–144 ppm on LD 2, 104–114 ppm on remaining days), with concentrations in milk (199 ppm on LD 2, 160–187 ppm on remaining days) 1.4–1.7 times those in the blood/plasma. At 4 hrs, concentrations in the blood/plasma (90–96 ppm on LD 2, 70–77 ppm remaining days) were reduced to 64–71% of the values observed at 2 hrs. Concentrations in the milk (141, 114, 136, 196 ppm on LD 2, 4, 8, 12, respectively) were also reduced to 71–73% of the values observed at 2 hrs on LDs 2, 4, and 8; however, concentrations in the milk at 4 hrs on LD 12 were 110% of that observed at 2 hrs. Concentrations in the milk were 2.5–2.7 times that of the blood/plasma at this time-point. Although the difference between the 2 dose levels was 10-fold, only a fourfold increase in concentration was noted for animals administered 500 mg/kg bw.

Study Type/Animal/PMRA#	Study Results
Acute oral toxicity Sprague Dawley rats PMRA# 1917262	LD_{50} (♂) = 2804 (1947-4037) mg/kg bw LD_{50} (♀) = 2000 (1354-2954) mg/kg bw LD_{50} (combined) = 2450 (1942-3090) mg/kg bw **Slight Toxicity** Clinical signs at ≥ 2000 mg/kg bw included hypoactivity, staggered gait, hunched posture, prostration, red stained face, miosis, lacrimation, excessive salivation, tachypnea, dyspnea, soft stool, yellow stained urogenital area, tonic or clonic convulsions, tremors and death. Deaths occurred on day of dosing or day 1. Surviving animals appeared normal by day 3.
Acute oral toxicity CD-1 mouse PMRA# 1917269	LD_{50} (♂) = 2450 (1801–3331) mg/kg bw LD_{50} (♀) = 2275 (1537–3369) mg/kg bw LD_{50} (combined) = 2371 (1884–2983) mg/kg bw **Low Toxicity** Clinical signs at ≥ 2000 mg/kg bw included dyspnea, tonic convulsions, tremors, staggered gait, hypoactivity and/or death. Deaths occurred on day of dosing. Surviving animals appeared normal by day 1.
Acute dermal toxicity Sprague-Dawley rats PMRA# 1917276	LD_{50} > 2000 mg/kg bw **Low Toxicity** Clinical signs were limited to red stained faces on the day of treatment.
Acute inhalation toxicity (nose-only) Wistar rats PMRA# 1917287	LC_{50} > 4.09 mg/L **Low Toxicity** No clinical signs of toxicity.
Eye irritation NZW rabbits PMRA# 1917289	MAS = 8.2 MIS = 14.8 (24 hrs) **Minimally irritating**
Eye irritation NZW rabbits PMRA# 1917297	MAS = 0 MIS = 7.7 (1 hr) **Non-irritating**
Dermal irritation NZW rabbits PMRA# 1917302	MAS = 0.06 MIS = 0.5 (1 hr) **Minimally irritating**
Dermal sensitization (Guinea Pig Maximisation test) Hartley guinea pigs PMRA# 1917307	Non-sensitizer

Study Type/Animal/PMRA#	Study Results
28-day dose range-finding (dietary) CD-1 mouse PMRA# 1917313	NOAEL not established as this was a dose range-finding study. ≥ 4612/5359 mg/kg bw/day: ↓ bwg 10303/12289 mg/kg bw/day: ↓ bw, body weight loss in initial wk of dosing; ↑ total protein and albumin (♂)
90-day (dietary) CD-1 mouse PMRA# 1917313	NOAEL = 4442/5414 mg/kg bw/day LOAEL = 10635/11560 mg/kg bw/day Effects at the LOAEL: ↓ bw, ↓ overall bwg, bw loss (wk 1)
28-day dose range-finding (dietary) Sprague Dawley rat PMRA# 1917308	NOAEL not established as this was a dose range-finding study. ≥ 1814/2183 mg/kg bw/day: ↓ bwg, ↓ fc, ↑ cholesterol (♂) 3720/4222 mg/kg bw/day: ↓ bw; ↓ glucose (♂); bw loss during first wk of dosing, ↓ bwg, ↓ fc (♀)
90-day (dietary) Sprague Dawley rat PMRA# 1917310	NOAEL = 34/38 mg/kg bw/day LOAEL = 336/384 mg/kg bw/day Effects at the LOAEL: ↑ vacuolation of adrenal cortex (♂); ↓ bw, ↓ overall bwg (♀)
7-day dose range-finding (capsule) Dog (Beagle) PMRA# 1917320	NOAEL not established as this was a dose range-finding study and limited to 1/sex/group. ≥ 100 mg/kg bw/day: ↑ soft stools; ↓ bwg (♂) 300 mg/kg bw/day: Vomiting, diarrhea and/or mucous stools, ↓ spleen wt; ↓ adrenal wt, ↓ testes wt, ↓ prostate wt (♂)
7 to 14-day dose range-finding (dietary) Beagle dog PMRA# 1917318	NOAEL not established as this was a dose range-finding study and limited to 1/sex/group. The dosing regimen for the test period was variable; doses not converted to mg/kg bw basis. ≥ 20000 ppm: ↓ fc (♀) ≥ 30000 ppm: Protein in urine, ↓ thymus wt; ↓ fc, ↓ adrenal wt (♂); bw loss, immature ovaries (♀) 40000 ppm: Vacuolation of renal tubule; vomiting, bw loss, ↓ spleen wt (♂); diarrhea (♀)
90-day oral (dietary) Beagle dog PMRA# 1917322	NOAEL(♂) = 307 mg/kg bw/day NOAEL(♀) not determined LOAEL = 307/58 mg/kg bw/day Effects at the LOAEL (♀): ↓ bw, ↓ bwg, ↓ fc Effects at LOAEL (♂): ↓ fe (first 2 wks), ↓ pituitary wt
1-year oral (dietary) Beagle dog PMRA# 1917325	NOAEL = 20/22 mg/kg bw/day LOAEL = 111/108 mg/kg bw/day Effects at the LOAEL: ↓ fe, ↓ thymus wt; ultimobranchial cyst in thymus (♂); ↓ bw/bwg, ↑ RBC, Hgb and Hct (♀)
14-day dermal dose range-finding	NOAEL not established as this was a dose range-finding study. ≥ 200 mg/kg bw/day: ↑ incidence slight to moderate atonia (impairment of

Study Type/Animal/PMRA#	Study Results
Sprague Dawley rat PMRA# 1917333	elasticity) at treated site
28-day dermal Sprague Dawley rat PMRA# 1917335	**Systemic toxicity:** NOAEL = 1000 mg/kg bw/day (highest dose level tested) LOAEL not established as no treatment-related effects noted. **Dermal irritation:** NOAEL = 1000/200 mg/kg bw/day LOAEL (♂) not established as no dermal irritation noted. LOAEL (♀) = 1000 mg/kg bw/day Effects at the LOAEL (♀): ↑ incidence and severity of acanthosis/hyperkeratosis in treated skin.
28-day inhalation Wistar rat PMRA# 1917341	NOAEL (♂) not determined as effects occurred down to the lowest dose tested. NOAEL (♀) = 60 mg/kg bw/day LOAEL = 60/179 mg/kg bw/day Effects at the LOAEL (♂): ↓ bw, ↓ bwg, fc Effects at the LOAEL (♀): ↑ thinning fur/hair loss; ↑ incidence protruding eyes (♀)
18-month oncogenicity (dietary) CD-1 mouse PMRA# 1917351, 1917355, 1917359, 1917363, 1917368, 1917372	NOAEL = 345/441 mg/kg bw/day LOAEL = 3694/4728 mg/kg bw/day Effects at the LOAEL: ↓ bw/bwg, ↓ platelet counts (wk 79); ↑ fc, ↓ fe, ↑ pigment in bone marrow – sternum, ↑ adrenal cortical cell hypertrophy (♂) No evidence of oncogenicity.
Two-year combined chronic toxicity/oncogenicity (dietary) Sprague Dawley rat PMRA# 1917381, 1917385, 1917388, 1917392, 1917396, 1917398, 1917401, 1917405, 1917409, 1917413, 1917417, 1917422, 1917425	NOAEL = 100/127 mg/kg bw/day LOAEL = 991/1333 mg/kg bw/day Effect at the LOAEL: ↓ bw/bwg, fc/fe, ↑ number of decedents recorded as thin; ↑ kidney effects (lymphohistiocytic infiltrate, pelvic mineralization and pelvic ulceration) (♂); ↑ uterine wt (♀) There were no treatment-related findings in recovery animals. **Tumours** Thyroid C-cell adenoma (♂): 7/59, 10/59, 10/60, 12/58, 15/60(25%) for 0, 3, 10, 100 and 991 mg/kg bw/day dose levels, respectively (trend: p=0.054; pair-wise control vs. high-dose: p=0.053) [Historical Control: mean = 9.8% (range of 1.7–24%)] Thyroid C-cell carcinoma (♂): 1/59, 0/59, 0/60, 0/58, 0/60 (not statistically significant) for 0, 3, 10, 100 and 991 mg/kg bw/day, respectively Evidence of tumourigenicity in ♂ at a dose level approximating the limit dose of testing.
One-generation reproduction (dietary) dose range-finding Wistar rat PMRA# 1917438, 1917440,	NOAELs not established as this was a dose range-finding study. **Parental toxicity:** ≥700/779 mg/kg bw/day: ↓ bwg and fc; ↓ bw (gestation and lactation) (♀) 1340/1507 mg/kg bw/day: Blood in urine (GD 14–21), soft feces (LD 6–21), small

Study Type/Animal/PMRA#	Study Results
1917444, 1917449, 1917454, 1917460	thymus, small spleen (1♀), red discoloration of ovaries (2♀) (♀) **Reproductive toxicity:** 1340/1507 mg/kg bw/day: ↓ mean implantations/dam, ↑ post-implantation loss, ↓ live pups at birth **Offspring Toxicity:** ≥ 779 mg/kg bw/day: ↓ pup bw (PND 14–21), ↓ bw/bwg post-weaning 1507 mg/kg bw/day: ↑ pup loss (PND 5–21); mortality (1♂ - PND 22; animal with low bw, soft brain noted at necropsy, possibly attributed to autolytic change)
Two-generation reproduction (dietary) Wistar rat PMRA# 1917438, 1917440, 1917444, 1917449, 1917454, 1917460	**Parental toxicity:** NOAEL = 241/268 mg/kg bw/day LOAEL = 822/907 mg/kg bw/day Effects at the LOAEL: ↓ bw/bwg, ↓fc (wks 1–2) [premating (P/ F_1 ♂, F_1♀], ↓ bw/bwg [gestation (P ♀), lactation (P/ F_1 ♀)], ↓ spleen wt (rel to brain; P); soft feces (P/F_1 ♀ - lactation) **Reproductive toxicity:** NOAEL = 241/268 mg/kg bw/day LOAEL = 822/907 mg/kg bw/day Effects at LOAEL: ↓ sperm motility (F_1), tubular degeneration of testes (F_1)(♂); ↓ primordial follicles (F_1), ↑ antral follicles (F_1), ↑ corpora lutea (F_1), ↓ uterus wt (F0 - rel to brain), ↑ uterine atrophy, vaginal effects (↑atrophy and/or vacuolar degeneration of mucosa) (♀) **Offspring Toxicity:** NOAEL = 268 mg/kg bw/day LOAEL = 907 mg/kg bw/day Effects at LOAEL: ↓ bw (F_1/F_2 - PND 14/21) and bwg (F_1/F_2 – throughout post-natal period), ↓ grip strength (forelimb and hindlimb; F_1), ↓ spleen wt (F_1/ F_2), ↓ thymus wt (abs and rel to brain; F_2), ↓ abs brain wt (F_2) No evidence of sensitivity of the young.
Developmental toxicity dose - range finding (gavage) Sprague Dawley rat PMRA# 1917472	NOAEL not established as this was a dose range-finding study. **Maternal toxicity:** 1000 mg/kg bw/day: bw loss (GD 6–7)↓ bwg, ↓ fc (GD 6–11) **Developmental toxicity:** There were no adverse effects on fetal development.
Developmental toxicity (gavage) Sprague Dawley rat PMRA# 1917476	**Maternal toxicity:** NOAEL = 300 mg/kg bw/day LOAEL = 1000 mg/kg bw/day Effects noted at LOAEL: Hypoactivity (1♀; GD 8–10), ↓ bwg (more pronounced GD 6–9), ↓ fc (GD 6–10), ↑ wc (GD 10–13) **Developmental toxicity:** NOAEL = 300 mg/kg bw/day LOAEL = 1000 mg/kg bw/day

Study Type/Animal/PMRA#	Study Results
	Effects noted at LOAEL: Delayed ossification (on a fetal basis) of metatarsals 2–5. No evidence of sensitivity of the young.
Developmental toxicity - single-dose administration range-finding (gavage) NZW rabbit PMRA# 1917494	NOAEL not established as this was a dose range-finding study in unmated female animals. ≥ 300 mg/kg bw/day: Clinical signs of toxicity (hypoactivity, sedation, "erythema reddening" of the nose and auricle) ≥ 1000 mg/kg bw/day: Abdominal position, ↓ fc, abnormal contents (hair ball) in stomach, grey-white plaque on stomach, dark red spot on stomach 2000 mg/kg bw/day: Panting, tremor, ptosis, side position
Developmental toxicity - 14-day dose range-finding (gavage) NZW rabbit PMRA# 1917494	NOAEL not established as this was a dose range-finding study in unmated female animals. ≥ 100 mg/kg bw/day: Coarse coat, dark brown discoloration and rough surface in liver, grey white plaque and rough surface in kidney (1♀) ≥ 300 mg/kg bw/day: Clinical signs of toxicity (hypoactivity, "erythema reddening" of the nose and auricle, sedation, panting), pale brown discoloration of liver, abnormal contents (hair ball) in stomach, dark red spot in fundic region of stomach 1000 mg/kg bw/day: Abdominal position, tremor, side position, ptosis, bradypnea, ↓ bwg, ↓ fc, ↓ wc, grey-white plaque in stomach, gallbladder distended with fluid Clinical signs ceased by day 6 of treatment except for hypoactivity, noted in high-dose animals until termination.
Developmental toxicity dose range-finding (gavage) NZW rabbit PMRA# 1917488	NOAELs not established as this was a dose range-finding study. **Maternal toxicity:** ≥ 100 mg/kg bw/day: Pale brown discoloration of liver, liver enlargement(1♀), gray white plaques on fundic region of stomach (6♀) ≥ 300 mg/kg bw/day: Clinical signs of toxicity (hypoactivity, panting, tremors) GD 6–10, erosion in stomach (1♀) 1000 mg/kg bw/day: Abortions (4♀; ≥ GD20), clinical signs of toxicity ("erythema reddening" of the nose and auricle, prone position, sedation) GD 6–9, bw loss, ↓ fc, dark red plaque in liver, dark red plaque in stomach **Developmental toxicity:** 1000 mg/kg bw/day: ↓ fetal bw (both sexes; only 2 litters)
Developmental toxicity (gavage) NZW rabbit PMRA# 1917498	**Maternal toxicity:** NOAEL = 52 mg/kg bw/day LOAEL = 125 mg/kg bw/day Effects at the LOAEL: Slight bw loss, ↓ bwg, ↓ fc, pale brown discoloration of liver, grey-white plaques in the fundic region of the stomach **Developmental toxicity:** NOAEL = 300 mg/kg bw/day LOAEL not established; no adverse effects noted up to the highest dose tested. No evidence of sensitivity of the young.

Study Type/Animal/PMRA#	Study Results
Bacterial reverse mutation Salmonella typhimurium TA98, TA100, TA1535, TA1537, E. coli WP2:vrA PMRA# 1917509	Negative Tested up to the limit concentration.
In vitro forward mutation assay in mammalian cells Mouse lymphoma L5178Y cells PMRA# 1917520	Negative Tested up to the limit concentration.
In vitro chromosomal aberration assay Chinese hamster lung cells PMRA# 1917532	Negative Tested up to the limit concentration.
In vivo micronucleus assay BDF1 mouse PMRA# 1917542	Negative No mortality, no clinical signs of toxicity.
Bacterial DNA Damage/Repair Bacillus subtilis $RecA^+$ H17, $RecA^-$ M45 PMRA# 1917552	Negative
Acute neurotoxicity (gavage) Sprague Dawley rat PMRA# 1917581, 1917582	NOAEL = 750/325 mg/kg bw LOAEL = 1500/750 mg/kg bw Effects at the LOAEL(♂): ↓ body temperature, ↓ motor activity (day1) Effects at the LOAEL(♀): ↓ rearing (day 1), ↓ motor activity (day 1) Time to peak effect = 3 hrs
90-day neurotoxicity (dietary) Sprague Dawley rat PMRA# 1917602, 1917605, 1917609	NOAEL = 33/40 mg/kg bw/day LOAEL = 327/400 mg/kg bw/day Effects at the LOAEL: ↑ motor activity relative to controls in later subsessions (wk 2); ↓ urine pools in open field (wks 4–13) (♂)
Developmental neurotoxicity (dietary) Sprague Dawley rat PMRA# 2109019	Maternal NOAEL = 237 mg/kg bw/day Maternal LOAEL = 784 mg/kg bw/day Effects at the Maternal LOAEL: ↓ bwg GD 6-9, 6-20 Developmental NOAEL = 79 mg/kg bw/day Developmental LOAEL = 237 mg/kg bw/day Effects at the Developmental LOAEL: equivocal ↑ motor activity counts (♀ - PND 21); motor activity counts were ↑ at the next higher dose level

Study Type/Animal/PMRA#	Study Results
	No evidence of sensitivity of the young, in consideration of the collective evidence from the neurotoxicity studies.
28-day immunotoxicity (dietary) CD-1 mouse PMRA# 2109023	NOAEL = 1053/1438 mg/kg bw/day LOAEL = not established (no effects noted) No evidence of dysregulation of the immune system.
28-day immunotoxicity (dietary) Sprague Dawley rat PMRA# 2109031	NOAEL = 425/430 mg/kg bw/day LOAEL = 992/1018 mg/kg bw/day Effects at the LOAEL: ↓ fc; ↓bw/bwg (♂) No evidence of dysregulation of the immune system.
Developmental immunotoxicity study and range-finding for the DNT study (dietary) Sprague Dawley rat PMRA# 1917619	Purpose of study was to determine dose levels for the definitive DNT study, assess functional immune status of F_1 progeny exposed in utero, during lactation, and for 5 wks following weaning, and to assess the need for immuno-toxicological endpoints in a DNT study. Maternal NOAEL = 1035 mg/kg bw/day Maternal LOAEL = not established (no effects noted) Offspring NOAEL = 318 mg/kg bw/day Offspring LOAEL = 1035 mg/kg bw/day Effects at LOAEL: ↓ bw (PND 13–57 ♂; PND 13–36, 57–64 ♀) No immunological adverse effects on antibody-forming cell response or Natural Killer cell activity. Sensitivity of the young at a dose level exceeding the limit dose.

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Dermal (all durations)[2]	Dog 1-year dietary toxicity	NOAEL = 20 mg/kg bw/day Decreased thymus weight in both sexes, decreased bw/bwg and RBC effects in females	100
Intermediate- to long-term inhalation[3]	Dog 1-year dietary toxicity	NOAEL = 20 mg/kg bw/day Decreased thymus weight in both sexes, decreased bw/bwg and RBC effects in females	100
Non-dietary oral ingestion (acute)	Rabbit gavage developmental toxicity	NOAEL = 125 mg/kg bw Clinical signs (for example, hypoactivity, tremors)	100
Non-dietary oral ingestion (short- to intermediate- term)	90-day dog and 1-year dog dietary toxicity (combined results)	NOAEL = 22 mg/kg bw/day Decreased bw/bwg in females	100

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Aggregate (short-term)	Oral 90-day dog and 1-year dog dietary toxicity (combined results) Inhalation Rat 28-day inhalation toxicity Dermal	Oral NOAEL = 22 mg/kg bw/day Decreased bw/bwg in females Inhalation LOAEC = 0.22 mg/L (approximately 60 mg/kg bw/day) Decreased bw/bwg in males Not applicable	Oral 100 Inhalation 300
Aggregate (intermediate- to long-term)[2,3]	All routes Dog 1-year dietary toxicity	All routes NOAEL = 22 mg/kg bw/day Decreased bw/bwg in females	All routes 100
Cancer	An increase in the incidence of thyroid C-cell adenomas was noted in male rats at a dose level approaching the limit dose, with no corresponding increase in carcinoma. The toxicology reference values selected for the non-cancer risk assessment are protective of these findings.		

[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, end-use-product-specific dermal absorption factors were used in a route-to-route extrapolation.
[3]Since an oral NOAEL was selected, an inhalation absorption factor of 100% was used in route-to-route extrapolation.

Table 5 Applicator Dermal and Inhalation Exposure and Risk Assessment

Formulation	Amount Handled Per Day (kg a.i./day)	Unit Exposure Values (µg/kg a.i. handled)		Dermal Exposure (mg/kg bw/day)	Inhalation Exposure (mg/kg bw/day)	Dermal + Inhalation Exposure (mg/kg bw/day)	Combined MOE
		Dermal	Inhalation				
Aerosol (ready-to-use; applicator only)	0.042 [1]	146598.1	1646	0.07696	0.000864	0.07783	257
Dust (loading and application)	0.0034 [2]	155694	2711	0.002347	0.0001135	0.002461	8130

[1] Amount Handled per Day (kg a.i./day) = 14 cans/day × Net Contents (600 g) × Guarantee (0.5%) × Conversion Factor (kg/1000 g)
[2] Amount Handled per Day (kg a.i./day) = 1.34 kg product/day × Guarantee (0.25%)
[3] Exposure (mg/kg bw/day) = Amount Handled Per Day (kg a.i./day) × Absorption Value × Unit Exposure (µg/ kg ai handled) × Unit Conversion (mg/ 1000 µg) ÷ 80 kg bw
[4] MOE = NOAEL = 20 mg/kg bw/day (intermediate-term reference value) ÷ Exposure; Target MOE = 100

Table 6 Dermal Exposure to Dinotefuran from Treated Hard and Soft Surfaces[1]

Exposure Scenario		Lifestage	Deposited Residue (µg/cm^2)	Fraction transferred	Transferable Residue (µg/cm^2)	TC (cm^2/hr)	ET (hr/day)	Dermal Exposure (mg/kg/day)	Dermal MOE
Perimeter/ Spot (Coarse & Pin Stream)/ Bed bug	Soft surface	Adults	5.5	0.06	0.33	6800	8	0.08078	250
		Children 1<2 years			0.33	1800	4	0.07776	260
	Hard surface	Adults		0.08	0.44	6800	2	0.02693	740
		Children 1<2 years			0.44	1800	2	0.05184	390
Crack and crevice	Soft surface	Adults	1.1	0.06	0.066	6800	8	0.01616	1200
		Children 1<2 years			0.066	1800	4	0.01555	1300
	Hard surface	Adults		0.08	0.088	6800	2	0.00539	3700
		Children 1<2 years			0.088	1800	2	0.01037	1900

[1] Refer to the USEPA (2012) Section 7 for a full description of the algorithms used to determine exposure.

Table 7 Child (1< 2 years) Hand-to-Mouth Exposure to Dinotefuran[1]

Exposure Scenario	Fraction ai on hands	Dermal Exposure (mg/hr)	Hand residue loading (mg/cm^2)	Fraction of hand mouthed	Exposure Time (hours/day)	Incidental Oral Exposure (mg/kg/day)	Incidental Oral MOE
Perimeter/Spot/Bed bug (Coarse & Pin Stream)							
Soft surface	0.15	0.6	0.0446	0.13	4	0.002026	10900
Hard Surfaces		0.8	0.0594		2	0.001351	16300
Crack and crevice							
Soft surface	0.15	0.12	0.0089	0.13	4	0.000405	54300
Hard Surfaces		0.16	0.0119		2	0.000270	81400

[1] Refer to the USEPA (2012) Section 7 for a full description of the algorithms used to determine exposure.

Table 8 Child (1< 2 year) Object-to-Mouth Exposure to Dinotefuran[1]

Exposure Scenario	Deposited Residue (µg/cm^2)	Fraction of residue transferred to object	Object Residue (µg/cm^2)	Exposure Time (hours/day)	Extraction by Saliva	Incidental Oral Exposure (mg/kg/day)	Incidental Oral MOE
Perimeter/Spot/Bed bug (Coarse & Pin Stream)							
Soft surface	5.5	0.06	0.330	4	0.48	0.00431	5100
Hard Surfaces		0.08	0.440	2	0.48	0.00288	7650
Crack and crevice							
Soft surface	1.1	0.06	0.066	4	0.48	0.00086	25500
Hard Surfaces		0.08	0.088	2	0.48	0.00058	38300

[1] Refer to the USEPA (2012) Section 7 for a full description of the algorithms used to determine exposure.

References

A. List of Studies/Information Submitted by Registrant

PMRA Document Number | References

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B. Additional Information Considered

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