Proposed Registration Decision PRD2012-16

NeemAzal Technical, containing Azadirachtin

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Overview

Proposed Registration Decision for NeemAzal Technical, containing Azadirachtin

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of NeemAzal Technical and TreeAzin Systemic Insecticide, containing the technical grade active ingredient azadirachtin, to control emerald ash borer and various insect pests that feed on the foliage of hardwood and softwood trees.

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

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of NeemAzal Technical and TreeAzin Systemic Insecticide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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

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

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

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

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

What Is Azadirachtin?

Azadirachtin is the main component of a mixture of chemical compounds with insecticidal properties extracted from seeds of the tropical neem tree (*Azadirachta indica*). The precise mode of action is unknown; however, azadirachtin does affect insect hormones, interfering with moulting in immature insects and inhibiting reproduction in adult insects. Azadirachtin also has repellant properties, deterring insects from feeding and adult insects from laying eggs on treated plants. Formulated as TreeAzin Systemic Insecticide and injected into the trunks of host trees, it can provide control of emerald ash borer and of various insect pests that feed on the foliage of hardwood and softwood trees.

Health Considerations

Can Approved Uses of NeemAzal Technical Affect Human Health?

TreeAzin Systemic Insecticide, containing NeemAzal Technical, is unlikely to affect your health when used according to label directions.

Potential exposure to NeemAzal Technical may occur when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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.

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

In laboratory animals, NeemAzal Technical was of low acute toxicity via the oral and dermal routes of exposure. It was slightly toxic via the inhalation route, and therefore the hazard statement “CAUTION POISON” must appear on the label. NeemAzal Technical was not irritating to the skin, but was mildly irritating to the eyes, and caused an allergic skin reaction. Consequently, the hazard statements “CAUTION EYE IRRITANT” and “POTENTIAL SKIN SENSITIZER” are required on the label.

The end-use product TreeAzin Systemic Insecticide was of low acute toxicity to laboratory animals via the oral, dermal and inhalation routes of exposure. TreeAzin Systemic Insecticide was not irritating to skin, but was mildly irritating to the eyes. Consequently, the hazard statement “CAUTION EYE IRRITANT’ is required on the label. It caused an allergic skin reaction, and as such, the hazard statement “POTENTIAL SKIN SENSITIZER” is required on the label.

The toxicology database for NeemAzal Technical did not contain the full array of studies normally required for pesticide registration. In the available studies there was no evidence to suggest that NeemAzal Technical damaged genetic material. Health effects in animals given repeated oral doses of NeemAzal Technical included effects on the blood, liver, thyroid and kidney. When NeemAzal Technical was given to pregnant animals, effects on the developing fetus (irregular bone ossification and heart abnormalities) were observed at a dose that also caused toxic effects in the mother, indicating that the young do not appear to be more sensitive to NeemAzal Technical than the adult animal. However, it is not possible to completely describe the potential human health effects of NeemAzal Technical due to the poor quality and limited nature of the available toxicology database. There is literature information reporting adverse reproductive effects in humans and other animals with other related neem compounds.

Although the toxicology database was not complete, consideration was given to the available toxicology studies that were deemed to be acceptable. The use of an additional factor in the risk assessment also serves to further reduce the allowable level of human exposure to Neemazal Technical. In addition, based on the fact that the product is injected directly into trees by licensed Pest Control Operators using a specific, closed delivery system, the exposure is expected to be low.

Residues in Water and Food

An analysis of the residues of azadirachtin in water and food was not required as there are no proposed food uses, and contamination of drinking water is not expected.

Risks in Residential and Other Non-Occupational Environments

Potential exposure and risks to bystanders are expected to be negligible if label directions and precautionary measures are followed.

For bystanders, the exposure is expected to be much less than for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Occupational Risks From Handling TreeAzin Systemic Insecticide

Occupational risks are not of concern when TreeAzin Systemic Insecticide is used according to the label directions, which include protective measures.

Commercial applicators who mix, load, or apply TreeAzin Systemic Insecticide using the EcoJect Tree Injection System can come in direct contact via skin and/or through inhalation exposure. Therefore, the label specifies that TreeAzin Systemic Insecticide must only be used with the EcoJect Tree Injection System and anyone mixing/loading and/or applying TreeAzin Systemic Insecticide must wear long sleeved shirt and long pants, or coveralls over short sleeves and short pants, chemical-resistant gloves and goggles or a face shield during handling, loading, and application of product, and removal, clean-up, and repair of injection equipment. The label also specifies that entry to treated areas by bystanders is restricted until all insecticide is injected into the trees and the drilled holes are sealed. This ensures that there is no potential exposure to TreeAzin Systemic Insecticide from injection holes of host trees after application.

Taking into consideration these label statements, and the expectation of the exposure period for workers, the risks to these individuals are not a concern.

Environmental Considerations

What Happens When NeemAzal Technical Is Introduced Into the Environment?

NeemAzal Technical, containing the active ingredient azadirachtin, is injected into trees to control defoliating and burrowing insects. The risks to earthworms, birds, wild mammals, fish, terrestrial plants, amphibians, aquatic invertebrates, algae, or aquatic vascular plants from the use of azadirachtin as a tree injection is minimal. Risk to pollinators that may be exposed to residues in nectar and pollen from treated trees could, however, not be ruled out. To mitigate the potential risk to pollinators, precautionary and advisory label statements are required on the label and the treatment of hardwood tree species is restricted to the post-bloom period.

When NeemAzal Technical is injected into trees, azadirachtin is translocated from the trunk to other parts of the tree. The extent of translocation may be influenced by a variety of factors, including tree species, climatic conditions, and irrigation. Azadirachtin concentrations are highest in the leaves shortly after treatment and then gradually decline over time, primarily due to hydrolysis, such that the concentration in leaves of trees treated in spring and early summer are very low at leaf senescence.

Non-target organisms, such as birds, mammals and pollinators that feed on fruits, pollen or nectar of treated trees could be exposed to NeemAzal Technical. NeemAzal Technical is, however, not expected to pose a risk to birds and mammals. NeemAzal Technical is highly toxic to insect larvae and thus, has the potential to pose a risk to honeybees if the brood is exposed to contaminated pollen or nectar brought back to the hive by the adults. Similarly, NeemAzal Technical could pose a risk to other arthropods that feed on tree pollen and nectar of treated trees.

Non-target soil dwelling and aquatic invertebrates could also be exposed to NeemAzal Technical residues when the leaves of treated trees fall in autumn; however, because azadirachtin concentrations are low in leaves at senescence, a low environmental risk is expected from this exposure pathway. Biodegradation is expected to be important when the leaves of treated trees fall to soil or water.

Value Considerations

What Is the Value of TreeAzin Systemic Insecticide?

When injected into the trunks of host trees, TreeAzin Systemic Insecticide can provide control of emerald ash borer and various foliage-feeding insect pests.

TreeAzin Systemic Insecticide applied as an injection into the trunks of ash trees can provide control of emerald ash borer, a pest whose larvae bore under the bark of the trees, making them very difficult to control. If not controlled, emerald ash borer usually kills its host trees in North America, and to date the primary means of control has been to remove and destroy infested trees. Trunk injection of TreeAzin Systemic Insecticide can also substantially reduce damage to their respective host trees by a variety of foliage-feeding insect pests. TreeAzin Systemic Insecticide provides a new alternative active ingredient with a new mode of action for control of emerald ash borer and foliage-feeding pests of trees. Application by trunk injection helps conserve natural enemies of pests as well as other non-target organisms that would be exposed to foliar applications of insecticides.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of TreeAzin Systemic Insecticide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with TreeAzin Systemic Insecticide on the skin or through inhalation, anyone mixing, loading and/or applying TreeAzin Systemic Insecticide must: 1) wear a long sleeved shirt and long pants, or coveralls over short sleeves and short pants, chemical-resistant gloves and goggles or a face shield during handling, loading, and application of product and removal, clean-up and repair of injection equipment, 2) use only with the EcoJect Tree Injection System, and 3) restrict entry into treated areas until all insecticide is injected into the trees and the drilled holes are sealed.

Environment

TreeAzin Systemic Insecticide could pose a risk to pollinators. Statements informing the users of the potential risks to these organisms are specified on the product label. Also, to reduce pollinator exposure, application to hardwood trees must be made post-bloom.

Next Steps

Before making a final registration decision on NeemAzal Technical, containing azadirachtin, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on NeemAzal Technical, containing azadirachtin (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

NeemAzal Technical, containing Azadirachtin

1.0 The Active Ingredient, Its Properties and Uses

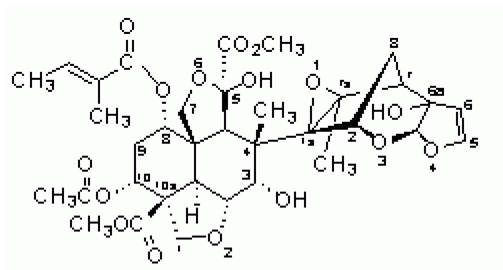
1.1 Identity of the Active Ingredient

Active substance	Azadirachtin
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	Azadirachtin A: 1H,7H-naphtho[1,8-bc:4,4a-c']difuran-5,10a(8H)-dicarboxylic acid, 10-(acetyloxy)octahydro-3,5-dihydroxy-4-methyl-8-[(2-methyl-1-oxo-2-butenyl)oxy]-4-(3a,6a,7,7a,tetrahydro-6a-hydroxy-7a-methyl-2,7-methanofuro[2,3-b]oxireno[e]oxepin-1a(2H)-yl)-dimethylester, [2aR-[2aα,3ß,4ß(1aR*,2S*,3aS*,6aS*,7S*, 7aS*),4aß,5α,7aS*,8ß(E),10ß,10aα,10bß]] Azadirachtin B: Not assigned
2. Chemical Abstracts Service (CAS)	Azadirachtin A: dimethyl [2aR-[2aα,3β,4β(1aR*,2S*,3aS*,6aS*,7S*,7aS*), 4aβ,5α,7aS*,-8β(E),10β,10aα,10bβ]]-10-(acetyloxy) octahydro-3,5-dihydroxy-4-methyl-8-[(2-methyl-1-oxo-2-butenyl)oxy]-4-[(3a,6a,7,7a)-tetrahydro-6a-hydroxy-7a-methyl-2,7-methanofuro[2,3-b]oxireno[e]oxepin-1a(2H)-yl]-1H,7H-naphthol[1,8-bc:4,4a-c']difuran-5,10a(8H)-dicarboxylate Azadirachtin B: dimethyl [2aR-[2aα,3β,4β(1aR*,2S*,3aS*,6aS*,7S*,7aS*), 4aβ,5α,7aS*,-8β(E),10β,10aα,10bβ]]-10-[(2-methyl-1-oxo-2-butenyl)oxy]-octahydro-3,5-dihydroxy-4-methyl-8-hydroxy-4-[(3a,6a,7,7a)-tetrahydro-6a-hydroxy-7a-methyl-2,7-methanofuro[2,3-b]oxireno[e]oxepin-1a(2H)-yl]-1H,7H-naphthol[1,8-bc:4,4a-c']difuran-5,10a(8H)-dicarboxylate

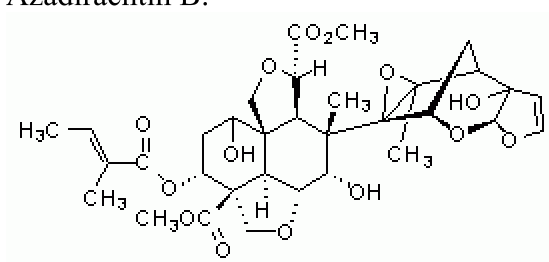
CAS number	Azadirachtin A:	11141-17-6
	Azadirachtin B:	95507-03-2
Molecular formula	Azadirachtin A:	$C_{35}H_{44}O_{16}$
	Azadirachtin B:	$C_{33}H_{42}O_{14}$
Molecular weight	Azadirachtin A:	720.7
	Azadirachtin B:	662.7

Structural formula

Azadirachtin A:



Azadirachtin B:



Purity of the active ingredient Azadirachtin (A+B) at 36.65 %

1.2 Physical and Chemical Properties of the Active Ingredient and End-use Product

Technical Product—NeemAzal Technical

Property	Result
Colour and physical state	Brown to yellow solid powder
Odour	Nutty odour
Melting range	Partially liquefies at 120°C, decomposes above 200°C
Boiling point or range	N/A - the product is a solid
Density	0.71 g/mL
Vapour pressure at 20°C	Estimated at 10 Pa for both Azadirachtin A and B
Henry’s law constant at 20°C	1.25×10^{-21} (atm m^3/mole)

Property	Result	
Ultraviolet (UV)-visible spectrum	λ_{max} = 215 nm	
Solubility in water at 20°C	0.57 g/L	
Solubility in organic solvents at 20°C (g/L)	Solvent	Solubility
	Acetone	> 200
	Ethyl acetate	> 200
	Dichloromethane	> 200
	Isopropanol	51.51
	Toluene	15.46
	n-Hexane	1.83
n-Octanol-water partition coefficient (K_{ow})	Azadirachtin A:	log K_{ow} = 0.79 (estimate)
	Azadirachtin B:	log K_{ow} = 1.29 (approximate)
Dissociation constant (pK_a)	N/A (no functional group that can dissociate)	
Stability (temperature)	Product stable to elevated temperatures (50°C for 28 days)	

End-use Product—TreeAzin Systemic Insecticide

Property	Result
Colour	Dark yellow
Odour	Strong unpleasant alcohol and cider-like odour
Physical state	Liquid
Formulation type	Solution
Guarantee	5.00%
Container material and description	HDPE bottles
Density	0.85 g/mL
pH of 1% dispersion in water	4.33
Oxidizing or reducing action	Not an oxidizing or reducing agent
Storage stability	Stable over one year in commercial packaging at ambient temperature
Corrosion characteristics	Not corrosive to commercial packaging
Explodability	Not explosive

1.3 Directions for Use

TreeAzin Systemic Insecticide is formulated for application by injection into the trunks of trees using the EcoJect Tree Injection System. The product is to be applied no more than once per year at rates ranging from 1 mL to 5 mL (0.05-0.25 g a.i.) per centimetre of trunk diameter at breast height (DBH) for control of emerald ash borer and several foliage-feeding insect pests (see Appendix I, Table 14). Refer to the product label for complete details of the directions for use.

1.4 Mode of Action

Azadirachtin has been reported to affect the production of ecdysone, the insect moulting hormone, which plays roles both in juvenile development and in egg production by adult females. It also has repellent properties, inhibiting both feeding and oviposition. However, the precise mechanism(s) by which azadirachtin acts are unknown and the Insecticide Resistance Action Committee (IRAC) currently classifies it as a compound of unknown or uncertain mode of action.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

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

2.2 Method for Formulation Analysis

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

2.3 Methods for Residue Analysis

High-performance liquid chromatography methods with ultraviolet (UV) detection or tandem mass spectrometry (HPLC-MS/MS) 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 plant and 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

NeemAzal Technical is an insect antifeedant and growth regulator containing the active ingredient azadirachtin at a concentration of 36.7%. Azadirachtin is one of many limonoid compounds found in an extract prepared from the seed kernels of the neem tree, *Azadirachta indica*, endemic to India, Africa, Indonesia and South America.

In addition to azadirachtin, NeemAzal Technical also contains other compounds which are not completely identified and for which the toxicity is not known. Therefore, for the purpose of the current risk assessment the doses in the toxicology studies have not been adjusted for the purity of azadirachtin.

Overall, the NeemAzal Technical database is of poor quality, with most studies lacking chemical identification or stability data and/or adequate haematology, organ weight and histopathology assessments. Many studies provided duplicate, erroneous or questionable data, limiting the confidence in the overall database. Finally, dietary analysis was not performed in most studies, and therefore the actual doses received by the animals cannot be confirmed. No data were submitted to elucidate the toxicokinetics of NeemAzal Technical. However, the toxicology database did include acceptable acute toxicity and genotoxicity studies, a 28-day and a 90-day dietary study in the rat, a developmental toxicity study in the rat and a supplemental 21-day neurotoxicity study in the hen.

NeemAzal Technical was of low acute toxicity in rats via the oral and dermal routes of exposure and slightly acutely toxic via the inhalation route. It was mildly irritating to the eyes of rabbits, but was not irritating to rabbit skin. NeemAzal Technical was a dermal sensitizer when tested by the Maximization method in guinea pigs.

The end-use product TreeAzin Systemic Insecticide was of low acute toxicity to rats via the oral, and inhalation routes of exposure, and was of low acute toxicity via the dermal route of exposure in rabbits. TreeAzin Systemic Insecticide was mildly irritating to the eyes of rabbits but not irritating to rabbit skin. It was considered to be a dermal sensitizer when tested in guinea pigs via the Buehler method.

The submitted toxicology database contained a 28-day and a 90-day dietary study in the rat conducted with NeemAzal Technical. Both studies were considered to be acceptable; however, the 28-day study was conducted for range-finding purposes and thus did not assess a full complement of endpoints. Effects in these studies included increases in liver, thyroid and brain weight, histopathological changes in the liver (hepatocytes with eosinophilic cytoplasm, hepatocellular hypertrophy) and thyroid (follicular cell hypertrophy), and alterations in hematology and clinical chemistry parameters. There was no repeat-dose dermal study provided for review.

Neither of the submitted long term studies intended to assess chronic toxicity and the carcinogenic potential of NeemAzal Technical were considered acceptable for regulatory purposes due to numerous deficiencies in study design and conduct. NeemAzal Technical was not mutagenic in bacterial and mammalian species in vitro and was found to be negative for inducing structural chromosomal aberrations in mice in vivo. However, in the absence of adequate oncogenic studies in rodents, the potential carcinogenicity of NeemAzal Technical cannot be determined.

A 21-day neurotoxicity study in the hen was conducted with NeemAzal-F 5% (a 5% suspension of azadirachtin in polyethylene oxide). There were no clear indications of neurotoxicity observed, however single mortalities were recorded in the low and high dose groups, and mid- and high dose hens had reduced egg yield. The study was considered supplemental due to its limited evaluation.

Reproductive and developmental toxicity studies were available for NeemAzal Technical as well as NeemAzal-F 5%. Neither of the reproductive toxicity studies were considered acceptable for regulatory purposes. Assessments in the studies were limited and did not include the recording of several reproductive organ weights, sperm assessments, or an evaluation of sexual maturity. Only one developmental toxicity study was conducted according to current test guidelines and considered acceptable for regulatory purposes. In this study conducted with NeemAzal technical, there was an increase in the number of fetuses with irregular ossification of vertebral centers and intraventricular septal defects, as well as the presence of a 14^{th} rib at a higher dose level. The effects in fetuses occurred at dose levels which also resulted in decreased body weight gain in the dams, indicating that the developing young were not more sensitive to the effects of NeemAzal Technical than the maternal animals.

Studies performed with various neem extracts in several species (rat, monkey and baboon) have demonstrated reproductive and developmental toxicity (as discussed in the Australian review of 2001; PMRA Number 1780128). Neem extracts have been shown to lower serum testosterone in male animals, decrease sperm production, cause testicular degeneration, cause decreased fertility, increase resorptions and abortions and cause fetal deaths. In addition, there is clinical evidence that neem extracts can be used as human contraceptives to reduce sperm production and motility, and also to prevent implantations and induce abortions in females. The collective evidence supports the notion that neem extracts are developmental and reproductive toxins. In the absence of an adequate reproductive toxicity study in the current database, the potential for NeemAzal Technical to cause reproductive effects cannot be ruled out.

Overall, the toxicology database for NeemAzal Technical is of poor quality and is not complete, lacking acceptable studies for assessment of toxicokinetics, chronic toxicity, carcinogenicity, and reproductive toxicity. Consideration was given to the credible toxicology studies that were available in the toxicology database and the fact that the end-use product is to be applied only by licenced Pest Control Operators (Commercial class product), using a method which limits exposure (tree injection using the EcoJect system). In view of the gaps in the toxicology database, in particular for reproductive toxicity, a database uncertainty factor was applied to the risk assessment for TreeAzin Systemic Insecticide as an added measure of protection. However, the gaps in the toxicology database will have to be addressed for any future submissions involving NeemAzal Technical.

Results of the acceptable toxicology studies conducted on laboratory animals with NeemAzal Technical and its associated end-use product are summarized in Appendix I, Tables 2 and 3. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 4.

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found at the PMRA website. Incidents from Canada and the United States were searched and reviewed for azadirachtin. There are no incidents related to NeemAzal Technical, containing azadirachtin, in the PMRA incident reporting database.

3.1.1 *Pest Control Products Act* Hazard Characterization

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

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database for NeemAzal Technical did not contain an acceptable reproductive toxicity study, and contained only one acceptable developmental toxicity study in a single species (rats).

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of the young compared to parental animals in the developmental toxicity study conducted with NeemAzal Technical in rats. There is evidence in the literature that various neem extracts demonstrate reproductive and developmental toxicity in several animal species, and that neem extracts can prevent implantations and induce abortions in humans. However, concern for these findings is tempered by the fact that the reproductive effects identified in the literature occurred at much higher dose levels than the NOAEL chosen for the current human health risk assessment for NeemAzal Technical.

The 10-fold factor required under the *Pest Control Products Act* was reduced to 1-fold as the gaps in the toxicology database, and subsequent residual uncertainty with respect to pre- and post-natal toxicity, have been addressed through the application of a database uncertainty factor of 10-fold in the risk assessment.

3.2 Acute Reference Dose (ARfD)

The establishment of an ARfD is not required as there are no proposed food uses, and contamination of drinking water is not expected.

3.3 Acceptable Daily Intake (ADI)

The establishment of an ADI is not required as there are no proposed food uses, and contamination of drinking water is not expected.

Cancer Assessment

Due to the absence of adequate oncogenic studies in rodents, the potential carcinogenicity of NeemAzal Technical cannot be assessed.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Short-term and intermediate-term dermal exposure

Occupational exposure to TreeAzin Systemic Insecticide is characterized as short- to intermediate-term in duration, and may occur via the dermal route of exposure. The NOAEL of 7.7 mg NeemAzal Technical/kg bw/day from the 90-day dietary study in rats was considered appropriate for risk assessment purposes. The NOAEL was based on changes in hematology and clinical chemistry parameters, organ weight changes, and histopathology of the liver and kidney at the LOAEL of 32 mg NeemAzal Technical/kg bw/day. The target margin of exposure (MOE) is 1000, which includes the standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, along with an additional 10-fold database uncertainty factor to address the gaps in the toxicology database.

3.4.1.1 Dermal Absorption

In the absence of chemical specific dermal absorption data for TreeAzin Systemic Insecticide, a 100% dermal absorption value was used in the health risk assessment.

3.4.2 Occupational Exposure and Risk

Commercial applicators may be exposed to TreeAzin Systemic Insecticide when mixing, loading, or applying this product to trees using the EcoJect Tree Injection System. A commercial applicator may be exposed over a full work day of 8 hours for several weeks intermittently from April to August. There is potential for short- to intermediate term dermal and inhalation exposure to workers when mixing, loading, and applying TreeAzin Systemic Insecticide.

The tree injection process using the EcoJect Tree Injection System requires intensive field work including drilling holes, mixing, loading, application, clean up, repair, and filling drilled holes which would take several hours to complete. The extent of exposure depends on the skill and experience of the worker and the field conditions of the tree being injected. Although the exposure during application using the EcoJect Tree Injection device is expected to be low, there is potential for accidental exposure during open pouring of TreeAzin Systemic Insecticide into the reservoir of the EcoJect Tree Injection System, through leaks in injection equipment, and through leaks at the site of injection.

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Tree injection application method specific or chemical-specific exposure data were not submitted or available for assessing human exposures during pesticide handling activities. In the generic pesticide handler exposure database (PHED), applicator data for various types of methods of application exist, but there is no tree injection application specific exposure scenario subset/data. Dermal and inhalation exposure estimates for workers mixing, loading, and applying TreeAzin Systemic Insecticide using the EcoJect Tree Injection System were generated using a surrogate scenario from the PHED. Exposure was estimated using the PHED Liquid Open Pour M/L exposure scenario. The exposure estimates are based on mixers/loaders/applicators wearing a single layer of personal protective equipment (PPE) and gloves. Although the PHED Liquid Open Pour M/L scenario is not specific to tree injection, it is the most representative scenario available to estimate exposure from tree injection using the EcoJect Tree Injection System. The PHED Liquid Open Pour M/L does not take into account exposure from applying a product, however, applicator exposure to TreeAzin Systemic Insecticide when using the EcoJect Tree Injection System is expected to be minimal. The potential exposure during application is limited to leaks that can occur in application equipment and/or at the site of the injection hole. Leaks are known to occur infrequently, thus potential applicator exposure is covered by the PHED Liquid Open Pour M/L Scenario. Furthermore, there is no mixing required when using TreeAzin Systemic Insecticide. Using the PHED Liquid Open Pour M/L Scenario as a surrogate for tree injection using the EcoJect Tree Injection System is not expected to underestimate exposure to commercial applicators when mixing/loading/applying TreeAzin Systemic Insecticide.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and 100% 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 70 kg adult body weight. The application rate was calculated with a guarantee of 13.6% NeemAzal Technical due to the treatment of NeemAzal Technical as an integrated systems product (ISP) for the purpose of evaluating toxicity. TreeAzin Systemic Insecticide will be referred to as 13.6% ISP for the purpose of estimating exposure and risk. The values used to determine exposure and risk for workers are outlined in Table 1a below.

Exposure estimates were compared to the toxicological endpoints (no observed adverse effects levels) to obtain the margin of exposure (MOE); the target MOE is 1000. Exposure estimates and calculated MOEs can be found in Table 1b below. The MOE for M/L/A exposure is above the level of concern (>1000). Although the exposure estimate does not include applicator exposure, the calculated MOE is considered adequate for M/L/A given there is no mixing and applicator exposure is expected to be minimal. Based on the above information, the calculated MOE is considered acceptable for mixer/loader/applicator provided the EcoJect Tree Injection System is used and personal protective equipment (a long sleeved shirt and long pants, or coveralls over short sleeves and short pants, chemical-resistant gloves and goggles or a face shield) are worn during mixing, loading and application of the product.

Table 1a: Mixer/Loader/Applicator Dermal Exposure estimates and MOE

Application Rate [1] (g ISP per cm DBH)	PHED Scenario	Trees Treated (per day)	Maximum DBH [4] (cm)	Dermal/Inhalation Absorption
0.578	Liquid, Open Pour M/L[2]	200[3]	60	100%

1 Maximum Application Rate = 5 mL × 13.6% × 0.85 g/mL = 0.578 g ISP per cm DBH
2 PHED Liquid, Open Pour M/L Scenario for single layer, with gloves. Dermal: 51.14 µg/kg ISP handled; Inhalation: 1.60 µg/kg ISP handled (light).
3 200 trees treated per day was estimated from a previous research authorization (PMRA Submission number 2003-3443) and from information collected during the 2006 Minor Use Tour.
4 Diameter at breast height or 1.3 m above the ground

Table 1b: Mixer/Loader/Applicator Dermal Exposure estimates and MOE

PHED Scenario	Application Rate[2] (g ISP per cm DBH)	kg ISP handled per day[3]	Dermal Unit Exposure (µg/kg/day)[4]	Inhalation Unit Exposure (µg/kg/day)[5]	Dermal MOE[6]	Inhalation MOE[7]	Combined MOE[8] Target: 1000
Liquid, Open Pour M/L[1]	0.578	6.94	5.07	0.159	1520	4.86×10^4	1473

1 PHED Liquid, Open Pour M/L Scenario for single layer, with gloves
2 Application rate day (ISP refers to NeemAzal Technical): 5 mL per cm DBH TreeAzin × 0.85 g/mL × 13.68% NeemAzal = 0.578 g ISP per cm DBH
3 Amount handled per day: 0.578 g ISP per cm DBH × 60 cm DBH × 200 trees/day × 1 kg/1000g = 6.94 kg ISP
4 Dermal Unit Exposure:

$$\frac{6.94 \text{ kg ISP handled per day} \times 51.14\ \mu\text{g/kg ISP handled} \times 100\% \text{ dermal absorption}}{70 \text{ kg BW}} = 5.07\ \mu\text{g/kg bw/day}$$

5 Inhalation Exposure (light work):

$$\frac{6.94 \text{ kg ISP handed per day} \times 1.60\ \mu\text{g/kg ISP handled} \times 100\% \text{ inhalation absorption}}{70 \text{ kg BW}} = 0.159\ \mu\text{g/kg bw/day}$$

6 Dermal MOE:

$$\frac{\text{NOAEL (7.7 mg/kg bw/day)}}{0.00507 \text{ mg/kg bw/day}} = 1520$$

7 Inhalation MOE:

$$\frac{\text{NOAEL (7.7 mg/kg bw/day)}}{1.59 \times 10^{-4} \text{ mg/kg bw/day}} = 4.86 \times 10^4$$

8 Combined MOE:

$$\frac{\text{NOAEL (7.7 mg/kg bw/day)}}{(0.00507 + 1.59 \times 10^{-4} \text{ mg/kg bw/day})} = 1473$$

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers re-entering areas where trees were treated with TreeAzin Systemic Insecticide. The major route of exposure for workers re-entering areas where trees were treated with TreeAzin Systemic Insecticide is through the skin. Exposure via inhalation is expected to be negligible due to the systemic application method. Potential postapplication exposure to workers may result from the contact with the surface (injection holes, bark, and leaves) of treated trees during tree maintenance (pruning, thinning, shaping), and scouting. Tree maintenance activities are expected to occur during fall and winter when the tree is not actively growing. This is months following injection, which occurs from May to August.

There was no passive dosimetry or biological monitoring study available for postapplication exposure. In addition, there was no dislodgeable foliar residue study (DFR) or outdoor treated tree surface residue data available and there are no standard residue values for tree injection methods. Due to the lack of available data, a quantitative postapplication assessment was not conducted. However, given the timing of postapplication worker activities, residues are expected to be low at the time of exposure. Studies (Grimalt et al. 2011, Sundaram 1996, and McKenzie et al. 2010) estimated that it would take 5 to 20 days for residues within leaves to dissipate by 50%. In addition, due to the systemic application process, it is unlikely that residues will be available on the surface of the leaves. Exposure to workers is further mitigated by the requirement of injection holes to be sealed before re-entry into the treatment area. Thus, the risk of dermal postapplication exposure is expected to be minimal.

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Post-application Exposure and Risk

There is potential for residential postapplication exposure to bystanders (adults and children) resulting from commercial application to trees in residential outdoor areas. The exposure is limited to dermal contact with injection holes, bark, and leaves of a treated tree. Contact with injection holes is mitigated by the following label statement: “Entry to treated areas by bystanders is restricted until all insecticide is injected into the trees and drilled holes are sealed.” As with postapplication worker exposure, the postapplication residential exposure is expected to be minimal due to the systemic method of application and the rate of dissipation of TreeAzin Systemic Insecticide.

3.5 Food Residues Exposure Assessment

Based on the proposed use pattern, a food residues exposure assessment was not required for this application.

3.6 Exposure from Drinking Water

3.6.1 Concentrations in Drinking Water

Azadirachtin concentrations in drinking water were not modelled because a low environmental exposure is expected to result from trunk injections.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

NeemAzal Technical is an extract from the neem tree. All of its components have not been identified, and its composition is subject to chemical fluctuations. The main insecticidal activity of NeemAzal Technical is attributed to azadirachtins, a family of steroid-like tetranortriterpenoids (limonoids). These molecules possess a multi-ringed structure and a range of polar and non-polar substituents. The nature of these substituents affect the solubility of the molecule in solvents; and indirectly their presence or absence in neem extracts following different manufacturing processes, and the fate of the molecule in the environment. Azadirachtin A and azadirachtin B, together represent 36.65% of NeemAzal Technical. While other NeemAzal components may be biologically active, given the relatively low environmental exposure expected to result from tree injections, further characterisation of this neem extract and its potential transformation products were not required for the environmental assessment.

When NeemAzal Technical is injected into trees, it is translocated from the trunk into other parts of the tree where it controls defoliating and burrowing insects. The components of NeemAzal Technical are very soluble in water. Based on their low vapour pressure and Henry's law constant, azadirachtin A and B are not expected to volatilize from environmental surfaces (soil, water, plants). Photolysis may occur in leaves, but the contribution of this process in the dissipation of NeemAzal Technical is unknown. Hydrolysis can be an important route of dissipation of azadirachtin A in neutral to alkaline conditions. The physical and chemical properties of azadirachtin are summarized in Section 1.2 of this document and hydrolysis rates are summarised in Appendix I, Table 5.

A study on the fate of the active ingredient in ash trees was required for the environmental assessment of NeemAzal Technical. Azadirachtin was shown to be readily taken up by white and green ash trees of different sizes. While azadirachtin concentrations in leaves were variable, they were highest shortly after treatment, and subsequently declined over time to a low concentration near the level of quantification at the time of leaf senescence. Concentrations near the limit of quantification were also measured in new leaves, approximately one year after treatment suggesting that some NeemAzal residues remain in the tree after leaf fall. Appendix I, Tables 6 and 7 present leaf concentrations in green and white ash trees, shortly after treatment. Appendix I, Table 8 presents average azadirachtin concentrations in trees growing under different conditions in urban scenarios and at various times after trunk injection of TreeAzin Systemic Insecticide.

Because trees are treated individually by injection, limited environmental exposure is expected. Non-target organisms that feed on treated trees (including pollen, nectar, fruits, seeds and leaves) could nevertheless be exposed. Terrestrial and aquatic organisms could also be exposed to fallen leaves of treated trees. However, because the NeemAzal Technical concentrations in senescent leaves are low, and because the leaves from treated trees are expected to disperse, exposure from fallen leaves is expected to lead to very low environmental concentrations. Biotransformation and hydrolysis are expected to be a major route of dissipation for NeemAzal Technical leaf residues. The results of the biotransformation studies are summarised in Appendix I, Table 9.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur.

Once injected into the tree, the active components of NeemAzal Technical are translocated to leaves, and may also move to pollen, nectar, fruits and seeds that are a potential food source for non-target organisms. Estimated environmental exposure concentrations (EECs) were calculated for these potential food sources, taking into consideration the application rate and the dissipation of the pesticide between applications.

Ecotoxicology information usually includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. The extent of the data is usually dependant on use pattern. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern. If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

The highest potential for exposure of non-target organisms to NeemAzal Technical is expected to be for birds, mammals and pollinators that feed directly on treated trees. Terrestrial and aquatic organisms could also be exposed to NeemAzal Technical residues in the fallen leaves of treated trees, however exposure is expected to be limited.

4.2.1 Risk to Terrestrial Organisms

A risk assessment of NeemAzal Technical was undertaken for terrestrial organisms. A summary of terrestrial toxicity data for azadirachtin is presented in Appendix I, Table 10 and the accompanying screening level risk assessment are presented in Appendix I, Table 11 for terrestrial organisms other than birds and mammals, and Appendix I, Table 12 for birds and mammals.

In comparison to traditional application methods, trunk injection is expected to result in less environmental exposure since the pesticide is injected directly into selected trees. While exposure to soil-dwelling organisms and terrestrial plants is expected to be minimal, birds and mammals that feed on fruits, seeds or other parts of treated trees or that are attracted by the target pest infesting the tree could be exposed to NeemAzal Technical. Similarly, honeybees and other pollinators could be exposed to NeemAzal Technical when they consume the nectar and the pollen of treated trees. As no data were available for azadirachtin concentrations in seeds, fruits, pollen or nectar of trees following trunk injections, the mobility of NeemAzal active components in the phloem is unknown, and concentrations in potential food sources were estimated based on monitoring data in leaves.

The 95th percentile of the azadirachtin concentration in leaves of medium and large sized trees, collected shortly after treatment, and corrected for the maximum application rate, was used as a surrogate for concentrations in fruits, seeds, nectar and pollen (Appendix I, Table 7). Smaller sized trees (2 cm in diameter) were excluded in the assessment since the product is unlikely to be used for small trees. The estimated daily exposure (EDE) for birds and mammals was calculated from this azadirachtin concentration expressed on a dry weight basis (18 mg a.i./kg dw). For honeybees, food consumption is typically expressed on a fresh weight basis and the corresponding concentration in pollen and nectar following initial application was 10 mg a.i./kg fw. The risk to pollinators associated with a post-bloom treatment was also evaluated using leaf concentrations at approximately one year after treatment. The azadirachtin concentration were very low (near the level of quantification) and the calculated surrogate azadirachtin concentration was 0.025 mg a.i./kg.

The risk assessment of NeemAzal Technical and its associated end-use product, TreeAzin Systemic Insecticide, was based on toxicity data to birds (bobwhite quail), mammals (rat) and honeybees. Appendix I, Table 10 summarises the effects of azadirachtin on potential non-target organisms. Appendix I, Tables 11 and 12 respectively, present the risk quotients to pollinators, and to birds and mammals.

Bees (pollinators)

Two exposure scenarios were considered in the risk assessment for bees. In the first, the treated trees were assumed to produce both pollen and nectar, of which nectar was assumed to contain a 40% sugar concentration. In the second scenario, trees were assumed to produce only pollen. Since bees require sugar, primarily obtained from nectar sources, for development and energy, the exposure scenario including nectar and pollen was expected to be higher. The sugar requirement and consumption of different castes of bees (including larvae (worker and drone) and adult (forager and nurse) stages) were also considered in the risk assessment.

Acute oral and contact exposure to azadirachtin did not result in significant mortality or sublethal effects in adult honeybees, and the risk quotients did not exceed the level of concern. In contrast, low concentrations of a formulated oil-free neem extract injected into the bottom of larval cells reduced the survival of first and fourth instar honeybee larvae, and with this endpoint, risk quotients were above the level of concern. The post-bloom application scenario risk quotients calculated with the brood toxicity endpoint and the one-year-after-treatment surrogate azadirachtin concentration remained above the level of concern for trees that produce both nectar and pollen, but were below the level of concern for trees that produce only pollen (Appendix I, Table 11).

It should be noted that there exists a high level of uncertainty associated with the risk analysis based on surrogate azadirachtin concentrations, and with the use of larval toxicity endpoint; however, the current risk assessment is expected to provide a conservative estimate of risk. While adult foraging bees could be exposed directly to residues in pollen and nectar of treated trees, the exposure pathway for the brood and the queen is more complicated. Because these bees remain in the hive, they can only be exposed to contaminated pollen and nectar through the worker bees. Exposure could also be affected by the proximity of the treated trees to the hive, the availability of alternative sources of food, the stability of the active ingredient, and the timing of treatment in relation to bloom. The translocation pattern between tree species may also vary and be influenced by environmental/climatic conditions. A screening survey of open literature confirms the greater sensitivity of insect larval stages and the potential effects of neem extracts on honeybees.

Because a potential risk to pollinators was identified, precautionary and advisory label statements are required on the label and application to hardwood species is restricted to the post-bloom period.

Birds

Azadirachtin has a low toxicity to birds. In acute oral and dietary studies conducted with the bobwhite quail, azadirachtin had no treatment-related effects on mortality or clinical signs of toxicity and no treatment-related abnormalities were observed upon necropsy. Similarly, in a reproduction study with the bobwhite quail, azadirachtin had no treatment-related effects on the parental generation, reproduction parameters and hatched chicks. Appendix I, Table 10 presents the toxicity endpoints for terrestrial organisms. Risk quotients (Appendix I, Table 12) calculated from the most sensitive endpoint and the highest surrogate azadirachtin concentration are below the level of concern.

Mammals

Environmentally relevant endpoints from acute and developmental toxicity studies with the rat were used to determine risk to small terrestrial mammals. Azadirachtin is practically non-toxic to rats on an acute basis. In one developmental toxicology study, concentrations of 225 mg/kg bw/day lead to an increased number of fetuses with irregular vertebral centers, and intra ventricular septal defects. The no observable effect level (NOEL) was set as 18.3 mg a.i./kg bw/day. In another developmental study with rats, the lowest tested concentration, 250 mg a.i./kg bw/day, lead to an increase incidence of dead fetuses (fetal and litter basis), and increased pre-implantation loss. Appendix I, Table 10 presents the toxicity endpoints for terrestrial organisms. Risk quotients (Appendix I, Table 12) calculated from the most sensitive endpoint and the highest surrogate azadirachtin concentration are below the level of concern.

Based on azadirachtin concentrations in leaves, birds and mammals are not expected to be at risk from the use of TreeAzin Systemic Insecticide as a tree injected insecticide.

Non-target plants, earthworms and beneficial arthropods

Non-target plants, earthworms and beneficial arthropods could be exposed to the active components of NeemAzal Technical from fallen leaves. However, based on the use pattern and the low azadirachtin concentrations in leaves at senescence, this exposure is expected to be low.

4.2.2 Risks to Aquatic Organisms

Aquatic organisms could be exposed to the active components of NeemAzal Technical from fallen leaves. However, based on the use pattern and the low azadirachtin concentrations in leaves at senescence, this exposure is expected to be low. A supplementary study investigated the potential effects of treated tree senescent leaves on terrestrial and aquatic organisms. In the microcosm tests, leaves from trees treated with NeemAzal Technical and collected at senescence had no significant adverse effects on litter-dwelling earthworms, *Eisenia fetida*, aquatic stonefly nymphs, *Pteronarcys dorsata*, or aquatic crane fly larvae, *Tipula sp.* The only significant adverse effect observed was a reduction in microbial decomposition of leaf material collected from trees treated in autumn and collected shortly after treatment.

NeemAzal Technical in fallen leaves of treated trees is not expected to pose a risk to non-target plants, soil dwelling or aquatic organisms.

4.2.3 Incident Reports

As of May 2012, the PMRA is not aware of any Canadian or American incident reports related to adverse effects on wildlife or natural vegetation from azadirachtin.

5.0 Value

5.1 Description of Pest Problem

Emerald ash borer is an invasive wood-boring beetle that attacks all species of ash trees, with the larvae boring under the bark of the trees and disrupting the transport of water and nutrients within the trees. With few natural enemies in Canada and very little resistance in the native species of ash, this pest can kill healthy ash trees within two or three years of infestation. Until very recently, no pest control products were registered in Canada for use against this pest or any similar wood-boring pests of living trees. The primary means of control has been to remove and destroy infested trees, resulting in the loss of many thousands of ash trees since the pest was first identified in Canada approximately 10 years ago.

The remaining pests on the label of TreeAzin Systemic Insecticide are foliage-feeding pests (defoliators and leafminers). Damage caused by these pests ranges from minor cosmetic damage to foliage all the way to tree mortality, depending on the severity and duration of defoliation.

5.2 Effectiveness Against Pests

Data were submitted from a total of 14 efficacy trials, 12 conducted in Canada and 2 conducted in the northern United States between 2001 and 2006. These trials included 4 against emerald ash borer, 3 against spruce budworm, 2 against gypsy moth, and a single trial each against jack pine budworm, forest tent caterpillar, arborvitae leafminer, birch leafminer, and pine false webworm.

The submitted efficacy data demonstrated that TreeAzin Systemic Insecticide may provide high levels of control of emerald ash borer even at very low application rates (~0.002 - 0.05 g a.i./cm DBH), at least when applied to very small trees (~2 cm DBH) before they are exposed to attack. Larger trees (5-8 cm DBH) that had been exposed to attack prior to treatment required higher application rates (~0.1 g a.i./cm DBH) for acceptable control, and in large trees (~37 cm DBH) only the upper proposed application rate (0.25 g a.i./cm DBH) provided acceptable control of larvae developing in the main trunk of the tree. Considering the difficulty of detecting emerald ash borer infestations before they become severe, the proposed application rates of 0.1 g a.i./cm DBH for "prophylactic treatment" (before signs of infestation become apparent) and 0.25 g a.i./cm DBH for large (>30 cm DBH) or infested trees is acceptable.

For defoliating Lepidoptera, trunk injections of TreeAzin Systemic Insecticide can reduce defoliation substantially in both hardwood and softwood trees when applied at the rate of 0.15 g a.i./cm DBH. Other application rates were tested in only a few trials and did not produce any clear evidence of any rate effect. Data from a single trial against leafmining Lepidoptera larvae showed results similar to those for defoliating Lepidoptera, so a label claim for the relevant leafminers (arborvitae leafminers) is acceptable. A general label claim for "leafminers" is not accepted, however, because that term includes pests in at least four different orders of insects, two of which were not represented in the efficacy trials (Diptera and Coleoptera) and one of which (Hymenoptera) was well controlled at a lower application rate (see below).

For sawflies, data from a single trial against each of a leafmining species on a hardwood host (birch) and a defoliating species on a softwood host (pine) showed very high efficacy at low application rates (0.05 and 0.005 g a.i./cm DBH, respectively), indicating that an application rate of 1 mL product (0.05 g a.i.) per centimetre DBH is acceptable for control of sawflies.

5.2.1 Acceptable Efficacy Claims

The submitted efficacy data provided for all of the pest claims proposed for the label of TreeAzin Systemic Insecticide are acceptable, except that the claim for leafminers is unacceptably broad and must be limited to the relevant species (arborvitae leafminers and birch leafminer). The range of application rates for emerald ash borer is accepted as proposed, but a single application rate of 3 mL product (0.15 g a.i.) per centimetre DBH was shown to be effective for all other proposed pests except sawflies, for which the rate of 1 mL product (0.05 g a.i.) per centimetre DBH provided a high level of control. A maximum of one application per tree per year is acceptable, along with the recommendation that trees not be treated every year.

5.3 Phytotoxicity

No evidence of phytotoxicity was reported, although no trials were submitted that specifically assessed phytotoxicity. The application method of trunk injection does cause some damage to the trees and therefore the label includes a recommendation that trees not be treated every year.

5.4 Economics

No economic analysis was conducted for this product evaluation.

5.5 Sustainability

5.5.1 Survey of Alternatives

Only two other products, one containing the organophosphate acephate and one containing the neonicotinoid imidacloprid, are currently registered in Canada for use against emerald ash borer, both by application through trunk injection. Numerous products containing various active ingredients are registered for use against most of the foliage-feeding pests on the label of TreeAzin Systemic Insecticide (see Appendix I, Table 13); however, only one alternative active ingredient (acephate) is registered for application by trunk injection and one other (dimethoate, another organophosphate) is registered for soil drench and “paint on” (to tree trunks) applications. All of the alternative active ingredients (including acephate and dimethoate) are registered for broadcast foliar applications. A few of the alternatives are microbial or newer chemical active ingredients, but most belong to older chemical classes (carbamates, organophosphates, pyrethroids).

5.5.2 Compatibility with Current Management Practices Including Integrated Pest Management

TreeAzin Systemic Insecticide is compatible with current management practices and is well suited for integrated pest management. With the application method of trunk injection, only insects feeding on the trees are exposed to the insecticide, allowing for conservation of natural enemies and other non-target organisms that would be exposed to foliar applications of insecticides.

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

According to Whalon et al. (2004-2012), no instances of resistance to azadirachtin have been reported to date. Although the possibility of development of resistance to azadirachtin cannot be ruled out, limiting application of TreeAzin Systemic Insecticide to no more than once per year and recommending that trees not be treated every year will help to minimize selection pressure for resistance.

5.5.4 Contribution to Risk Reduction and Sustainability

The application method of trunk injection provides a means of targeting the treatment to pests of the trees while minimizing exposure of humans and the environment to the product.

TreeAzin Systemic Insecticide provides a new alternative active ingredient with a new mode of action to aid in management of all of the pests on the product label.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

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

During the review process, the components of NeemAzal Technical and their transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

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

- The components of NeemAzal Technical do not meet the Track1 criteria and will not form any transformation products which meet the Track 1 criteria. NeemAzal Technical is a naturally occurring substance and is not expected to be persistent or bioaccumulative in the environment.
- There are no Track 1 formulants in the technical product or end-use product.
- There are no Track 1 contaminants in the technical product or end-use product.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade NeemAzal Technical and the end-use product TreeAzin Systemic Insecticide do not contain any formulants or contaminants of health or environmental concern identified in the Canada Gazette, Part II, Volume 139, Number 24, pages 2641–2643: List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.

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

7.0 Summary

7.1 Human Health and Safety

Overall, the toxicology database for NeemAzal Technical is of poor quality and is not complete, lacking acceptable studies for assessment of toxicokinetics, chronic toxicity, carcinogenicity, and reproductive toxicity. There is evidence in the scientific literature that various neem extracts have demonstrated reproductive and developmental toxicity in several animal species. In

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

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

[8] DIR2006-02, *PMRA Formulants Policy*.

addition, neem extracts are known to prevent implantations, induce abortions and have spermicidal effects in humans. Consideration was given to the credible toxicology studies that were available in the toxicology database and the fact the end-use product is to be applied only by licenced Pest Control Operators (Commercial class product), using a method which limits exposure (tree injection using the EcoJect system). In view of the gaps in the toxicology database, in particular for reproductive toxicity, a database uncertainty factor was applied to the risk assessment for TreeAzin Systemic Insecticide as an added measure of protection. However, the gaps in the toxicology database will have to be addressed for any future expansion of use pattern involving NeemAzal Technical.

Mixers, loaders, and applicators handling TreeAzin Systemic Insecticide and workers re-entering treated areas are not expected to be exposed to residues that result in an unacceptable risk when TreeAzin Systemic Insecticide is used according to label directions. The personal protective equipment on the product label is adequate to protect chemical handlers. Considering that postapplication work occurs months after treatment, a restricted entry interval is not required on the label. Residential exposure to adults and children who may come into contact with trees treated with TreeAzin Systemic Insecticide is not expected to result in an unacceptable risk when TreeAzin Systemic Insecticide is used according to label directions.

7.2 Environmental Risk

The risks from the use of azadirachtin as a tree injection to earthworms, birds, wild mammals, fish, terrestrial plants, amphibians, aquatic invertebrates, algae, or aquatic vascular plants is minimal.

Based on the toxicity to brood, risk to pollinators that may be exposed to residues in nectar and pollen from treated trees could not be ruled out. To mitigate the potential risk to pollinators, precautionary and advisory label statements are required on the label and the treatment of hardwood tree species is restricted to the post-bloom period.

7.3 Value

TreeAzin Systemic Insecticide has value for control of emerald ash borer and several foliage-feeding insect pests when injected into the trunks of trees attacked by these pests.

8.0 Proposed Regulatory Decision

Health Canada’s PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of NeemAzal Technical and TreeAzin Systemic Insecticide, containing the technical grade active ingredient azadirachtin, to control emerald ash borer and various insect pests that feed on the foliage of hardwood and softwood trees.

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

List of Abbreviations

♂	male
♀	female
µg	micrograms
a.i.	active ingredient
ADI	acceptable daily intake
ARfD	acute reference dose
atm	atmospheres
AZD	azadirachtin
bw	body weight
bwg	bodyweight gain
CAS	Chemical Abstracts Service
cm	centimetres
CV	coefficient of variation
d	day
DAT	day(s) after treatment
DBH	diameter [of tree trunk] at breast height
DFR	dislodgeable foliar residues
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
dw	dry weight
EDE	estimated daily exposure
EEC	estimated environmental exposure concentration
ESI	electrospray ionization
fc	food consumption
FIR	food ingestion rate
fw	fresh weight
g	gram
HDPE	high-density polyethylene
HPLC	high performance liquid chromatography
h	hour
IRAC	Insecticide Resistance Action Committee
ISP	Integrated systems product
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC	liquid chromatography
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
LOQ	limit of quantitation
m	metre
MCV	mean cell volume
mg	milligram

mL	millilitre
M/L	Mixer/Loader
M/L/A	Mixer/Loader/Applicator
MAS	maximum average score for 24, 48 and 72 hours
MIS	maximum irritation score
MOE	margin of exposure
MS	mass spectrometry
N/A	not applicable
ND	no data available
ng	nanograms
nm	nanometres
NOAEL	no observed adverse effect level
NOEL	no observed effect level
Pa	pascals
pg	picogram
PHED	Pesticide Handlers Exposure Database
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
RBC	red blood cells
RQ	risk quotient
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
UV	ultraviolet
wt	weight

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Tree	N/A	azadirachtin A and B	LC-ESI-MS	0.02 mg/kg in most matrices 0.05 mg/kg in Norway maple foliage	2077664
Soil	N/A	azadirachtin A	HPLC-UV	0.4 µg/g	1521447

Table 2 Toxicity Profile of TreeAzin Systemic Insecticide Containing NeemAzal Technical

Study Type/Animal/PMRA No.	Study Results
Acute oral toxicity Sprague Dawley rats PMRA #1773261	LD_{50} > 2000 mg/kg bw Low toxicity
Acute dermal toxicity New Zealand White rabbits PMRA #1773262	LD_{50} > 2000 mg/kg bw Low toxicity
Acute inhalation toxicity (nose-only exposure) Sprague Dawley rats PMRA #1773263	LC_{50} > 2.07 mg/L Low toxicity
Eye irritation New Zealand White rabbits PMRA #1773264	MAS = 8, MIS = 14.7, at 24 h Mildly irritating
Dermal irritation New Zealand White rabbits PMRA #1773635	MAS = 0, MIS = 0 Non- irritating
Dermal sensitization (Buehler test) Hartley guinea pigs PMRA #1773266	Sensitizer

Table 3 Toxicity Profile of NeemAzal Technical

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

Study Type/Animal/PMRA No.	Study Results
Acute oral toxicity Sprague Dawley rats PMRA #1521420	LD_{50} > 5000 mg/kg bw Low toxicity
Acute dermal toxicity Sprague-Dawley rats PMRA #1521421	LD_{50} > 2000 mg/kg bw Low toxicity
Acute inhalation toxicity Sprague Dawley rats PMRA #1521422	LD_{50} > 0.72 mg/L Slightly toxic
Eye irritation New Zealand White rabbits PMRA #1521424	MAS = 0, MIS = 0 Non-irritating
Dermal irritation New Zealand White rabbits PMRA #1521423	MAS = 0. MIS = 0.5, at 1 h Non-irritating
Dermal sensitization (Maximization method) Dunkin/Hartley guinea pigs PMRA #1521425	Sensitizer
28-day dietary (Range-finding) Sprague Dawley rats PMRA #1521428	Study considered supplemental, no NOAEL established. Effects noted at the lowest dose tested (322/301 mg/kg bw/day) included: ↑ liver wt, ↑thyroid wt, hepatocytes with eosinophilic cytoplasm (♂/♀); ↓bwg & fc, ↑thyroid follicular cell hypertrophy (♀)

Study Type/Animal/PMRA No.	Study Results
90-day dietary toxicity Sprague Dawley rats PMRA #1521427	NOAEL = 7.7/9.4 mg/kg bw/day (♂/♀) LOAEL = 31.6/35.7 mg/kg bw/day (♂/♀) Based on ↑ glucose (♂/♀); ↑RBC, ↓MCV, ↑clotting time, ↑absolute brain wt,↑liver wt, ↑basophilic infiltration of the kidney tubules (♂); ↑ fatty deposits in the liver (♀).
Developmental toxicity VAF/Plus rats PMRA #1521438	**Maternal toxicity:** NOAEL = 50 mg/kg bw/day LOAEL = 225 mg/kg bw/day Based on post-dosing salivation, ↓ bwg during the first 2 days of treatment. **Developmental toxicity:** NOAEL = 50 mg/kg bw/day LOAEL = 225 mg/kg bw/day Based on an ↑ number of fetuses with irregular ossification of vertebral centers and intraventricular septal defects.
Gene mutations in bacteria *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1538 and TA 1537; *E. Coli* WP2uvrA PMRA #1521440	Negative
Gene mutations in mammalian cells in vitro Chinese hamster ovary cells (HGPRT locus) PMRA 31521441	Negative
Micronucleus assay (in vivo) ICR mice PMRA #1521442	Negative
21-day Neurotoxicity (NeemAzal-F5%) Leghorn hens PMRA #1521443	Study considered supplemental, no NOAEL established. Effects noted included single mortalities at the low (160 mg/kg bw/day) and high (1000 mg/kg bw/day) doses. No evidence of neurotoxicity.

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for NeemAzal Technical

Exposure Scenario	Study	Point of Departure and Endpoint	Target MOE[1]
Short- to intermediate - term dermal[2]	90-day dietary in rats	NOAEL = 7.7 mg/kg bw/day Based on changes in hematology and clinical chemistry parameters, organ weight changes, and histopathological changes in the liver and kidney.	1000

[1]MOE refers to a target MOE for occupational and residential assessments
[2]Since an oral NOAEL was selected, a dermal absorption factor of 100% was used in a route-to-route extrapolation

Table 5 Summary of Dissipation Rates for the Hydrolysis of Azadirachtin

Compound	Temperature (°C)	pH	Half-life (days)	Comments	PMRA No. / Reference
Submitted studies					
azadirachtin A (in NeemAzal)	30	4 7 8	10.7 4.8 1.0	Experimentally determined.	1521450
	40	4 7 8	2.5 1.3 0.2	Experimentally determined. Average of two replicates.	1521450
	20	4 7 8	49.9 19.5 4.4	Extrapolated.	1521450
Published literature					
azadirachtin A	20	4 7 9	19.2 12.9 0.1 (2 h)	Buffered solutions.	Sundaram et al. (1995)
	20	8.1 ± 0.5	6.9	Pond water.	Sundaram et al. (1995)
azadirachtin (type not specified)	35	5 7 8	11.5 2.4 0.5	Buffered solutions.	Szeto and Wan (1996)
	25	7	11	Buffered solutions.	Szeto and Wan (1996)
	35	6.2 7.3 8	21 2 0.5	Natural waters.	Szeto and Wan (1996)

Table 6 Azadirachtin Leaf Concentrations Shortly after Trunk Injection.

Treatment rate mg AZD/cm (DBH)	Tree diameter cm (DBH)	DAT	AZD concentration[1] (mg/kg dw)	AZD concentration[1] (mg/kg fw)	Corrected AZD concentrations[2] (mg/kg dw)	Corrected AZD concentrations[2] (mg/kg fw)	PMRA No.
54.5	2[3]	7	0.3	0.17	1.38	0.79	1773274
54.5	2[3]	7	10	5.76	45.87	26.43	1773274
54.5	2[3]	7	11	6.34	50.46	29.07	1773274
54.5	2[3]	7	21	12.10	96.33	55.50	1773274
200	20	2	2.00	1.15	2.50	1.44	1997345
200	20	2	2.17	1.25	2.71	1.56	1997345
200	20	2	2.26	1.3	2.82	1.63	1997345
200	20	2	4.60	2.65	5.75	3.31	1997345
200	20	2	5.47	3.15	6.83	3.94	1997345
200	20	2	0.87	0.5	1.08	0.63	1997345
200	20	2	1.04	0.6	1.30	0.75	1997345
200	20	2	1.91	1.1	2.39	1.38	1997345
200	20	2	2.95	1.7	3.69	2.13	1997345
200	20	2	4.34	2.5	5.42	3.13	1997345
200	20	2	5.03	2.9	6.29	3.63	1997345
200	20	2	7.64	4.4	9.55	5.50	1997345
200	5	NS[4]	10.03	5.78	12.54	7.23	2050350
200	5	NS[4]	2.05	1.18	2.56	1.48	2050350
200	5	NS[4]	1.58	0.91	1.97	1.14	2050350
250	22	11	2.5	1.44	2.50	1.44	1773274
250	22	11	9	5.18	9.00	5.18	1773274
250	22	11	15	8.64	15.00	8.64	1773274
250	22	11	18	10.37	18.00	10.37	1773274
250	22	11	20	11.52	20.00	11.52	1773274

[1] Shaded values were estimated on a fresh weight basis based on the fresh:dry weight ratio of 1.73, for ash tree leaves, calculated from measured azadirachtin concentrations in PMRA 1997345.
[2] AZD concentration corrected for the maximum application rate of 250 mg a.i./cm (DBH).
[3] Values for calliper-sized trees were excluded because very small trees are unlikely to be treated.
[4] NS: Not specified- Trees were injected in autumn and leaf sampled shortly after treatment at a one week interval.

Table 7 Summary of Azadirachtin Leaf Concentrations Shortly after Trunk Injection

		Corrected AZD concentrations[1] (mg/kg dw)	Corrected AZD concentrations[1] (mg/kg fw)
All trees	95th percentile	49.77	28.67
	Median	5.59	3.22
	Maximum	96.33	55.50
Excluding calliper-sized trees[2]	95th percentile	18.10	10.43
	Median	4.56	2.63
	Maximum	20.00	11.52

[1] AZD concentration corrected for the maximum application rate of 250 mg a.i./cm (DBH).
[2] Values for calliper-sized trees were excluded because very small trees are unlikely to be treated.

Table 8 Mean Foliar Residues of Total Azadirachtins (A +B) Observed in Green and White Ash Trees Growing under Different Conditions in Urban Scenarios and at Various Times after Stem Injection of TreeAzin at a Rate of 0.2 g a.i. cm^{-1} DBH (PMRA No. 1997345)

Species	Type	DAT	N	Mean Foliar Residue (mg/kg)		
				(fw)	(dw)	CV
Green Ash	Boulevard	2	5	1.93	3.35	46
Green Ash	Park	2	4	0.98	1.70	58
White Ash	Park	2	4	3.08	5.35	30
Green Ash	Boulevard	70	5	0.05	0.08	41
Green Ash	Park	70	4	0.09	0.15	56
White Ash	Park	70	4	≤ 0.01	≤ 0.02	22
Green Ash	Boulevard	365	5	≤ 0.01	≤ 0.02	23
Green Ash	Park	365	4	0.02*	0.03	58
White Ash	Park	365	3	≤ 0.01	≤ 0.02	43

DAT = Days After Treatment; fw = fresh weight; dw = dry weight; CV = coefficient of variation

Kurskal-Wallis ANOVA on ranks followed by Dunn's method of multiple comparisons performed on initial (DAT 2) data, showed a significant difference ($P < 0.05$) between residue levels observed in white ash and green ash growing in the park, but not among green ash growing under park and boulevard conditions.

Values shown with a ≤ symbol indicate are all at or below analytical limits of quantitation on a fresh weight basis.

*The highest azadirachtin concentration in leaves, one year after treatment was used as surrogate to represent concentration in pollen and nectar in a post-bloom treatment scenario. This value was corrected for a 250 mg/cm DBH application rate ($0.02 \times 250/200 = 0.025$).

Table 9 Summary of Aerobic Soil Biotransformation for Azadirachtin A

Soil	Temp (°C)	DT_{50} (d)	DT_{90} (d)	Kinetics	Comment	PMRA No. / Reference
Submitted studies						
Sand (standard soil 2.1)	20	2.9	9.8	Log-linear $y = -0.1024x + 1.9952$ $r^2=0.999$	Not persistent.	1521452
Loamy sand (standard soil 2.2)	20	3.8	15.9	Log-linear $y = -0.058x + 1.9222$ $r^2=0.962$	Not persistent.	1521452
Sandy loam (standard soil 2.3)	20	1.9	7.5	Log-linear $y = -0.1239x + 1.9304$ $r^2=0.986$	Not persistent.	1521452
Sand (standard soil 2.1)[1]	20	9.9	32.9	SFO $y = -0.65e^{-0.07x}$	Not persistent.	1521451
Published literature						
Forest nursery soil	22	26	--	Not reported.	Study conducted under greenhouse conditions (16 h light: 8 h dark) Slightly persistent	Sundaram (1996)

[1]Degradation of several azadirachtin (A, B, D and I). DT_{50} and DT_{90} calculated R Excel fate module (April, 2012).

Table 10 Effects on Non-Target Organisms

Organism	Exposure	Test substance	Endpoint value	Comments/ Degree of toxicity[1]	PMRA No.
Terrestrial Arthropods					
Earthworm	35d microcosm study	Senescent leaves of NeemAzal treated-trees	N/A	No effects on survival, leaf consumption rates, growth rates or cocoon production.	2050350
Honeybees	48h-Oral	Azadirachtin technical; toxicity value based on azadirachtin A	LD_{50} > 8.1 µg azadirachtin A/bee	Moderately toxic	From extended study evaluation summary in 1787073
	48h-Contact	Azadirachtin technical; toxicity value based on azadirachtin A	LD_{50} > 11.8 µg azadirachtin A/bee	Relativley nontoxic	From extended study evaluation summary in

Organism	Exposure	Test substance	Endpoint value	Comments/ Degree of toxicity[1]	PMRA No.
					1787073
	Brood/hive	Azadirachtin technical; toxicity value based on azadirachtin A	1st instar: LD_{50} = 55 pg/ larval cell, or 37 µg a.i./g bw	Scientifically sound study. Most sensitive endpoint.	(Naumann and Isman, 1996)
			fourth instar: LD_{50} = 5.9 ng/ larval cell, or 61 µg a.i./g bw		
	Brood/hive (semi-field, tunnel tents)	NeemAzal T/S (1% azadirachtin)		Reduction in foraging activity. Reduction in brood development. Increased brood termination rate.	(Shawki *et al.*, 2005)
	Brood/hive laboratory study	Neem oil (35 EC);		Removal of eggs and young larvae. Neglect of surviving larvae that led to starvation.	(Abrol D.P., Kumar R. (2000) cited in Shawki *et al.*, 2005)
		Partially purified neem (*Azadirachta indica* A. Juss) seed fractions, NN 18–701, NN 18–705, NN 18–79a and NN 18–79b		Maximum mortality immediately before larval-pupal ecdysis. Insect growth disrupting activity attributed by the author to neem seed fractions NN 18–705 and NN 18–79a, and appeared independent	(Sharma *et al.*, 1980) Abstract only.

Organism	Exposure	Test substance	Endpoint value	Comments/ Degree of toxicity[1]	PMRA No.
				of feeding inhibition.	
Birds					
Bobwhite quail	Acute	NeemAzal technical	LD_{50} > 4000 mg NeemAzal/kg bw; or LD_{50} > 1000 mg azadirachtin A/kg bw	Practically non-toxic	1787175
	5d-Dietary	NeemAzal technical	LD_{50} > 1078 mg NeemAzal/kg bw; or LD_{50} > 270 mg azadirachtin A/kg bw	Practically non-toxic	1787176
	Reproduction	azadirachtin technical	NOEL = 71.2 mg azadirachtin technical/kg bw; or NOEL = 8.4 mg azadirachtin A/kg bw		From extended study evaluation summary in 1787073
Mammals					
Rat	Acute	NeemAzal Technical	LD_{50} ≥5000 mg/kg bw		1521420
	Developmental toxicity	NeemAzal Technical	NOAEL = 18.3 mg a.i./kg bw/day based on increased number of fetuses with irrigular vertebral centers, and intra ventricular septal defects at a dose of 225 mg a.i./kg bw/day		1521438
Aquatic Arthropods					
stonefly nymphs and crane fly larvae	16d-Microcosm study	Senescent leaves of NeemAzal treated-trees	N/A	No effects on survival or leaf consumption rates.	2050350

[1] Atkins *et al.*(1981) for bees and USEPA classification for others, where applicable

Table 11 Risk to Honeybees

Bee cast	Daily consumption (sugar/pollen[1] per day in mg)	Exposure from nectar[1] (µg a.i./day)	Exposure from pollen (µg a.i./day)	Exposure from food (µg a.i./day)	LD_{50} (µg a.i./bee)	RQ
During or pre-bloom application to trees that produces nectar and pollen: Assuming a 40% sugar concentration in nectar, 10.4 mg a.i./kg nectar, and 10.4 mg a.i./kg pollen						
Worker larvae	11.9 / 1.1	0.30888	0.011232	0.320112	0.000055[2]	>1000
Drone larvae	15.1 / ND	0.3928	0	0.3928	0.000055[2]	>1000
Adult forager	128.0 / 0.0	3.328	0	3.328	8.1[3]	0.4
Nurse bee	0.0 / 12.0	0	0.1248	0.1248	8.1[3]	< 0.1
During or pre-bloom application to trees that only produce pollen consumed by bees: Assuming exposure from pollen only and 10.4 mg a.i./kg pollen						
Worker larvae	11.9 / 1.1	0	0.011232	0.011232	0.000055[2]	204
Drone larvae	15.1 / 0.0	0	0	0	0.000055[2]	< 0.1
Adult forager	128.0 / 0.0	0	0	0	8.1[3]	< 0.1
Nurse bee	0.0 / 12.0	0	0.1248	0.1248	8.1[3]	< 0.1
Post-bloom application to trees that produces nectar and pollen: Assuming a 40% sugar concentration in nectar, 0.025 mg a.i./kg nectar, and 0.025 mg a.i./kg pollen						
Worker larvae	11.9 / 1.1	0.0007425	0.000027	0.0007695	0.000055[2]	14
Drone larvae	15.1 / 0.0	0.000944231	0	0.000944231	0.000055[2]	17
Adult forager	128.0 / 0.0	0.008	0	0.008	8.1[3]	< 0.1
Nurse bee	0.0 / 12.0	0	0.0003	0.0003	8.1[3]	< 0.1
Post-bloom application to trees that only produce pollen consumed by bees : Assuming exposure from pollen only and 0.025 mg a.i./kg pollen						
Worker larvae	11.9 / 1.1	0	0.000027	0.000027	0.000055[2]	0.5
Drone larvae	15.1 / 0.0	0	0	0	0.000055[2]	< 0.1
Adult forager	128.0 / 0.0	0	0	0	8.1[3]	< 0.1
Nurse bee	0.0 / 12.0	0	0.0003	0.0003	8.1[3]	< 0.1

[1] From Rortais et al. (2005); ND = No data available
[2] single exposure; survival assessed after 6 days
[3] 48 hours oral exposure LD_{50}
Risk Assessment based on Rortais et al. (2005). No uncertainty factors were used to modify the assessment endpoint.

Table 12 Risk to Birds and Mammals

Organism Weight (g)	FIR (g dw diet/day)	EDE (mg a.i./kg bw/day)	Risk Assessment Endpoint	RQ[1]
Birds				
20	5.1	4.59	NOEL = 8.4 mg azadirachtin A/kg bw	0.54
100	19.9	3.582	NOEL = 8.4 mg azadirachtin A/kg bw	0.43
1000	58.1	1.046	NOEL = 8.4 mg azadirachtin A/kg bw	0.12

Organism Weight (g)	FIR (g dw diet/day)	EDE (mg a.i./kg bw/day)	Risk Assessment Endpoint	RQ[1]
Mammals				
15	2.2	0.0679	NOEL = 18.3 mg a.i./kg bw/day	0.14
35	4.5	0.0595	NOEL = 18.3 mg a.i./kg bw/day	0.13
1000	68.7	0.0318	NOEL = 18.3 mg a.i./kg bw/day	0.07

[1] Because the most sensitive endpoints were NOELs, no uncertainty factors were used to modify the assessment endpoint.

Table 13 Alternative Active Ingredients Registered in Canada for Pests on the Label of TreeAzin Systemic Insecticide

Pest(s)	Alternative Active Ingredients
Emerald ash borer	Organophosphate: acephate; Neonicotinoid: imidacloprid
Gypsy moth	Carbamate: carbaryl; Organophosphates: acephate, phosmet, trichlorfon; Pyrethroids: permethrin, pyrethrins; Spinosyn: spinosad; *Bacillus thuringiensis*: *Bacillus thuringiensis* var. *kurstaki*; Benzoylurea: diflubenzuron; Nuclear Polyhedrosis Virus: LydiNPV
Tent caterpillars	Carbamate: carbaryl; Organophosphates: acephate, malathion, phosmet, trichlorfon; Pyrethroids: d-trans allethrin, lambda-cyhalothrin, deltamethrin, permethrin, d-phenothrin, tetramethrin; Spinosyn: spinosad; *Bacillus thuringiensis*: *Bacillus thuringiensis* var. *kurstaki*
Spruce budworm	Carbamates: carbaryl, methomyl; Organophosphates: acephate, dimethoate, malathion, trichlorfon: Pyrethroids: deltamethrin, permethrin; *Bacillus thuringiensis*: *Bacillus thuringiensis* var. *kurstaki*; Diacylhydrazine: tebufenozide
Jack pine budworm	*Bacillus thuringiensis*: *Bacillus thuringiensus* var. *kurstaki*; Diacylhydrazine: tebufenozide
Arborvitae leafminers	Organophosphate: diazinon
Sawflies (label claims for one or more species, mostly excluding the species below)	Carbamate: carbaryl; Organophosphates: acephate, chlorpyrifos, dimethoate, malathion, trichlorfon; Pyrethroids: deltamethrin, permethrin, pyrethrins; Neonicotinoid: acetamiprid; Spinosyn: spinosad; Rotenone; Nuclear Polyhedrosis Viruses: NeabNPV, NeleNPV; Soaps (potassium salts of fatty acids)
Birch leafminer	Carbamate: carbaryl; Organophosphates: acephate, diazinon, dimethoate, phosmet
Pine false webworm	None

Table 14 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Proposed Label Claim		PMRA Supported Use Claim	
Pest	**Rate**	**Pest**	**Rate**
Emerald ash borer	2 mL per cm DBH as a prophylactic treatment and 5 mL per cm DBH for attacked trees or trees >30cm DBH	Accepted as proposed.	
Gypsy moth Tent caterpillars Leaf miners Spruce budworm Jack pine budworm Sawflies	2 – 5 mL per cm DBH	Gypsy moth Tent caterpillars Spruce budworm Jack pine budworm Arborvitae leafminers	3 mL per cm DBH
		Sawflies, including Birch leafminer and Pine false webworm	1 mL per cm DBH

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
1135067	2005, Chemistry Requirements, DACO: 2.1,2.2,2.3,2.4,2.5,2.6,2.7,2.8,2.9 CBI
1135068	Manufacturing Summary for NeemAzal Technical, DACO: 2.11.1 CBI
1135069	Description of Starting Materials for NeemAzal Technical, DACO: 2.11.2 CBI
1135070	Starting Material Specifications and Material Safety Data Sheets for NeemAzal Technical, DACO: 2.11.2 CBI
1135071	Detailed Production Process Description, DACO: 2.11.3 CBI
1135072	Establishing Certified Limits, DACO: 2.12.1 CBI
1135073	1997, Preliminary Analysis of Five Batches of NeemAzal Technical, DACO: 2.12.1,2.13.3 CBI
1135074	Specifications, DACO: 2.12.2 CBI
1135075	Enforcement Analytical Method for the Determination of Azadirachtin in NeemAzal Technical, DACO: 2.13.1,2.13.2 CBI
1135076	Other Impurities Associated with the Active Ingredient, DACO: 2.13.4 CBI
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