Proposed Re-evaluation Decision PRVD2018-10

Azadirachtin and Its Associated End-use Product

Consultation Document

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Proposed Re-evaluation Decision

Under the authority of the *Pest Control Products Act*, all registered pesticides must be regularly re-evaluated by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet current health and environmental safety standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports, and other regulatory agencies. The PMRA applies internationally accepted risk assessment methods as well as current risk management approaches and policies to all re-evaluations.

Azadirachtin is a botanical insecticide extracted from seeds of the tropical neem tree (*Azadirachta indica*). Azadirachtin adversely affects insect hormones and also acts as a feeding deterrent. It is registered as a Commercial product.

This document presents the proposed regulatory decision for the re-evaluation of azadirachtin as well as the science evaluation on which the proposed decision was based. All products containing azadirachtin registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period, during which the public, including the pesticide manufacturers and stakeholders, may submit written comments and additional information to the PMRA. The final re-evaluation decision will be published taking into consideration the comments and information received.

Outcome of Science Evaluation

Azadirachtin has value as a management tool to manage various insect pests of trees in forests, woodlots, urban and residential landscapes. Applied as a tree injection, it offers an alternative application method to foliar sprays and is important for insect pest management where there are limited, if any other active ingredients registered to control pests indicated on the label.

With respect to human health, azadirachtin is of low acute toxicity via the oral and dermal routes of exposure and slightly acutely toxic via the inhalation route. It is mildly irritating to the eyes and is a dermal sensitizer, but is not irritating to the skin. Under the current conditions of use, potential risk to human health from azadirachtin is not expected to be of concern.

Azadirachtin could enter the environment when used to control tree pests. However, when used according to the current label directions, azadirachtin is not expected to pose risks of concern to the environment.

Proposed Regulatory Decision for Azadirachtin

Under the authority of the *Pest Control Products Act* and based on the evaluation of currently available scientific information, products containing azadirachtin are being proposed for continued registration in Canada.

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health and the environment that must be followed by law. As a result of the re-evaluation of azadirachtin, no further risk mitigation measures for product labels are being proposed.

International Context

Azadirachtin is currently acceptable for use in other Organization for Economic Co-operation and Development (OECD) member countries, including the United States, Australia, New Zealand and European Union Member States. As of 10 January 2018 no decision by an OECD member country to prohibit any uses of azadirachtin for health or environmental reasons has been identified.

Next Steps

The public including the registrants and stakeholders are encouraged to submit comments during the 90-day public consultation period[1] upon publication of this proposed re-evaluation decision.

All comments received during the 90-day public consultation period will be taken into consideration in preparation of re-evaluation decision document.[2] The re-evaluation decision document will include the final re-evaluation decision, the reasons for it and a summary of comments received on the proposed re-evaluation decision with PMRA's responses.

Additional Scientific Information

No additional data are required.

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

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

Science Evaluation

1.0 Introduction

Azadirachtin is a botanical insecticide extracted from seeds of the tropical neem tree (*Azadirachta indica*). Azadirachtin affects insect hormones, interfering with moulting in immature insects and reproduction in adult insects. It also has repellant properties, deterring insects from feeding and from laying eggs on treated plants.

Azadirachtin is a systemic insecticide and is injected into the trunks of host trees for control of specific insect pests of trees in forest, woodlot, urban and residential landscapes. The end use product is to be used only with the Ecoject system for tree injection. No more than one application per tree per year is permitted.

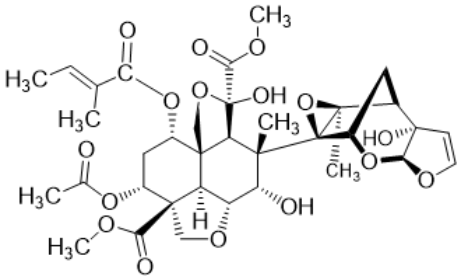
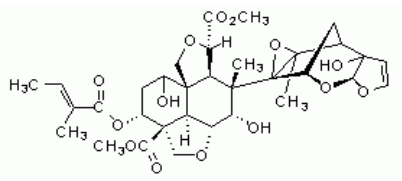
The registrant has indicated support for the re-evaluation of all products containing azadirachtin. Currently registered products containing azadirachtin are listed in Appendix I.

2.0 The Technical Grade Active Ingredient and Its Properties

2.1 Identity of the Technical Grade Active Ingredient

Active substances	Azadirachtin
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	Azadirachtin A: Dimethyl (2a*R*,3*S*,4*S*,4a*R*,5*S*,7a*S*,8*S*,10*R*,10a*S*,10b*R*)-10-acetoxy-3,5-dihydroxy-4-[(1a*R*,2*S*,3a*S*,6a*S*,7*S*,7a*S*)-6a-hydroxy-7a-methyl-3a,6a,7,7a-tetrahydro-2,7-methanofuro[2,3-*b*]oxireno[*e*]oxepin-1a(2*H*)-yl]-4-methyl-8-{[(2*E*)-2-methylbut-2-enoyl]oxy}octahydro-1*H*-naphtho[1,8*a*-*c*:4,5-*b*',*c*']difuran-5,10a(8*H*)-dicarboxylate Azadirachtin B: Not assigned

2. Chemical

Abstracts Service (CAS)	Azadirachtin A: Dimethyl (2a*R*,3*S*,4*S*,4a*R*,5*S*,7a*S*,8*S*,10*R*,10a*S*,10b*R*)-10-(acetyloxy)octahydro-3,5-dihydroxy-4-methyl-8-[[(2*E*)-2-methyl-1-oxo-2-buten-1-yl]oxy]-4-[(1a*R*,2*S*,3a*S*,6a*S*,7*S*,7a*S*)-3a,6a,7,7a-tetrahydro-6a-hydroxy-7a-methyl-2,7-methanofuro[2,3-*b*]oxireno[*e*]oxepin-1a(2*H*)-yl]-1*H*,7*H*-naphtho[1,8-*bc*:4,4a-*c'*]difuran-5,10a(8*H*)-dicarboxylate Azadirachtin B: 7*H*,8*H*-Furo[3',4':4,4a]naphtho[1,8-bc]furan-5,10a(1*H*)-dicarboxylic acid, octahydro-3,8-dihydroxy-4-methyl-10-[[(2*E*)-2-methyl-1-oxo-2-buten-1-yl]oxy]-4-[(1a*R*,2*S*,3a*S*,6a*S*,7*S*,7a*S*)-3a,6a,7,7a-tetrahydro-6a-hydroxy-7a-methyl-2,7-methanofuro[2,3-*b*]oxireno[*e*]oxepin-1a(2*H*)-yl]-, 5,10a-dimethyl ester, (2a*R*,3*S*,4*S*,4a*R*,5*S*,7a*S*,8*S*,10*R*,10a*S*,10b*R*)-
CAS number	Azadirachtin A: 11141-17-6 Azadirachtin B: 106500-25-8 (95507-03-2)
Molecular formula	Azadirachtin A: $C_{35}H_{44}O_{16}$ Azadirachtin B: $C_{33}H_{42}O_{14}$
Structural formula	Azadirachtin A:  Azadirachtin B: 
Purity of the active ingredients	Azadirachtin (A+B) at 36.65 %

2.2 Physical and Chemical Properties

Technical Product–NeemAzal Technical

Property	Result
Vapour pressure	3.6×10^{-10} mPa
Ultraviolet (UV) / visible spectrum	λ_{max} = 215 nm (Azadirachtin A in methanol)
Solubility in water at 20-25°C	260 mg/L
n–Octanol/water partition coefficient	Log K_{ow} = 0.0
Dissociation constant	Not applicable

3.0 Impact on Human Health

Based on the registered use pattern, exposure to azadirachtin may occur by working as a mixer/loader/applicator or by entering treated sites. Two key factors are considered when assessing health risks: the levels at which no health effects occur, and the levels to which people may be exposed. The 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. Continued registration is only supported for uses that are determined as having no health risks of concern.

3.1 Toxicological Summary

Azadirachtin is of low acute toxicity via the oral and dermal routes of exposure and slightly acutely toxic via the inhalation route. It is mildly irritating to the eyes, but is not irritating to the skin. Azadirachtin is a dermal sensitizer. Azadirachtin 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.

For the re-evaluation of azadirachtin, consideration was given to the available toxicology studies and the current use pattern for the registered product. As mentioned in PRD2012-16, the use of an additional factor in the risk assessment, along with low exposure from the tree injection use applied only by licensed Pest Control Operators using a specific, closed delivery system, serves to further reduce the allowable level of human exposure to azadirachtin. Any future use expansion of azadirachtin will have to address the information requirements for the corresponding use.

For more details of the toxicity profile, refer to NeemAzal Technical, containing Azadirachtin (PRD2012-16).

3.2 Pest Control Products Act Hazard Characterization

The *Pest Control Products Act* factor was previously assessed for azadirachtin and reduced to 1-fold (PRD2012-16) 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.

3.3 Occupational Exposure and Risk

Workers can be exposed to azadirachtin through loading or applying the product to trees using the EcoJect Tree Injection System or when entering a treated site to conduct activities such as pruning or scouting.

Based on the current use pattern, worker exposure (loading/application) to azadirachtin is expected to be mainly via the dermal and inhalation routes over a short- to intermediate-term duration (a commercial applicator may be exposed over a full work day of 8 hours for several weeks intermittently from April to August). Current label directions include personal protection

equipment (PPE) to protect workers handling azadirachtin (e.g., long sleeved shirt and long pants, or coveralls over short sleeves and short pants, and chemical resistant gloves and goggles or a face shield). The mixer/loader/applicator exposure for tree injection of azadirachtin is not of concern when the current label directions are followed. No additional risk mitigation measures are proposed.

For workers entering areas where trees were treated with azadirachtin dermal exposure is considered to be the primary route of exposure. Exposure via inhalation is expected to be negligible due to the application method (injection into the tree). Potential postapplication exposure to workers may result from 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, following injection, which occurs from May to August.

Given the timing of postapplication worker activities, residues are expected to be low at the time of post application activities. In addition, due to the current application method (tree injection), it is unlikely that residues will be available on the surface of the leaves. Therefore, under the current conditions of use, potential risk to post application workers is not expected to be of concern.

3.4 Non-occupational Exposure and Risk

Residential and Bystander 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, limited to dermal contact with injection holes, bark, and leaves of a treated tree. Contact with injection holes is mitigated by the current label statement, “Entry to treated areas by bystanders is restricted until all insecticide is injected into the trees” and as with postapplication worker exposure, postapplication residential exposure is expected to be minimal due to the systemic method of application and the rate of dissipation of azadirachtin.

Dietary Exposure and Risk: Azadirachtin is not to be applied to trees that will produce food. Potential exposure to drinking water is expected to be minimal from tree trunk injections. When current label directions are followed, potential dietary risk (food and water) is not expected to be of concern.

3.5 Aggregate Exposure and Risk

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential, and other non-occupational sources from all known or plausible exposure routes (oral, dermal and inhalation). For azadirachtin, aggregate exposure is not of concern as there are no food uses of azadirachtin, contamination of drinking water and bystander exposure is expected to be minimal.

3.6 Cumulative Exposure and Risk

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with a common mechanism of toxicity. For the current re-evaluation, the PMRA did not identify information indicating that azadirachtin shares a common mechanism of toxicity with other pest control products. Therefore, there is no requirement for a cumulative assessment at this time.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

NeemAzal Technical is an extract from seeds of the neem tree. The main insecticidal components, azadirachtin A and B, are steroid-like tetranortriterpenoids (limonoids) which 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). Hydrolysis can be an important route of dissipation of azadirachtin A in neutral to alkaline conditions. Biotransformation is expected to be a major route of dissipation in soil.

When azadirachtin is injected into trees, it is translocated from the trunk into other parts of the tree (for example to the pollen, nectar, fruits, seeds and leaves) where it controls insects. Although limited environmental exposure is expected from tree injection, non-target organisms (such as birds, mammals and pollinators) that feed directly on treated trees (including on the pollen, nectar, fruits, seeds and leaves) have the potential to be exposed. Terrestrial and aquatic organisms could also be exposed to fallen leaves of treated trees.

Based on a study on the fate of azadirachtin in ash trees growing under different scenarios in urban settings, it was determined that 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 (PRD2012-16).

4.2 Environmental Exposure and Risk

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. Estimated environmental concentrations (EECs) are levels of pesticide in various environmental media, such as food, water, soil and air. The EECs are calculated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (such as, 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 (for example, direct application at a maximum cumulative application rate) 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 (LOC). 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 (such as drift to non-target habitats) and might consider different toxicity endpoints.

Concentrations in potential food sources (pollen, nectar, fruits and seeds) for bees (pollinators), birds and small terrestrial mammals, were estimated based on surrogate monitoring data in leaves collected shortly after treatment.

Acute oral and contact exposure to azadirachtin did not result in significant mortality or sublethal effects in adult honeybees, and the potential risks were below the level of concern. However, potential risks to pollinators were identified by brood toxicity endpoint data and the one-year-after-treatment surrogate azadirachtin concentrations. Therefore, precautionary and advisory label statements are currently included on the end-use product label: “TOXIC to bee brood. This product is systemic and is transported upwards through the tree. Bees may be exposed to residues in floral pollen and/or nectar resulting from tree injections. Application to hardwood trees must be made post-bloom.” No additional risk mitigation measures are proposed.

Based on the current use pattern, potential risks to birds and mammals were below the level of concern (PRD2012-16). Exposure to azadirachtin from fallen leaves to other non-target plants, earthworms and beneficial arthropods is expected to be low based on the use pattern and the low azadirachtin concentrations in leaves at senescence.

Potential risks to aquatic organisms from exposure to azadirachtin from fallen leaves are expected to be minimal. However, based on the toxicity of azadirachtin to aquatic organisms (fish), an environmental precautionary statement “Toxic to aquatic organisms” is currently included on the end-use product label (PRD2012-16).

5.0 Value

Azadirachtin has value as a pest management tool to manage emerald ash borer, gypsy moth, tent caterpillars, spruce and Jack pine budworms, arborvitae leafminers, European elm scale, red elm bark weevil and sawflies of trees in forests, woodlots, urban and residential landscapes.

Azadirachtin is important for insect pest management in forests, woodlots, urban and residential landscapes because there are either none or limited other active ingredients registered to target listed pests. Applied as a tree injection, it offers an alternative application method to foliar sprays.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

In accordance with the PMRA Regulatory Directive DIR99-03, the assessment of azadirachtin against Track 1 criteria of Toxic Substances Management Policy (TSMP) under the Canadian Environmental Protection Act was conducted in PRD2012-16. It determined that:

- Azadirachtin is not expected to be persistent or bioaccumulative in the environment. Azadirachtin does not meet all Track 1 criteria and will not form any transformation products which meet the Track 1 criteria.

6.2 Contaminants and Formulants of Health or Environmental Concern

During the re-evaluation of azadirachtin, possible contaminants in the technical grade active ingredient were compared against the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern maintained in the Canada Gazette.[3] The list is used as described in the PMRA Notice of Intent NOI2005-01[4] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[5] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). Based on the manufacturing process used, impurities of human health or environmental concern as identified in the Canada Gazette are not expected to be present in the product.

7.0 Incident Reports

As of 10 January 2018 there have been no incidents involving azadirachtin reported to the PMRA.

One environmental incident was reported to the USEPA Ecological Incident Information System, as of 5 October 2015. In this case, azadirachtin and beta-cyfluthrin were suspected to have been responsible for honeybee mortality, but the lab results were negative for both active ingredients.

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3 *Canada Gazette*, Part II, Volume 139, Number 24, 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, 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.*

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

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

8.0 Conclusions

Azadirachtin has value in providing a pest management option to manage various insects in trees. With respect to human health, it is of low acute toxicity profile via the oral and dermal routes, and slightly acutely toxic via the inhalation route. The toxicology database for azadirachtin was considered sufficient for the current limited use pattern. When the current label directions are followed, potential risk to human health and the environment is not expected to be of concern.

Appendix I Registered Azadirachtin Products as of 10 January 2018

Registration Number	Marketing Type	Registrant Name	Product Name	Formulation type	Guarantee
30558	Technical Grade Active Ingredient	E.I. D Parry (India) Inc.	NeemAzal Technical	Dust	36.65%
30559	Commercial	BioForest Technologies Inc.	TreeAzin Systemic Insecticide	Solution	5%

References

A. Information Considered in the Chemistry Assessment

List of Studies/Information Submitted by the Registrant

PMRA Document Number	Reference
1135068	Manufacturing Summary for Neemazal Technical, DACO: 2.11.1
1135069	Description of Starting Materials for Neemazal Technical, DACO: 2.11.2
1135070	Starting Material Specifications and Material Safety Data Sheets for Neemazal Technical, DACO: 2.11.2
1135071	Detailed Production Process Description, DACO: 2.11.3
1135073	1997, Preliminary Analysis of Five Batches of NeemAzal Technical, DACO: 2.12.1,2.13.3
1135078	2003, Ten Batch Analysis of Neemazal Technical for, DACO: 2.13.4
1135079	2005, Chemical and Physical Properties, DACO: 2.14
1135080	1996, Partition Coefficients of Various Constituents of NeemAzal in n-Octanol/Water, DACO: 2.14.11
1135082	Real time Storage Stability of Neemazal Technical, DACO: 2.14.14
1135083	1995, Report Melting Point, DACO: 2.14.4
1135084	1995, Determination of the Poured Weight and the Tapped Volume of Neemazal, DACO: 2.14.6
1135085	1995, Water Solublity of Neemazal, DACO: 2.14.7
1135087	1995, Solubility in Organic solvents, DACO: 2.14.8
1135088	Estimation of Vapor Pressure Azadirachtin A and B, DACO: 2.14.9
2839096	2017, Re-evaluation 2016-3693 Azadirachtin Data requirements Reg No. 30558 - Submission of Docs, DACO: 0.8.20,2.11,2.13.3

B. Information Considered in the Human Health and Environmental Assessments

Additional Published Information

PMRA Document Number	Reference
2193023	PRD2012-16: *NeemAzal Technical, containing Azadirachtin*