Proposed Registration Decision PRD2018-05

2,6-Diisopropylnaphthalene
Aceto Amplify II

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Overview

Proposed Registration Decision for 2,6-Diisopropylnaphthalene

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 Amplify Technical and Aceto Amplify II, containing the technical grade active ingredient 2,6-diisopropylnaphthalene (hereinafter referred to as 2,6-DIPN), to be used as a sprout inhibitor for potatoes in storage.

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 Amplify Technical and Aceto Amplify II.

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. 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 the Canada.ca website at https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management.html.

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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 2,6-DIPN, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on 2,6-DIPN, 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 2,6-DIPN?

2,6-DIPN is a plant growth regulator (PGR), which inhibits sprouting of potatoes in storage.

Health Considerations

Can Approved Uses of 2,6-DIPN Affect Human Health?

Aceto Amplify II, containing 2,6-DIPN, is unlikely to affect your health when used according to label directions.

Potential exposure to 2,6-DIPN may occur through the diet or when handling the product for application. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which exposure is well below levels that cause no effects in animal testing are considered acceptable for continued 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-containing products are used according to label directions.

In laboratory animals, 2,6-DIPN was of low acute toxicity by the oral, dermal and inhalation routes of exposure. It was minimally irritating to the eye and skin, and did not cause an allergic skin reaction. Based on these findings, hazard statements for acute toxicity are not required on the labels.

The end-use product has the same toxicity profile as 2,6-DIPN.

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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*.

Registrant-supplied short-term animal toxicity test, a prenatal developmental toxicity test, genotoxicity tests, and foreign reviews were assessed for the potential of 2,6-DIPN to cause target organ systemic toxicity, developmental toxicity, genotoxic and various other effects. Currently available information from the published scientific literature was also used to characterize the toxicity. There was no indication that the young were more sensitive than the adult animal. Adverse effects in animals given repeated high doses resulted in effects on organs (adrenal, kidney and liver) and reduced body weights.

The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occur in animal studies.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Dietary exposure to 2,6-DIPN may occur through consumption of treated potatoes; however, it is anticipated that the consumption of food commodities that have been treated with 2,6-DIPN will not pose a health risk of concern to any segment of the population, including infants, children, adults and seniors.

Available toxicology data indicates that 2,6-DIPN is of low toxicity and any potential residues of 2,6-DIPN are expected to decline in potato tissue following application. As the end-use product is used indoors, no risk due to exposure from drinking water is anticipated.

Risks in Residential and Other Non-Occupational Environments

Estimated risk for residential and other non-occupational exposure is not of concern.

There are no residential uses for Aceto Amplify II, as the product will be used in commercial potato storage facilities. Therefore, risk due to residential and bystander exposure is not a concern.

Occupational Risks From Handling Aceto Amplify II

Occupational risks are not of concern when Aceto Amplify II is used according to the label directions, which includes protective measures.

During loading and handling, individuals can come in direct contact with 2,6-DIPN by skin or eye contact or breathing the dust. For this reason, the label specifies that handlers and loaders should wear protective eyewear and a dust mask.

Due to the closed and automated nature of the application system, no applicator exposure is expected. Occupational bystander exposure to 2,6-DIPN is also not expected to occur due to the nature of the application.

Exposure for re-entry activities that take place before the ventilation period is considered to potentially represent a high exposure scenario where the primary routes of exposure are inhalation and dermal. Precautionary statements (for example, wearing of personal protective equipment), including restricted-entry intervals (REIs), are aimed at mitigating exposure, and are considered to adequately protect individuals from such exposure.

Exposure from postapplication activities is expected to be low, and not of concern.

Environmental Considerations

What Happens When 2,6-DIPN Is Introduced Into the Environment?

When Aceto Amplify II, containing 2,6-DIPN, is used according to the proposed label directions, no risks of concern to the environment are expected.

Aceto Amplify II is proposed for indoor treatment of stored potatoes. When Aceto Amplify II is used according to the proposed label directions, no direct exposure of birds, aquatic organisms, non-target plants and non-target insects to 2,6-DIPN is expected to occur. Thus, the potential for exposure is minimal and no risks of concern are expected to non-target organisms in aquatic or terrestrial ecosystems.

Value Considerations

What Is the Value of Aceto Amplify II?

Aceto Amplify II, containing 2,6-DIPN, inhibits sprouting of potatoes in storage.

The registration of Aceto Amplify II will provide Canadian potato growers and processors another non-conventional product for sprout inhibition on potatoes in storage. Furthermore, the application of Aceto Amplify II in conjunction with chlorpropham (CIPC) provides superior sprout inhibition on potatoes when compared to the application of either product alone.

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 Aceto Amplify II to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

An REI is included on the label for Aceto Amplify II which specifies that workers are not allowed to enter into the treated area until two (2) hours of mechanical ventilation (fans should circulate outside air) or four (4) hours of passive ventilation (windows, vents and doors should be opened), or until all visible aerosol has settled.

Early-entry workers entering into the treated areas during application, or prior to ventilation or settling of aerosol fog, must wear coveralls over a long sleeved shirt and long pants, shoes plus socks, chemical-resistant gloves, protective eyewear, and a respirator with a NIOSH-approved organic vapour-removing cartridge with a pre-filter approved for pesticides or a NIOSH-approved-canister approved for pesticides.

Next Steps

Before making a final registration decision on 2,6-DIPN, the PMRA will consider any 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

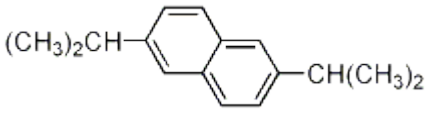
When the PMRA makes its registration decision, it will publish a Registration Decision on 2,6-DIPN (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

2,6-Diisopropylnaphthalene

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	2,6-Diisopropylnaphthalene
Function	Plant growth regulator
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	2,6-di(propan-2-yl)naphthalene
2. Chemical Abstracts Service (CAS)	2,6-bis(1-methylethyl)naphthalene
CAS number	24157-81-1
Molecular formula	$C_{16}H_{20}$
Molecular weight	212.3
Structural formula	
Purity of the active ingredient	100%

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

Technical Product—Amplify Technical

Property	Result
Colour and physical state	White crystalline solid
Odour	Odourless
Melting range	67.8-69.9°C
Boiling point or range	Not applicable
Bulk density at 25°C	0.49 g/mL
Vapour pressure at 25°C	81.3 mPa
Henry's law constant at 20°C	7.4×10^{-3} atm. m^3/mole and 1/H = 3.3

Property	Result
Ultraviolet (UV)-visible spectrum	No significant absorbance expected at $\lambda > 350$ nm
Solubility in water at 20°C	0.023 ppm
Solubility in organic solvents at 20°C	Solvent — Solubility (ppm) Acetone — 339,183 Iso-octane — 190,401 1-Octanol — 39,559
n–Octanol-water partition coefficient (K_{ow})	Not available (low solubility in water)
Dissociation constant (pK_a)	Not applicable (does not dissociate)
Stability (temperature, metal)	Stable for 28 days at 50°C; stable when exposed to aluminum and zinc metal for 28 days at 50°C; unstable when exposed to copper metal for 28 days at 50°C (approximately 7% loss in active ingredient content was observed); stable for 100 hours when exposed to UV light.

End-Use Product—Aceto Amplify II

Property	Result
Colour	White
Odour	Odourless
Physical state	Crystalline solid
Formulation type	Granule
Guarantee	100%
Container material and description	Plastic bag, 50-1050 kg
Bulk density at 25°C	0.49 g/mL
pH of 1% dispersion in water	5.5-6.5
Oxidizing or reducing action	Exposure to oxidizing agent should be avoided.
Storage stability	Known to be stable under normal conditions; stable when stored in the packaging material for 28 days at 50°C.
Corrosion characteristics	Not expected to be corrosive to the plastic packaging material.
Explodability	Not expected to be explosive.

1.3 Directions for Use

Aceto Amplify II, containing 100% 2,6-DIPN, will provide sprout inhibition on potatoes in storage. Aceto Amplify II may be applied during potato storage once at a rate up to 2.5 kg per 100 tonnes of potato tubers, or multiple times at an accumulated rate up to 2.5 kg per 100 tonnes of potato tubers.

Application of Aceto Amplify II in conjunction with CIPC-containing products will provide improved sprout inhibition on potatoes in storage when compared to either product alone.

1.4 Mode of Action

2,6-DIPN is a chemically synthesized molecule and does not occur naturally. It is functionally and structurally similar to three sprout inhibition compounds, in the chemical group of naphthalenes, that are naturally occurring in potatoes. The naphthalenes are thought to assist in sprout inhibition through hormonal 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 impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

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

2.3 Methods for Residue Analysis

No methods are required to quantify residues of 2,6-DIPN due to its low toxicity (see Section 3.0 for additional details).

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for 2,6-DIPN was conducted. The registrant submitted acute toxicity studies, a prenatal developmental toxicity study and a subchronic toxicity study. The database is considered complete and consists of toxicity studies currently required for hazard assessment purposes for non-conventional pesticides. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices (GLP). In addition, a submitted foreign review and information from the published scientific literature were used to supplement the assessment.

Acute studies on 2,6-DIPN found it to be of low toxicity via the oral, dermal, and inhalation routes of exposure. It was minimally irritating to the eyes and skin in rabbits, and is not a dermal sensitizer in guinea pigs.

Studies from the published scientific literature were considered on the metabolism of 2,6-DIPN in rodents. Following a single oral administration of 2,6-DIPN (100 mg/kg bw) dissolved in olive oil (40 mg/mL), to rats, approximately 85% of the dose was absorbed from the gastrointestinal tract within 48 hours. The absorption seems to be rapid as the maximum blood level of 2,6-DIPN was observed within 2-hours post-dosing. Only a small amount of unchanged parent compound was excreted in urine. The maximum levels of 2,6-DIPN were measured within 4-hour postdosing in the liver, kidney, heart, spleen, brain and muscle, which decreased with time. The skin and adipose tissue took a longer time (10 hours) to reach the maximum level than the other tissues. Also, the content and disappearance of 2,6-DIPN in the adipose tissue were higher and slower than those in the other tissues.

In a rat metabolism study, 2,6-DIPN (dissolved in olive oil) was administered orally to six male Wistar rats at a dose of 240 mg/kg/day for 15 days. The metabolic pathway of 2,6-DIPN was found to proceed exclusively through oxidation of the isopropyl side-chain. From the urine, five unconjugated metabolites were isolated and identified: 2,6-naphthalenedi(2-propan)-2-ol, 2-[6-(1-hydroxy-1-methyl)ethylnaphthalen-2-yl]-2-propionic acid, 2,6-naphthalenedi-2-propionic acid, 2-[6-(1-hydroxy-1-methyl)ethylnaphthalen-2-yl]-2-hydroxypropionic acid, and 2-[6-(1-hydroxy-1-methyl)ethylnaphthalen-2-yl]-1,2-propanediol along with a small amount of the unchanged parent compound. The presence of glucuronides of five metabolites mentioned above was also reported. Moreover, the quantitative determination of metabolites in 24-hour urine after a single oral administration (100 mg/kg bw) indicated that these five metabolites were the major urinary metabolites of 2,6-DIPN, and that the total urinary excretion of metabolites was approximately 23% of the dose (19.40% unconjugated and 3.73% conjugated).

In a subchronic oral toxicity study in rat (90-day), there were no mortalities or treatment-related necropsy findings. Mean body weight gains were statistically significantly lower for males and females at high dose (207 and 244 mg/kg bw/day for males and females, respectively). Treatment-related absolute and/or relative statistically significant organ weight increases included adrenal, kidney and liver at high dose. Also, increased incidence and severity of centrilobular hepatocytic hypertrophy of liver, tubular nephrosis of kidney, and increased incidence and severity of cortical cell hypertrophy of adrenal glands were observed in both sexes. There were no treatment-related histomorphological changes at the low and mid doses. The LOAEL was 207 and 244 mg/kg bw/day for males and females, respectively, based on decreased body weights and food consumption, clinical pathology changes, and microscopic findings. The NOAEL was 104 and 121 mg/kg bw/day for males and females, respectively.

In a developmental toxicity study in rats, there were no mortalities, treatment-related necropsy findings or treatment-related changes in maternal animals. Food consumption and maternal body weight gain was reduced in the mid and high dose groups (150 and 500 mg/kg bw/day). In the high dose group, mean fetal body weight was reduced, and a statistically non significant increase in incidence of a skeletal alteration (cartilaginous changes in the vertebral column), at a maternally toxic dose, was noted. The maternal LOAEL was 150 mg/kg bw/day based on

reduction in bodyweight gain and food consumption, and the maternal NOAEL was 50 mg/kg bw/day. The developmental LOAEL is 500 mg/kg bw/day based on a reduction in fetal bodyweight and observed skeletal malformation. The developmental NOAEL is 150 mg/kg bw/day. In turn, this provides for a sufficient margin between the maternal and developmental NOAEL to adequately address observed fetal effects.

No evidence of mutagenic potential of 2,6-DIPN was observed in a battery of in vitro and in vivo genotoxicity assays, such as bacterial reverse mutation assay (Ames test), an in vivo/in vitro unscheduled DNA synthesis in rat primary hepatocytes at two timepoints, and an in vivo mouse micronucleus assay. However, in a mouse lymphoma study, 2,6-DIPN was weakly positive in the absence of metabolic activation and equivocal in the presence of metabolic activation; in both cases, it was tested up to cytotoxic concentrations. The mutagenic potential of 2,6-DIPN was considered to be of no concern based on a weight of evidence evaluation of mutagenicity data.

There are no data requirements for chronic toxicity, immunotoxicity, neurotoxicity or carcinogenicity studies. There is no evidence of carcinogenic potential for 2,6-DIPN in the available published literature. The results of the subchronic toxicity study and the genotoxicity/mutagenicity studies did not indicate that 2,6-DIPN has carcinogenic potential.

The toxicity profile of the end-use product is the same as that of 2,6-DIPN.

Results of the toxicity studies conducted on laboratory animals with 2,6-DIPN are summarized in Appendix I, Table 1.

Incident Reports

2,6-DIPN is a new active ingredient pending registration for use in Canada, and there are currently no incident reports. Once products containing 2,6-DIPN are registered, the PMRA will monitor for incident reports.

3.2 Occupational, Residential and Bystander Exposure and Risk Assessment

3.2.1 Dermal Absorption

Dermal absorption of 2,6-DIPN from the proposed use of Aceto Amplify II is not expected because the product is a granular solid.

3.2.2 Use Description

Aceto Amplify II is a commercial end-use product that is applied post-harvest, indoors to stored potatoes using automated thermal-generating fogging equipment. The thermal generator, located outside the storage building, vapourizes the product into a sealed storage area and the fog is re-circulated within the closed storage area for 2–4 hours. After this period, the treated storage area is completely ventilated for a minimum of 2–4 hours before workers may enter the treated area. Workers are not permitted to enter the treated area until the ventilation period is complete, and the aerosol has visibly settled.

Aceto Amplify II may be applied to stored potatoes once at a rate up to 2.5 kg per 100 tonnes of potato tubers, or multiple times at an accumulated maximum rate up to 2.5 kg per 100 tonnes of potato tubers. Generally, potatoes are treated every 30–90 days.

Workers can be exposed to 2,6-DIPN when handling and loading Aceto Amplify II into the machine, or when re-entering a treated area before the ventilation period is complete.

3.2.3 Mixer, Loader, and Applicator Exposure and Risk

Aceto Amplify II is applied to potatoes using automated fogging equipment with an open loading system. Workers can be exposed to 2,6-DIPN when manually loading (pouring) the granular product into the receptacle of the fogging unit. There are no mixing activities.

Although the dermal and inhalation toxicity of Aceto Amplify II is low, due to the physical nature of the granular product, dust may form during handling and loading, which may cause ocular and respiratory irritation. Therefore, workers are required to wear protective eyewear and a dust mask during all handling and loading activities.

Applicators/workers remain outside the enclosed storage area during the automated fogging application. Due to the automated nature of the closed application system, no exposure for applicators is expected.

Precautionary statements (for example, wearing of personal protective equipment) on the end-use product label aimed at mitigating exposure are considered adequate to protect individuals from any unnecessary risk due to occupational exposure. Overall, occupational risks for handlers, loaders and applicators are acceptable and not of concern when label directions are followed, which include PPE.

3.2.4 Postapplication Exposure and Risk

There is a potential for post-application exposure to workers by the dermal and inhalation routes upon entry into the storage areas that have been treated with 2,6-DIPN for cleaning and maintenance activities and for visual inspections and handling of the potatoes at the time of shipping.

Most postapplication activities will take place after the mandatory ventilation period is complete, at which time the end-use product would have been vented out of the warehouse. Therefore, dermal and inhalation exposure will be low, and is not of concern.

If workers need to enter the treated storage area during fogging, or before the ventilation period is complete, there is a potential for dermal and respiratory irritation from exposure to the vapour generated during fogging. Therefore, workers entering before the end of the ventilation period are required to wear coveralls over a long sleeved shirt and long pants, shoes plus socks, chemical-resistant gloves, protective eyewear, and a respirator with a NIOSH-approved organic vapour-removing cartridge with a prefilter approved for pesticides or a NIOSH-approved-canister approved for pesticides.

Precautionary (for example, wearing of personal protective equipment) statements on the end-use product label aimed at mitigating exposure are considered adequate to protect individuals from any unnecessary risk due to post-application exposure.

3.2.5 Residential and Bystander Exposure and Risk

There are no residential uses for Aceto Amplify II.

In addition, bystander exposure is not expected to be of concern from the use of the end-use product. The end-use product will be used in commercial potato storage facilities where bystanders are not expected to be present. The storage facilities are to be closed and sealed from all entry during application, with warning signs posted on the doors indicating that entry is not permitted during treatment. Consequently, residential and bystander exposure is not of concern.

3.3 Food Residue Exposure Assessment

3.3.1 Food

Dietary exposure to 2,6-DIPN may occur through consumption of treated potatoes; however, it is not expected to be of concern. Available toxicology data indicates that 2,6-DIPN is of low acute oral toxicity, unlikely to be toxic via repeated oral exposure, and is not a developmental toxicant or a mutagenic substance.

Residue studies provided by the applicant demonstrated that residues of 2,6-DIPN in potato tissue declined over time.

Considering all available information, no health risks of concern are anticipated from the presence of residues of 2,6-DIPN on food.

3.3.2 Drinking Water

As 2,6-DIPN is proposed for indoor, post-harvest use on stored potatoes, exposure via drinking water is minimal. The label has necessary mitigative measures to prevent contamination of drinking water from the proposed use of 2,6-DIPN. In addition, the toxicity of 2,6-DIPN is low. Consequently, no risk due to exposure from drinking water is anticipated.

3.3.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

Calculations of acute reference doses (ARfDs) and acceptable daily intakes (ADIs) are not required for 2,6-DIPN.

Based on all the available information and hazard data, the PMRA concludes that 2,6-DIPN is of low toxicity. While a quantitative risk assessment was not required, the available toxicity data demonstrates that there would be a sufficient margin to take into account the developmental effects noted in the database.

3.3.4 Aggregate Exposure and Risk

Based on available information, there is reasonable certainty that no harm will result from aggregate exposure of residues of 2,6-DIPN to the general Canadian population, including infants and children, when the end-use product is used as labelled. This includes all anticipated dietary (food and drinking water) exposures.

3.3.5 Cumulative Assessment

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with a common mechanism of toxicity. The PMRA did not identify information indicating that 2,6-DIPN shares a common mechanism of toxicity with other pest control products. Therefore there is no requirement for a cumulative risk assessment at this time.

3.3.6 Maximum Residue Limits

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine whether the consumption of the maximum amount of residues, that are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally established as a maximum residue limit (MRL) under the *Pest Control Products Act* for the purposes of the adulteration provision of the *Food and Drugs Act*. Health Canada sets science-based MRLs to ensure the food Canadians eat is safe.

Dietary risk to humans from the proposed post-harvest use of 2,6-DIPN on stored potatoes is not of concern because of the low toxicity profile of the active ingredient and the fact that the submitted data demonstrate that residues decline over time. Therefore, the specification of an MRL, under the *Pest Control Products Act*, will not be required for 2,6-DIPN.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Aceto Amplify II is proposed for indoor treatment of stored potatoes. When Amplify Aceto II is used according to the proposed label directions, no direct exposure of birds, aquatic organisms, non-target plants and non-target insects to 2,6-DIPN is expected to occur. Thus, very limited exposure of terrestrial and aquatic ecosystems is expected.

4.2 Environmental Risk Characterization

Given the use pattern, very limited exposure of terrestrial and aquatic ecosystems is expected; therefore, no risks of concern to non-target organisms in aquatic or terrestrial ecosystems are expected.

4.2.1 Incident Reports

No incident reports were available. This is a new active ingredient in Canada and incident reports are not expected.

5.0 Value

Once potatoes are harvested, washed, and placed in storage, they will start to sprout after a short period of time. Potato sprout inhibitors are important elements supporting the potato processing industry.

Value information submitted for review included data from two studies conducted in Idaho, US and Bicester, UK, a scientific paper, and use history information from one source in the US. Single and multiple applications of 2,6-DIPN provided short-term sprout inhibition on potatoes. The application of 2,6-DIPN in conjunction with CIPC provided superior sprout inhibition on potatoes when compared to the application of either product alone. Potato tuber quality (assessed as weight loss, fry colour, and disease and defect) was not diminished as a result of the application of Aceto Amplify II.

CIPC is the most commonly used chemical registered for potato sprout inhibition in storage. In addition to CIPC, 1,4-dimethylnaphthalene, 3-decen-2-one, and maleic hydrazide are also registered for the same use. Refer to Appendix 1, Table 2 for details of the alternatives for potato sprout inhibition in storage.

The claim of potato sprout inhibition in storage with either Aceto Amplify II alone or with CIPC-containing products is supported. The registration of Aceto Amplify II may provide potato growers and processors a useful tool to be used alone or with CIPC formulations for enhanced sprout inhibition, while maintaining tuber quality. Refer to Appendix 1, Table 3 for details of the supported uses.

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*].

2,6-DIPN and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and were evaluated against the Track 1 criteria. Available information indicates that 2,6-DIPN is readily biodegradable. 2,6-DIPN and its transformation products do not meet the persistence criteria for TSMP.

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 2,6-DIPN does not contain any contaminants of health or environmental concern identified in the *Canada Gazette.*

The end-use product, Aceto Amplify II, does not contain any contaminants or formulants of health or environmental concern identified in the *Canada Gazette*. The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Summary

7.1 Human Health and Safety

The available information for 2,6-DIPN is adequate to qualitatively and semi-quantitatively identify the toxicological hazards that may result from human exposure to 2,6-DIPN. It is of low acute toxicity, minimally irritating, and is not a skin sensitizer. Rat metabolism studies indicate that 2,6-DIPN is readily absorbed and metabolized through oxidation of the isopropyl side-chain. In a rat 90-day dietary study, there were no mortalities, and mean body weight gains were affected at high dose along with organ weight increases and histomorphological changes. In the

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

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

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

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

rat prenatal developmental toxicity study, there was an increase in incidence of one skeletal malformation at a maternally toxic dose; however, there is a sufficient margin between the maternal and developmental NOAEL to adequately address this effect. The evidence available suggests that 2,6-DIPN is not immunotoxic, neurotoxic, genotoxic, mutagenic or carcinogenic.

Workers can be exposed to 2,6-DIPN when manually loading the granular product into the fogging unit, and thus, will be required to wear protective eyewear and a dust mask during all handling and loading activities. Exposure for applicators is not expected since the fogging equipment is an automated, closed application system whereby applicators remain outside the sealed storage area during application. Post-application exposure will occur primarily by the dermal and inhalation routes. For workers entering the treated area during fogging, or before the ventilation period is complete, there is a potential for dermal and respiratory irritation. Precautionary statements (for example, wearing of personal protective equipment) on the end-use product label aimed at mitigating exposure are considered adequate to protect individuals from any unnecessary risk due to occupational exposure.

Residential and bystander exposure is minimal and not of concern since there are no residential uses for Aceto Amplify II, and the product is used in commercial potato storage facilities where bystanders are not expected to be present.

Aceto Amplify II is proposed for indoor use on stored potatoes. The active ingredient has a low toxicity profile, and residues on treated potatoes are expected to diminish over time and from washing, peeling and cooking practices. Consequently, dietary risk to humans from the proposed uses of Aceto Amplify II in food and drinking water will be low and not of concern when the product is used according to label instructions.

7.2 Environmental Risk

Given the use pattern of Aceto Amplify II, very limited exposure of terrestrial and aquatic ecosystems is expected for the proposed uses of 2,6-DIPN; therefore, no risks of concern to non-target organisms in aquatic or terrestrial ecosystems are expected.

7.3 Value

The registration of Aceto Amplify II will provide Canadian potato growers and processors another non-conventional product for sprout inhibition in storage. Furthermore, the application of Aceto Amplify II in conjunction with CIPC provides superior sprout inhibition on potatoes when compared to either product alone.

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 Amplify and Aceto Amplify II, containing the technical grade active ingredient 2,6-diisopropylnaphthalene, to be used as a sprout inhibitor for potatoes in storage.

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

2,6-DIPN	2,6-diisopropylnaphthalene
µg	micrograms
°C	degrees Centigrade
♀	female
♂	male
a.i.	active ingredient
ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
CAS	Chemical Abstracts Service
CIPC	chlorpropham
d	day
DIPN	diisopropylnapthalene
DNA	deoxyribonucleic acid
g	gram
GLP	Good Laboratory Practices
H	hour
ha	hectare(s)
HPLC	high performance liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOEC	low observed effect concentration
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
mg	milligram
mL	millilitre
MAS	maximum average score
mg	milligram
MIS	maximum irritation score
MOE	margin of exposure
MRL	maximum residue limit
N/A	not applicable
NOAEL	no observed adverse effect level
N/R	not required
PCPA	*Pest Control Products Act*
PGR	plant growth regulator
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency

ppm	parts per million
REI	restricted-entry intervals
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
UV	ultraviolet

Appendix I Tables and Figures

Table 1 Toxicity Profile of 2,6-DIPN

Study Type/Animal/PMRA #	Study Results
Acute Oral Toxicity Rat, Sprague-Dawley PMRA# 2478874	LD_{50} > 5000 mg/kg bw Low toxicity
Acute Dermal Toxicity Rabbit, New Zealand albino PMRA# 2478875	LD_{50} > 5000 mg/kg bw Low toxicity
Acute Inhalation Toxicity Rat, Sprague-Dawley PMRA# 2478876	LC_{50} > 2.60 mg/L Low toxicity
Eye Irritation Rabbit, New Zealand albino PMRA# 2478877	MAS [a] = 0.19/110 MIS [b] = 3.14/110 (1 hr) Minimally irritating
Skin Irritation Rabbit, New Zealand albino PMRA# 2478878	MAS = 0.06/8 MIS = 1.0/8 (1 hr) Minimally irritating
Skin Sensitization (Buehler method) Guinea pig/Hartley albino PMRA# 2478879	Negative Non-sensitizer
90-Day Dietary Rat (Crl:CD® IGS BR rats) PMRA# 2478880	NOAEL = 1,500 ppm (♂ = 104 mg/kg/d; ♀ = 121 mg/kg/d) LOAEL = 3,000 ppm (♂ = 207 mg/kg/d; ♀ = 244 mg/kg/d), based on lower body weight gain, organ weight increases and histomorphologic changes in organs.
Developmental Toxicity Rat (Crl:CD® IGS BR rats) PMRA# 2478881	<u>Maternal</u> NOAEL = 50 mg/kg/d LOAEL = 150 mg/kg/d based on reductions in body weight gain and food consumption. <u>Developmental</u> NOAEL = 150 mg/kg/d LOAEL = 500 mg/kg/d based on reduction in fetal bodyweight and an observed but not statistically significant increase in incidence of a skeletal alteration (Fusion of cartilaginous bands in the cervical centra). No evidence for sensitivity of the young

Study Type/Animal/PMRA #	Study Results
Bacterial Reverse Mutation Assay *S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP2 *uvr*A PMRA# 2478881	Negative
Mouse Lymphoma Mutagenesis Assay L5178Y TK+/- PMRA# 2478883	Weakly positive without S9 activation at doses of 10 to 30 µg/mL Equivocal with S9 activation at doses of 25 to 90 µg/mL
In Vivo Mammalian Micronucleus Assay CD-1 mice PMRA# 2478884	Negative
In vivo/in vitro Unscheduled DNA Synthesis Adult ♂ Fischer 344 rats/F344 rat hepatocytes PMRA# 2478885	Negative

[a] MAS = Maximum Average Score for 24, 48, and 72 hrs
[b] MIS = Maximum Irritation Score (average)

Table 2 Alternative active ingredients for sprout inhibition on potatoes in storage

TGAI	Example of the EPs	Pest claims
Chlorpropham (CIPC)	Sprout Nip 980 Potato Sprout Inhibitor (Reg. No. 27213)	Suppresses sprouts of potatoes in storage.
Maleic hydrazide	Royal MH 60 SG (Reg. No. 18143)	Controls sprouts and shrinkage of potatoes and onions in storage by pre-harvest application.
3-decen-2-one	SmartBlock (Reg. No. 30889)	Controls sprouts of potatoes by damaging or destroying growing meristem of sprouting potato tubers for 1-3 months per application.
1,4-dimethylnaphthalene	1,4Signt (Reg. No. 29837)	Delays potato sprouting, along with maintaining tuber firmness and deducing respiration, resulting in less water loss.

Table 3 Use Claims That Are Supported for Aceto Amplify II

Items	Use claims that are supported
Application rate	A single application at a rate not to exceed 2.5 kg per 100 tonnes of potatoes, or multiple applications not to exceed an accumulated rate of 2.5 kg per 100 tonnes of potatoes. The minimum application rate is 0.25 kg per 100 tonnes of potatoes.
Efficacy claim	For short term sprout inhibition on potatoes.
Host claim	Potatoes.
Application timing	Prior to the end of the natural dormancy period and sprouting occurs and as well after bruises and cuts have healed (normally a minimum of two weeks after storing).
Number of application	One or multiple times.
Co-application	Co-application with CIPC formulations.
Application method	Using thermal fogger by professional applicators.

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