Proposed Registration Decision PRD2021-05

Alcohol anhydrous, Restrain Fuel, Restrain Ethylene Generator Model B100, Restrain Ethylene Generator Model B200

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Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6607 D
Ottawa, Ontario K1A 0K9

Internet: canada.ca/pesticides
hc.pmra.publications-arla.sc@canada.ca
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
hc.pmra.info-arla.sc@canada.ca

Canada

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Overview

Proposed registration decision for alcohol anhydrous

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Restrain Technical, Restrain Fuel, Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200, containing or using the technical grade active ingredient alcohol anhydrous, for use in outdoor air-cooled and mechanically cooled storage areas for sprout inhibition of potatoes and onions or in greenhouses for ripening acceleration of tomatoes.

Alcohol anhydrous (also known as denatured ethanol or ethyl alcohol) is currently registered as a sanitizer. It is registered for domestic use as a sanitizer for hard non-porous surfaces and fabrics.

For details, see Proposed Re-evaluation Decision PRVD2018-04, *Ethyl Alcohol and Its Associated End-use Products*, and Re-evaluation Decision RVD2018-25, *Ethyl Alcohol and Its Associated End-use Products*.

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

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of alcohol anhydrous and Restrain Fuel, Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200.

What does Health Canada consider when making a registration decision?

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

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

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

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. 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 Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides section of Canada.ca.

Before making a final registration decision on alcohol anhydrous, Restrain Fuel, Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200, Health Canada's PMRA will consider any comments received from the public in response to this consultation document.[3] Health Canada will then publish a Registration Decision[4] on alcohol anhydrous, Restrain Fuel, Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada's response to these comments.

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

What is alcohol anhydrous?

Alcohol anhydrous (called denatured ethanol on the product labels) is the active ingredient of Restrain Fuel and is converted to ethylene by the Restrain Ethylene Generators. Ethylene is a naturally occurring plant growth regulator that inhibits sprouting of potatoes and onions and accelerates ripening and colouring of tomatoes.

Health considerations

Can approved uses of alcohol anhydrous and ethylene affect human health?

Alcohol anhydrous and ethylene are unlikely to affect human health when used according to label directions.

Potential exposure to ethylene may occur when handling and applying these products. 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 levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed.

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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*.

Based on registrant-supplied published scientific literature and publicly available information, the technical grade active ingredient, Restrain Technical, and the end-use product, Restrain Fuel, are considered to be of low acute oral, dermal, and inhalation toxicity, severely irritating to the eyes, minimally irritating to the skin, and are not dermal sensitizers. Published scientific literature and publicly available information also supports that ethylene, produced by the devices, Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200, is considered to be of low acute inhalation toxicity.

Additional information from the published scientific literature and publicly available information was assessed for the potential of denatured alcohol and ethylene to cause short-term toxicity, developmental toxicity, genotoxicity, and various other effects. Publicly available information states that repeated ingestion of ethanol, a major component of the denatured alcohol, by pregnant mothers has been shown to adversely affect the central nervous system (CNS) of the fetus, producing a collection of effects which together constitute the fetal alcohol syndrome. These effects include mental and physical retardation, disturbances of learning, motor and language deficiencies, behavioural disorders, and small head size. Long-term repeated oral exposure to ethanol in alcoholic drinks may result in the development of progressive liver injury with fibrosis or exacerbate liver injury produced from other causes. Treatment related adverse effects in animals administered repeated high doses of ethylene gas were not observed.

The risk assessment protects against the findings noted above as well as any other potential 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 acceptable.

Restrain Fuel is not applied to food or feed, but the ethylene generated by either device (Restrain Ethylene Generator Model B100 or Restrain Ethylene Generator Model B200) is proposed for use on tomatoes, potatoes, and onions. It is anticipated that the amount of ethylene present as a food residue after application will not exceed the naturally occurring ethylene background concentrations currently found in the environment or produced by fruit and vegetables. In addition, when the end-use products are used as directed by the label, the likelihood of Restrain Fuel and ethylene contaminating drinking water supplies is low and therefore not a health concern. Consequently, health risks from dietary exposure are acceptable for all segments of the population, including infants, children, adults and seniors.

Risks in residential and other non-occupational environments

Estimated risk for residential and other non-occupational exposure is acceptable.

Restrain Fuel as a precursor for the production of ethylene, generated from the devices, Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200, is proposed for use as a plant growth regulator on stored potatoes and onions and tomato plants in greenhouses. Product labels will include measures to reduce bystander exposure such as ensuring the exclusion of any unauthorized personnel from the treated areas and limiting re-entry to the worker responsible for the operation, cleaning, and maintenance of the devices. Residential and non-occupational exposure to Restrain Fuel, the devices and generated ethylene is therefore expected to be low when label directions are observed. Consequently, the risk to residents and the general public is acceptable.

Occupational risks from handling Restrain Fuel, Restrain Ethylene Generator Model B100, and Restrain Ethylene Generator Model B200

Occupational risks are acceptable when Restrain Fuel, Restrain Ethylene Generator Model B100, and Restrain Ethylene Generator Model B200 are used according to the label directions, which include protective measures.

Workers handling Restrain Fuel can come into direct contact with denatured alcohol through contact on the skin or in the eyes. To protect workers from exposure to Restrain Fuel, the labels require workers to wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes and protective eyewear during loading, application, clean-up and repair. If early entry is necessary before the levels of ethylene oxide, a principal metabolite of ethylene generated by the devices, are below the permissible level of 1 ppm (ACGIH TLV - TWA), workers will also be required to wear a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides, or a NIOSH-approved canister approved for pesticides.

The occupational risks are acceptable when the precautionary statements on the label are observed.

Environmental considerations

What happens when alcohol anhydrous, as part of Restrain Fuel used with Restrain Ethylene Generators, is introduced into the environment?

Restrain Fuel, containing 90% alcohol anhydrous (denatured ethanol) as an active ingredient, is converted to ethylene gas in situ when used with the Restrain Ethylene Generators. Ethylene is a naturally occurring plant growth regulator used to accelerate ripening of greenhouse tomatoes and reduce sprouting in stored potatoes and onions.

When ethylene gas is vented from greenhouse or storage facilities, this compound would be rapidly diluted in outdoor air to concentrations within naturally occurring levels. In addition, ethylene gas dissipates and degrades rapidly in the environment through chemical reactions in air in the presence of sun light. Due to the non-persistent nature of ethylene, it is not likely to travel long distances from where it is applied, or to accumulate in tissues of plants or animals.

Ethanol is essentially non-toxic to aquatic organisms while ethylene is slightly toxic to some aquatic species. Terrestrial plants are known to be sensitive to ethylene gas. Based on the proposed indoor use in greenhouse and storage facilities, and the fact that ethylene gas rapidly breaks down in air and does not readily enter soil or water, exposure of aquatic habitats is not expected, while exposure of terrestrial habitats would be to concentrations within naturally occurring levels.

When label directions are followed, the use of Restrain Fuel in Restrain Ethylene Generators is acceptable from an environmental perspective.

Value considerations

What is the value of Restrain Fuel, Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200?

The application of Restrain Fuel to generate 10 and 15 ppm ethylene to stored potatoes and onions, respectively, delays sprouting, inhibits sprout development, improves commodity quality, and therefore increases their market value. The application of Restrain Fuel to generate 1.4 ppm ethylene accelerates the ripening process and improves the ripening uniformity of greenhouse tomatoes.

Restrain Ethylene Generator Model B200 is specifically designed for conversion of Restrain Fuel to the recommended level of ethylene gas for use in storage facilities as well as in the greenhouse. Similarly, Restrain Ethylene Generator Model B100 is specifically designed for conversion of Restrain Fuel to the recommended level of ethylene gas for use in the greenhouse. Both generators are only to be used indoors under controlled environmental conditions.

Measures to minimize risk

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

The key risk-reduction measures being proposed on the labels of Restrain Technical, Restrain Fuel, Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200 to address the potential risks identified in this assessment are as follows.

Key risk-reduction measures

Human health

The signal words “DANGER – EYE IRRITANT” are required on the principal display panels of the labels for Restrain Technical and Restrain Fuel. Standard hazard and precautionary statements are also required on the technical grade active ingredient label and the end-use product label to inform workers of the eye irritation of the product.

Workers will be required to wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes and protective eyewear during loading, application, clean-up and repair. If early entry is necessary and the level of ethylene oxide is greater than 1 ppm, workers will also be required to wear a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides, or a NIOSH-approved canister approved for pesticides.

Next steps

Before making a final registration decision on alcohol anhydrous, Restrain Fuel, Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200, Health Canada’s PMRA will consider any comments received from the public in response to this consultation document. Health Canada will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada’s response to these comments.

Other information

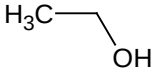
When the Health Canada makes its registration decision, it will publish a Registration Decision on alcohol anhydrous, Restrain Fuel, Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200 (based on the Science Evaluation of this consultation document). In addition, the test 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

Alcohol anhydrous, Restrain Fuel, Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200

1.0 The active ingredient, its properties and uses

1.1 Identity of the active ingredient

Active substance	Ethanol
Function	Plant Growth Regulator
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	Ethanol
2. Chemical Abstracts Service (CAS)	Ethanol
CAS number	64-17-5
Molecular formula	C_2H_6O
Molecular weight	46.068
Structural formula	
Purity of the active ingredient	90 %

1.2 Physical and chemical properties of the active ingredient and end-use product

Technical product—Restrain technical

Property	Result
Colour and physical state	colourless liquid
Odour	alcohol / ester odour
Melting range	- 115°C
Boiling point or range	72-83°C
Relative Density	0.7915
Vapour pressure at 20°C	5.87 kPa
Ultraviolet (UV)-visible spectrum	λ 210 nm A_{max}: 0.5

Property	Result
Solubility in water at 20°C	completely miscible
Solubility in organic solvents	soluble in ether, acetone, benzene
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} =-0.30
Dissociation constant (pK_a)	pK_a = 15.9 at 25 °C
Stability (temperature, metal)	stable under ambient conditions

End-use product—Restrain Fuel

Property	Result
Colour	colourless
Odour	alcohol / ester odour
Physical state	liquid
Formulation type	solution
Label concentration	90%
Container material and description	metal pail or drum
Relative Density	0.7915
pH of 1% dispersion in water	not required
Oxidizing or reducing action	incompatible with oxidizing agents
Storage stability	stable in commercial packaging
Corrosion characteristics	not corrosive to commercial packaging
Explodability	vapours can be explosive when ignited by open flame

1.3 Directions for use

Restrain Fuel is applied by the specifically designed Restrain Ethylene Generator Models B100 and B200.

1.3.1 Stored potatoes and onions

The Restrain Ethylene Generator Model B200 is to be installed when the storage temperature of 4-8°C has been reached for potatoes and potato eyes have started to develop or when the desired storage temperature has been reached for onion and onions have been dried and cured.

The generator is placed at the floor level or not greater than one metre above the floor in a position of good air circulation with at least 60 cm minimum free space surrounding and not above or close to a source of ignition. The Restrain Fuel product container is connected to the generator using a micro pump tube.

A B-ECHT sensor is connected to the generator and then placed 15 metres away in an area of good air circulation. The B-ECHT monitors ethylene concentration and then regulates the output rate of generator to maintain a constant level of ethylene in the storage atmosphere.

The storage room should have an empty volume of 200 m^3 or more for the normal cold store or 500 m^3 if it has been totally sealed to controlled atmosphere standards. The maximum size of the store depends on the room air leakage and the target level of ethylene.

Use the "Slow Start Up" as the standard procedure to initiate the application of Restrain Fuel in potato storage. The generator is automatically set to gradually increase the level of ethylene to 10 ppm over a 21-day period. After 21 days, the level of ethylene is maintained at 10 ppm for the duration of storage or until 5 days prior to planting for seed potatoes.

Use the program designated for onions as the standard procedure to initiate the application of Restrain Fuel in onion storage. The generator is automatically set to gradually increase the level of ethylene to 15 ppm and is then maintained at this level for the duration of storage.

When ethylene is introduced, the air must be circulated continuously to avoid the localized build-up of CO_2. Daily flushing fresh air (for a maximum of 6 hours) is recommended for reduction of the CO_2 level in the store. The machine and sensor should be checked daily for correct operation.

1.3.2 Greenhouse tomatoes

The Restrain Ethylene Generator Model B100 or Model B200 is to be installed when 10-80% of the greenhouse tomatoes show typical ripe colour. The generator is placed at floor level or not greater than one metre above the floor in a position of good air circulation with at least 60 cm minimum free space surrounding and not above or close to a source of ignition. The Restrain Fuel product container is connected to the generator using a micro pump tube. The Model B200 generator is connected with a B-ECHT sensor and then the sensor is placed 15 m away from the generator in an area of good circulation.

For the generator Model B100, one of the three settings, i.e., 1.44, 2.88, or 4.32 L product/24 hours is selected, to produce the recommended level of ethylene concentration at 1.4 ppm based on the volume of the greenhouse.

For the generator Model B200, the greenhouse should have an empty volume of 200 m^3 or more. The maximum volume of the greenhouse depends on the standard construction and room air leakage. Use the "Ripen Start Up" as the standard procedure to initiate the application of Restrain Fuel to generate 1.4 ppm ethylene for a 4.5-days period continuously. The machine and sensor should be checked daily for correct operation.

1.4 Mode of action

Restrain Fuel containing 90% denatured ethanol is converted to ethylene gas in situ using Restrain Ethylene Generators. Ethylene is a naturally occurring plant growth hormone that affects the growth, development, ripening, and senescence of the plant. Ethylene inhibits the development of sprouts on potatoes and onions at a specific concentration when potatoes and

onions break out of dormancy during storage. When exposed to a specific concentration of an external source of ethylene the ripening process of fruiting vegetables, including tomatoes, is accelerated and becomes more uniform.

2.0 Methods of analysis

2.1 Methods for analysis of the active ingredient

Standard analytical methods are available and used for the determination of the active ingredient and impurities.

2.2 Method for formulation analysis

Standard analytical methods are available and used for the determination of the active ingredient.

2.3 Methods for residue analysis

Residue methods are not applicable for these products.

3.0 Impact on human and animal health

3.1 Toxicology summary

A detailed review of the toxicological information was conducted in support of Restrain Technical, Restrain Fuel, and ethylene produced by the devices, Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200. The data package for Restrain Technical, Restrain Fuel, Restrain Ethylene Generator Model B100, and Restrain Ethylene Generator Model B200 is considered acceptable to assess the toxic effects that may result from exposure to denatured alcohol (ethanol, isopropanol, and ethyl acetate) and ethylene from the proposed uses. The data package consisted of published scientific literature and publicly available information on the acute oral, dermal, and inhalation toxicity, primary skin and eye irritation, and dermal sensitization for Restrain Technical, Restrain Fuel, and ethylene, as well as published scientific literature and publicly available information on short-term toxicity, prenatal developmental toxicity, and genotoxicity of the components of Restrain Technical and the ethylene generated by the devices.

Based on a review of the registrant-supplied published scientific literature and publicly available information, Restrain Technical, a denatured alcohol consisting of ethanol, isopropanol, and ethyl acetate, is considered to be of low acute oral toxicity (LD_{50} greater than 2000 mg/kg bw in rats), low acute dermal toxicity (LD_{50} greater than 2000 mg/kg bw in rabbits), low acute inhalation toxicity (LC_{50} greater than 2.0 mg/L), severely irritating to the eyes, minimally irritating to the skin, and is not a dermal sensitizer.

Restrain Fuel and Restrain Technical are of low acute oral, dermal, and inhalation toxicity, severely irritating to the eyes, minimally irritating to the skin, and not a dermal sensitizer.

Ethylene gas produced by the devices, Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200, is considered to be of low acute inhalation toxicity.

In a study in the published scientific literature, male and female Sprague-Dawley rats exposed to 1, 2, 3, 4, 5, and 10% ethanol in a liquid diet for 90 days experienced a treatment-related increase in hepatic centrilobular steatosis and an increased frequency and severity of Mallory bodies, acidophillic degeneration and necrosis at doses of 3% and above. Body weight gain was decreased with increasing dose while food and water consumption was reduced in the 10% group.

Male Sprague-Dawley rats exposed to 10 mg/L of ethanol for 3 days, followed by 25 mg/L for an additional 11 days (14 day total) on a continuous basis resulted in a decrease in cellularity in the spleen, thymus, and bone marrow. The proportions of lymphocytes and polymorphonuclear leukocytes in the peripheral blood were affected but the effects were not fully disclosed in the available information. There was also a decrease in erythroid progenitor cells in the bone marrow. This study was limited to the examination of the effects of ethanol on the immune and hematopoietic systems.

Publicly available information states that repeated ingestion of ethanol by pregnant mothers has been shown to adversely affect the CNS of the fetus, producing a collection of effects which together constitute the fetal alcohol syndrome. These affects include mental and physical retardation, disturbances of learning, motor and language deficiencies, behavioural disorders, and small head size.

The available literature suggests that ethanol is not expected to be genotoxic. This conclusion is based on repeated negative in vitro findings in bacterial mutagenic assays, micronucleus assays, chromosome aberration assays, cell mutation assays, sister chromatid exchanges, and DNA damage assays.

Publicly available information notes that long-term repeated oral exposure to ethanol in alcoholic drinks may result in the development of progressive liver injury with fibrosis or exacerbate liver injury produced from other causes.

The International Agency for Research on Cancer (IARC) has categorized alcoholic beverages as carcinogenic in humans, but not ethanol.

Published scientific literature and publicly available information regarding the neurotoxicity of ethanol suggests that the mechanism by which ethanol operates on the nervous system is related to its ability to fluidize lipids in membranes. The degree of intoxication has been shown to correlate with the fluidization of brain membranes. Air concentrations of 10 mg/L have been shown to be sufficient to cause CNS depression in humans and animals, marked by drowsiness, ataxia, narcosis, and death.

Ethylene is a naturally occurring gaseous chemical produced by all plant tissues and acts as an endogenous plant growth regulator. Ethylene is also a naturally occurring endogenous chemical in humans and laboratory animals and has been identified in the air exhaled by unexposed rats

and humans. Possible sources of endogenous ethylene in humans and laboratory animals include lipid peroxidation of unsaturated fats, oxidation of free methionine, oxidation of hemin in haemoglobin and metabolism of intestinal bacteria.

The most probable route of human exposure to ethylene, a gas, is by inhalation. Ethylene at high concentrations (up to 80 to 90% in oxygen) has a history of use as a clinical anaesthetic, with little associated toxicity. However, ethylene has been classified as an asphyxiant in Canada because its presence at high concentrations in air lowers the available oxygen concentration.

Ethylene is of low acute toxicity via the inhalation route of exposure in mice. In a subchronic inhalation study with Sprague-Dawley rats, there were no toxic effects at concentrations up to and including 10,000 ppm, the highest dose tested. In a chronic toxicity/oncogenicity inhalation study with Fischer 344 rats, no significant treatment-related findings or evidence of oncogenicity were observed at ethylene concentrations up to and including 3000 ppm, the highest dose tested. The available scientific information suggests that ethylene is not genotoxic. There is inadequate evidence in humans and experimental animals for carcinogenicity of ethylene. Overall, ethylene is not classifiable as to its carcinogenicity to humans (IARC classification - Group 3). Ethylene is not listed as a carcinogen by the National Toxicology Program (NTP) or Occupational Safety and Health Association (OSHA).

The toxicological concerns regarding ethylene are related to its principal metabolite, ethylene oxide. Ethylene oxide is genotoxic in numerous in vitro and in vivo test systems and is carcinogenic in mice and rats. Positive results have been obtained using the mouse lung tumour bioassay ($\geq$ 70 ppm) and the standard 2-year bioassays in mice and rats at concentrations $\geq$ 100 ppm. Based on these findings and on the proposed conditions of use for ethylene, it is unlikely that ethylene oxide concentrations would reach levels that would produce unacceptable genotoxic or carcinogenic risks.

Health incident reports

As of 23 December 2020, one human incident involving alcohol anhydrous along with other active ingredients, one domestic animal incident involving a herbicide containing ethylene and three human incidents involving devices had been submitted to the PMRA.

One human incident involving ozone-generating air purifying devices was considered relevant to the use pattern of the proposed end-use product and device. In this incident, three people were exposed when living in a home in which ozone-generating air purifying devices were being used. The reported effects in the three individuals include nose, eye and throat irritation that were considered related to the ozone-generating device. The reported exposure scenario of inhalation exposure of individuals to a vapour/gas generating device when placed in enclosed areas was considered relevant to the use pattern of the proposed end-use product/device in greenhouses. The remaining incidents either involved other device types (for example, bug zapping device) and/or exposure scenarios (for example, accidental ingestion when using the product) that were not considered relevant to the proposed product and devices.

The proposed labels of the commercial class end-use product and device contain appropriate precautionary statements and warnings to reduce the likelihood of exposure of operators to the ethylene gas converted from alcohol anhydrous by the devices in greenhouses. Hence, no additional mitigation measures are recommended based on the incident report review.

3.2 Occupational, residential and bystander exposure and risk assessment

3.2.1 Dermal absorption

Information was not submitted regarding the dermal absorption of denatured alcohol in the end-use product, Restrain Fuel, or the ethylene generated by the devices, Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200. The low toxicity and limited exposure is such that the potential for dermal absorption of the denatured alcohol is not a concern. Also, the potential dermal absorption of ethylene is not a concern because of the low toxicity and its physical form (i.e., gas).

3.2.2 Use description

The rate of application of Restrain Fuel depends on the crop being treated and the size of the storage area or greenhouse. For potatoes and onions stored in small areas subject to draft or leakage due to wind, the anticipated volume of Restrain Fuel used per day would be 0.1 to 0.3 L/day, for medium stores, the volume used would be 0.2 to 0.5 L/day, for large stores, the volume used would be 0.5 to 1.0L/day, and for extra-large storage areas, the volume used would be 1.0 to 2.0 L/day. For greenhouses, the rate of application of Restrain Fuel ranges from 1.44 L to 4.32 L every 24 hours, depending on the total greenhouse volume. The quantity of denatured alcohol handled is 0.071 to 1.42 g/day for the treatment of stored potatoes and onions and ranges from 1.03 to 3.07 g/day for greenhouse tomatoes.

The application rate of ethylene generated by either Restrain Ethylene Generator Model B100 or Restrain Ethylene Generator Model B200 is 1.75 mg/m^3 (1.4 ppm) for use in greenhouses having an empty volume greater than 200 m^3. The devices are used when the tomato plants have reached a Biologische Bundesanstalt, Bundessortenamt und CHemische Industrie (BBCH) index of 81 to 89 (81: 10% of fruits show typical fully ripe colour; 89: fruits have typical fully ripe colour). Application is performed continuously for 4.5 days. The rate of application of ethylene generated by Restrain Ethylene Generator Model B200 is 12.5 mg/m^3 (10 ppm) for use on stored potatoes and 19.0 mg/m^3 (15 ppm) for stored onions, each storage area having a minimum empty volume of at least 200 m^3. Restrain Ethylene Generator Model B200 is to be used when stored potatoes have reached the desired storage temperatures and eyes have started to develop. Treat stored onions when the desired storage temperature has been reached and the bulbs have been dried and cured. Application is continuous until the potatoes or onions are to be removed from storage (for seed potatoes, remove 5 days prior to planting).

3.2.3 Mixer, loader and applicator exposure and risk

Exposure to Restrain Fuel is characterized as short-term and intermediate in duration and is predominately by the dermal route, but incidental exposure to the eyes and by inhalation is possible when loading the product. Exposure to ethylene produced by Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200 is characterized as short-term in duration and is primarily by the inhalation route.

Workers must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes, and protective eyewear during loading of the Restrain Fuel containers, as well as during the application of ethylene, and the clean-up and maintenance of the ethylene generators. Additionally, a suitable respirator is required if the level of ethylene oxide is above the permissible level of 1 ppm (ACGIH TLV - TWA).

Overall, occupational risks to workers are acceptable when the precautionary statements, aimed at mitigating exposure, on the labels are observed.

3.2.4 Postapplication exposure and risk

Postapplication activities include the removal of any unused Restrain Fuel, the emptying, cleaning, and the removal of the Restrain Ethylene Generators, as well as harvesting tomatoes from the greenhouse and removal of potatoes and onions from storage. The restricted-entry statement on the product labels for Restrain Fuel and both of the Restrain Ethylene Generators requires that the treated areas be ventilated prior to re-entry. Also, individuals are not permitted entry into a treated area after application until the level of ethylene oxide is above the permissible level of 1 ppm (ACGIH TLV - TWA).

Consequently, the risks to workers due to postapplication exposure to individuals are considered acceptable when the precautionary statements described on the label are observed.

3.2.5 Residential and bystander exposure and risk

The handling of Restrain Fuel and the application of ethylene, generated from the devices, Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200, are proposed for indoor use. Label statements ensuring the exclusion of any unauthorized personnel from the treated areas except the operator during loading and canister removal of the fuel and limited re-entry by the worker responsible for the operation, cleaning, and maintenance of the devices are such that bystander and residential (non-user) exposures are not expected.

Consequently, the health risks to individuals in residential areas and bystanders are acceptable.

3.3 Food residue exposure assessment

3.3.1 Food

Restrain Fuel is not applied to food or feed, but ethylene generated by either devices (Restrain Ethylene Generator Model B100 or Restrain Ethylene Generator Model B200) is proposed for use on tomatoes, potatoes, and onions. It is anticipated that the amount of ethylene present as a food residue after application of the end-use product will not exceed the naturally occurring background concentration currently found in the environment or produced by fruit and vegetables.

Consequently, there is no health risk for the general population, including infants and children, or domestic animals.

3.3.2 Drinking water

The proposed uses of Restrain Fuel, as well as the gas, ethylene, produced by Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200 are not expected to result in environmental residues at any significant distance beyond the site of application and therefore are unlikely to enter neighbouring aquatic environments.

Consequently, the health risks from residues of denatured alcohol and ethylene in drinking water are acceptable.

3.3.3 Acute and chronic dietary risks for sensitive subpopulations

Calculations of acute reference doses and acceptable daily intakes are not required for ethylene. Based on all the available information and hazard data, this active ingredient is considered to be of low toxicity and exposure is not anticipated. As a result, there is no need to apply uncertainty factors to account for intra- and interspecies variability or have a margin of exposure given that a threshold for potential effects is not required. Further factoring of consumption patterns among infants and children, special susceptibility in these subpopulations to the effects of ethylene, including developmental effects from pre- or post-natal exposures, and cumulative effects on infants and children of this active ingredient and other registered products containing it, does not apply to this active ingredient. As a result, the PMRA has not used a margin of exposure approach to assess the risks of ethylene to human health.

3.3.4 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, and from all known or plausible exposure routes (oral, dermal and inhalation).

In an aggregate risk assessment, the combined potential risk associated with food, drinking water and various residential exposure pathways is assessed. A major consideration is the likelihood of co-occurrence of exposures. Additionally, only exposures from routes that share common toxicological endpoints can be aggregated.

Based on available information, there is reasonable certainty that no harm will result from aggregate exposure of denatured alcohol and ethylene to the general population in Canada, including infants and children, when Restrain Fuel, Restrain Ethylene Generator Model B100, and Restrain Ethylene Generator Model B200 are used as labelled. This includes all anticipated dietary (food and drinking water) exposures and all other non-occupational exposures (dermal and inhalation) for which there is reliable information.

3.3.5 Cumulative assessment

The *Pest Control Products Act* requires that Health Canada consider the cumulative exposure to pest control products with a common mechanism of toxicity. For the current evaluation, exposure to the denatured alcohol (anhydrous alcohol, isopropanol, and ethyl acetate) is limited to the installation and removal of the containers to/from the devices by the operator.

While other denatured alcohol-based pesticides share a common mechanism of action, residential exposure is not expected to be impacted. Consequently, a cumulative risk assessment is not necessary for the denatured alcohol.

Ethylene has the potential for non-occupational exposure during the venting process. However, as the exposure to ethylene is not expected to exceed levels normally found in the environment and is of low toxicity, the potential health risks from cumulative exposure to ethylene and ethylene-based pesticides are acceptable given the limited residential exposure based on the proposed use pattern.

3.3.6 Maximum residue limits

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine that 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 specified as a maximum residue limit (MRL) under the *Pest Control Products Act* for the purposes of adulteration provision of the *Food and Drugs Act*. Health Canada specifies science-based MRLs to ensure the food Canadians eat is safe.

It is anticipated that the amount of ethylene present as a food residue after application of the end-use product will not exceed the naturally occurring background concentration currently found in the environment or produced by fruit and vegetables, and it is not possible to distinguish between anthropogenic and naturally occurring concentrations of ethylene. As a result, under the *Pest Control Products Act*, an MRL could not be enforced and is not being proposed for the crops treated with ethylene.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

Previous environmental assessments of fate and behaviour of ethanol (also known as alcohol anhydrous) and ethylene are available in PRVD2018-04 and PRDD2001-04, respectively. A summary of fate data (from previous assessments and submitted documents) for ethanol and ethylene are presented in Appendix I, Table 2.

Ethanol in Restrain Fuel is in liquid phase and is transformed in situ by the Restrain Ethylene Generators to ethylene gas and water vapour. Based on the proposed indoor use pattern of Restrain Fuel and Restrain Ethylene Generators, no environmental exposure to ethanol is expected while exposure to ethylene gas would be limited to air. When ethylene gas is vented from greenhouse or storage facilities, this compound would be rapidly diluted in outdoor air to concentrations within naturally occurring levels.

Both ethanol and ethylene are volatile components of many plants and quickly degrade in the environment.

Ethanol is fully miscible in water while ethylene is slightly soluble. Hydrolysis of both compounds is not expected to be an important environmental fate process since these compounds lack functional groups that hydrolyze under environmental conditions (pH 5 to 9). Ethanol does not contain chromophores that absorb at wavelengths > 290 nm, while ethylene absorbs UV at 175.2 nm, therefore, neither compound is expected to be susceptible to direct photolysis by sunlight. If released to soil, both ethanol and ethylene are expected to have very high mobility based upon their log K_{oc}. Both ethanol and ethylene are highly volatile under field conditions based upon vapour pressure. Volatilization from moist soil and water surfaces is expected for both ethanol and ethylene based upon a Henry's Law constant; such volatilization is expected to be an important fate process for ethylene.

If released into water, ethanol and ethylene are not expected to adsorb to suspended solids and sediment based upon their log K_{oc}. Biodegradation of ethanol in water is expected based on degradation half-lives of 5-8 days in aerobic aquatic systems. Data on biodegradation of ethylene in soil or water were not available. An estimated bioconcentration factor (BCF) of 3 for ethanol and 2.6 for ethylene suggests the potential for bioconcentration of either compounds in aquatic organisms is low. Estimated volatilization half-lives of ethanol for a model river and model lake are 5 and 39 days, respectively, while for ethylene these volatilization half-lives are 2 hours and 2 days, respectively.

Based on their high vapour pressures, ethanol and ethylene are expected to exist solely as a vapour in the atmosphere. Vapour-phase ethanol and ethylene will be rapidly degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 5 days for ethanol and 15 hours for ethylene.

Due to its rapid degradation in the atmosphere in the presence of hydroxyl radicals, ethylene is not expected to undergo long-range transport in the atmosphere. Deposition to soil surfaces via wet or dry deposition is also highly unlikely, based on the combination of its high vapour pressure, short half-life in air and slight solubility.

Information from public literature indicate that about three quarters of atmospheric ethylene originates from natural sources, while one quarter is from anthropogenic sources. The main anthropogenic release is from burning of hydrocarbons and biomass. Ethylene concentrations in ambient air at rural and remote sites worldwide are generally in the range of < 1-5 $\mu g/m^3$. In urban and indoor air contaminated with combustion products, ethylene concentrations may reach 50 $\mu g/m^3$ and above 1000 $\mu g/m^3$ in heavy traffic areas. Much higher levels of ethylene are found in industrial and petrochemical plants (up to 5000 $\mu g/m^3$) and wood fire smoke (63000 $\mu g/m^3$).

4.2 Environmental risk characterization

Based on the proposed use pattern of Restrain Fuel, which limits applications to greenhouses and enclosed storage facilities, and given the natural occurrence of both ethanol and ethylene compounds, a qualitative risk assessment using a weight-of-evidence approach was performed to identify potential risks to terrestrial and aquatic organisms.

4.2.1 Risks to non-target species

A summary of toxicity data for ethanol and ethylene are presented in Appendix I, Table 3.

No studies on bees, birds and terrestrial plants were submitted. Data in published literature show that vascular plants are susceptible to ethylene. Effects of ethylene on growth and development of Canadian crop species have been reported following constant exposure at less than 60 $\mu g/m^3$ for 1 to 3 days. This is expected since ethylene is a natural plant hormone that plays a role in maturation of plants. Exposure of terrestrial plants as a result of Restrain Fuel use in greenhouse and storage facilities is not expected to exceed the natural background of ethylene in the environment.

With regards to aquatic organisms, ethanol is non-toxic to fish, aquatic invertebrates, freshwater algae and aquatic vascular plants. Ethylene is slightly toxic to fish on an acute basis, while it is slightly to practically non-toxic to the aquatic invertebrate *Daphnia magna*. Based on the proposed indoor use of Restrain Fuel, as well as the fact that ethylene gas does not readily partition to water, exposure of aquatic organisms is not expected.

Overall conclusion about potential risks to non-target organisms

The proposed use pattern limits application of Restrain Fuel to enclosed storage facilities or greenhouse using Restrain Ethylene Generators. No environmental exposure to ethanol is expected. Ethylene released outdoors, when the enclosed storage facilities or greenhouses are temporarily opened or vented, is unlikely to affect aquatic and terrestrial organisms. This compound is expected to be released in relatively small quantities (compared to releases from fossil fuel combustion and from industrial processes).

It will be quickly diluted in outdoor air at levels averaging the natural background in the environment and will not accumulate due to its rapid degradation. Therefore, the overall potential risk to terrestrial and aquatic organisms is negligible. No mitigation measures are required.

4.2.2 Incident reports

Environmental incident reports are obtained from two main sources, the Canadian pesticide incident reporting system (including both mandatory reporting from the registrant and voluntary reporting from the public and other government departments) and the USEPA Ecological Incident Information System (EIIS). Information on the reporting of incidents can be found on the Report a Pesticide Incident page of the Pesticides section on Canada.ca (http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/incident/index-eng.php).

The PMRA incident reporting database was searched for all human, domestic animal and environment incident reports involving the active ingredients ethanol and ethylene present in Restrain Fuel devices. As of 23 December 2020, no environment incident reports (including scientific studies) involving either alcohol anhydrous, ethylene, or devices relevant to the use of this product were reported to the PMRA.

The EPA Ecological Incident Information System (EIIS), which was last updated 5 October 2015, was searched and no environment incident reports related to alcohol anhydrous, ethylene or devices were found.

5.0 Value

Value information submitted for review included scientific rationales, use history information from Europe, data from research studies conducted on potatoes, onions, and greenhouse tomatoes in the United Kingdom, Germany, Spain, Poland, and the Netherlands

Once potatoes and onions are harvested and placed into storage, it is only a matter of time before they start to sprout. Sprouts on potatoes and onions cause loss of quality, weight, water content, etc. and therefore reduce marketability.

The application of Restrain Fuel using the Restrain Ethylene Generator Model B200 continuously at 10 ppm ethylene on potatoes in mechanically cooled and controlled atmospheres during storage delayed sprouting, inhibited sprout development, and maintained the quality (including flavour) of potato tubers for seed and consumption. The Restrain Fuel treatment inhibited potato sprouting by reducing numbers, length, and weight of sprouts. Treated seed potatoes had similar or better quality to the untreated seed potatoes, and resulted in more stems per tuber and higher tuber yield in the following field season.

The application of Restrain Fuel using the Restrain Ethylene Generator Model B200 continuously at 15 ppm ethylene on onions in mechanically cooled and controlled atmospheres during storage resulted in extended storage life, delayed sprouting, reduced internal sprouts, and improved bulb quality, as measured by bulb size, weight loss, texture, firmness, taste, and disease appearance.

The application of Restrain Fuel using the Restrain Ethylene Generator Model B100 and B200 at 1.4 ppm ethylene for 4.5 days accelerated greenhouse tomato ripening without negative impact on fruit quality, as determined by taste, refraction, acidity, % juice, and shelf-life.

Currently, several active ingredients, for example, chlorpropham, 1-octanol, 3-decen-2-one, and 2,6-DIPN, are registered to inhibit sprouting in stored potatoes and onions. Another active ingredient, maleic hydrazide, is registered for pre-harvest application to inhibit potato and onion sprouting during storage. The active ingredient ethephon (which breaks down to ethylene within the plant) is registered for acceleration of tomato ripening and uniformity.

The registrations of Restrain Fuel and its associated Restrain Ethylene Generators provides growers and distributors a new tool to manage sprouting of stored potatoes and onions and to improve ripening uniformity of greenhouse tomatoes.

6.0 Pest control product policy considerations

6.1 Assessment of the active ingredient under the toxic substances management policy

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, i.e., those that meet all four criteria outlined in the policy: 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*. The *Pest Control Products Act* requires that the TSMP be given effect in evaluating the risks of a product.

During the review process, Restrain Technical and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the conclusion that denatured ethanol and its transformation products do not meet all of the TSMP Track 1 criteria.

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

6.2 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the active ingredient as well as formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*[6] The list is used as described in the PMRA Science Policy Note SPN2020-01[7] and is based on existing policies and regulations, including the *Toxic Substance Management Policy* and *Formulants Policy*,[8] and taking into consideration the *Ozone-depleting Substances and Halocarbon Alternatives Regulations* under the *Canadian Environmental Protection Act, 1999, (*substances designated under the *Montreal Protocol).*

The PMRA has reached the conclusion that Restrain Technical (active ingredient: denatured ethanol) and its end-use product Restrain Fuel do not contain any formulants or contaminants identified in the *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 Proposed regulatory decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Restrain Technical, Restrain Fuel, Restrain Ethylene Generator Model B100 and Restrain Ethylene Generator Model B200, containing or using the technical grade active ingredient alcohol anhydrous, for use in outdoor air-cooled and mechanically cooled storage areas for sprout inhibition of potatoes and onions or in greenhouses for ripening acceleration of tomatoes.

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

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6 SI/2005-114, last amended on June 24, 2020. See Justice Laws website, Consolidated Regulations, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*

7 PMRA's Science Policy Note SPN2020-01, *Policy on the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under paragraph 43(5)(b) of the Pest Control Products Act.*

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

List of abbreviations

2,6-DIPN	2,6-Diisopropylnaphthalene
µg	micrograms
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ALS	acetolactate synthase
ARfD	acute reference dose
atm	atmosphere
BBCH	Biologische Bundesanstalt, Bundessortenamt und CHemische Industrie
BCF	Bioconcentration Factor
bw	body weight
CAS	Chemical Abstracts Service
cm	centimetres
CNS	central nervous system
d	days
DF	dry flowable
DIR	Regulatory Directive
DNA	deoxyribonucleic acid
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)
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EP	end-use product
ER_{25}	effective rate for 25% of the population
g	gram
h	hour(s)
ha	hectare(s)
HDT	highest dose tested
Hg	mercury
HPLC	high performance liquid chromatography
IARC	International Agency for Research on Cancer
IUPAC	International Union of Pure and Applied Chemistry
Kd	soil-water partition coefficient
KF	Freundlich adsorption coefficient
kg	kilogram
km	kilometre
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%
m^3	cubic metre
MAS	maximum average score
mg	milligram
mL	millilitre
mm Hg	millimetre of mercury
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
N/A	not applicable
N/R	not required
nm	nanometre
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
NTP	National Toxicology Program
NZW	New Zealand white
OC	organic carbon content
OM	organic matter content
OSHA	Occupational Safety and Health Association
PBI	plantback interval
PGR	Plant growth regulator
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
PRDD	Proposed Regulatory Decision Document
PRVD	Proposed Re-evaluation Decision
RSD	relative standard deviation
SC	soluble concentrate
SPN	Science Policy Note
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TGAI	Technical Grade Active Ingredient
TLV	threshold limit value
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
TWA	time weighted average
UAN	urea ammonium nitrate
UF	uncertainty factor

USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution

Appendix I Tables and figures

Table 1 List of supported uses

Items	Proposed label claims	Supported use claims
Application rates	Potatoes: Apply at 10 ppm ethylene continuously until potatoes are removed from the storage or until five days prior to planting (seed potatoes). Onions: Apply at 15 ppm ethylene continuously until onions are removed from the storage. Greenhouse tomatoes: Apply at 1.4 ppm ethylene for 4.5 days at the end of cultivation period.	Supported as proposed.
Efficacy claims and hosts	Inhibition of potato and onion sprouting in the storage and acceleration of greenhouse tomato ripening.	Supported as proposed.
Application methods	**Potatoes:** Install the Model B200 generator when desired temperature is reached in the store and eyes have started to develop. Place the generator at the floor level or not greater than one metre above the floor in a position of good circulation with at least 60 cm minimum free space surrounding it. Connect the Restrain Fuel container with the generator using a micro pump tube. Connect a B-ECHT Sensor with the generator and then place sensor 15 m away from the generator in an area of good circulation. Using the "Slow Start Up" procedure to initiate the application. The generator is automatically set to gradually increase the level of ethylene to 10 ppm over a 21-days period. After 21 days, the level of ethylene is maintained at 10 ppm for the duration of storage or until 5 days prior to planting (for seed potatoes). When ethylene is introduced, the air must be circulated continuously to avoid the localized build-up of CO_2. Daily flushing fresh air (for a maximum of 6 hours) is recommended for reduction of the CO_2 level.	Supported as proposed.

Items	Proposed label claims	Supported use claims
	Onions: Install Model B200 generator as described above for potatoes. Using the program designated for onions to initiate the application. The generator is automatically set to increase the level of ethylene to 15 ppm and is then maintained at this level. Air circulation and daily air flushing are also recommended. **Greenhouse Tomatoes:** Install the Model B100 or Model B200 generator when the crop has reached the growth stage BBCH 81-89. Place the generators on the floor or not greater than one metre above the floor with at least 60 cm minimum free space surrounding it. Connect the Restrain Fuel container with the generators using a micro pump tube. Also connect a B-ECHT Sensor with Model B200 generator and then place the sensor 15 m away from the generator in an area of good circulation. For the Model B100, choose one of the three settings, i.e., 1.44, 2.88, or 4.32 L product/24 hours, to produce the level of ethylene at 1.4 ppm based on the greenhouse size. For the Model B200, use the “Ripen Start Up” procedure to initiate the application. The generator is automatically set to generate ethylene at 1.4 ppm. Apply Restrain Fuel continuously for a 4.5-day period.	

Table 2 Environmental fate and behaviour of Restrain Fuel and its transformation product

Property	Result		Comment	Reference
	Ethanol	Ethylene		PMRA#
Water solubility	Fully miscible	131 mg/L at 20°C	Ethylene is slightly soluble	3066521
Vapour pressure	59.3 mm Hg at 25ºC	5.21×0^4 mm Hg at 25°C	High volatility under field conditions	3066521
UV/visible spectrum	Does not contain chromophores that absorb at wavelengths >290 nm,	Absorbs UV at 175.2 nm	Photolysis is not expected to be a route of dissipation in the environment	3066521
n-Octanol/water partition coefficient (log K_{ow})	-0.31	0.053-1.13	Low potential for bioconcentration in aquatic organisms	3066467 3066499
Henry's Law constant atm.m^3/mole at 25°C	5.0×10^{-6}	0.228	Expected to volatilize from moist soil or water surfaces	3066467 3066521
BCF	3	2.6	Low potential for bioconcentration.	3066467 3066521
Log K_{oc}	0.20	2-2.47	Low potential for adsorption to particles present in soil and sediment	3066467 3066499
Volatilization half-lives	5 d (model river) 39 d (model lake)	2 h (model river) 2 d (model lake)	Not expected to be subject to undergo long-range transport in the	3066467 3066521

Property	Result		Comment	Reference
	Ethanol	Ethylene		PMRA#
Atmospheric reaction half-life with photochemically-produced hydroxyl radicals	5 d	15 h	atmosphere	3066506 3066467 3066499
Atmospheric reaction with ozone half-life	40-45% relative to ethylene	6.5 d		3066499 3066457

Table 3 Acute toxicity to non-target organisms

Species	Result (mg/L)	Degree of toxicity[a]	Reference (PMRA#)
Ethanol			
Rainbow trout	96-h LC_{50}: 11200 - 13000	Practically non-toxic	3066457
Daphnia magna	48-h EC_{50}: 5012-12340	Practically non-toxic	3066457
Duckweed, *Lemna gibba*	7-d EC_{50}: 4432	N/A	3066457
Selenastrum capricornutum	96-h EC_{50}: 10000	N/A	3066457
Ethylene			
Daphnia magna	48-h EC_{50}: 53 -153	Slightly toxic	2604633
Rainbow trout	96-h LC_{50}: 55	Slightly toxic	2604633
Bluegill sunfish	96-h LC_{50}: 85	Slightly toxic	2604633
Fathead minnow	96-h LC_{50}: 116 – 120	Practically non-toxic	2604633
Channel catfish	96-h LC_{50}: 50	Slightly toxic	2604633
Selenastrum capricornutum	72-h EC_{50}: 72	N/A	2604633

[a] USEPA classification, where applicable; N/A, not applicable

References

A. List of studies/information submitted by registrant

1.0 Chemistry

PMRA document number	Reference
3066450	2019, DACO 2 - Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient (TGAI) on an Integrated System Product (ISP), DACO: 2.0, 2.1, 2.11, 2.11.1, 2.11.2, 2.11.3 ,2.11.4, 2.12, 2.12.1, 2.13, 2.13.1, 2.13.2, 2.13.3, 2.13.4, 2.14, 2.14.1, 2.14.10, 2.14.11, 2.14.12, 2.14.13, 2.14.14, 2.14.15, 2.14.16, 2.14.2, 2.14.3, 2.14.4, 2.14.5, 2.14.6, 2.14.7, 2.14.8, 2.14.9, 2.15, 2.16, 2.2, 2.3, 2.3.1, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 830.7000
3066458	2019, Certificate of Origin, Denatured alcohol grade DA-2I products, DACO: 2.11.2
3066461	2018, Product Specification, Denatured Ethyl Alcohol DA-2I Anhydrous, DACO: 2.12,2.12.1
3066463	2018, Residual Solvents and Organic Volatile Impurities Statement, DACO: 2.11.4,2.13.4,2.15
3200519	2005 Validation of a [CBI removed] Method for the Quantitative Analysis of Active Ingredient and Impurity Content in Ethylene Gas and 5-Batch Analysis of Ethylene in Nitrogen Samples for Active Ingredient and Impurity Content CBI
3066527	2017, Restrain Generator 740, Five Batch Analysis of the Impurity [CBI removed] in Catalytic Produced Ethene, DACO: 4.8
3066528	2017, Restrain Generator 740, Five Batch Analysis of the Impurity [CBI Removed] in Catalytic Produced Ethene, DACO: 4.8

2.0 Human and animal health

PMRA document number	Reference
3066451	2019, DACO 4 - Toxicology, DACO: 4.1,4.2,4.2.1,4.2.2,4.2.3,4.2.4,4.2.5,4.2.6,4.2.9,4.3,4.3.1,4.3.2,4.3.4,4.3.6,4.3.8, 4.5,4.5.2,4.5.4,4.5.5,4.8
3066452	2019, DACO 6 - Metabolism/Toxicokinetic Studies, DACO: 6.1,6.2,6.3,6.4
3066467	2019, HSDB: Ethanol, CASRN: 64-17-5, DACO: 4.1, 4.2, 4.2.1, 4.2.3, 4.2.4, 4.3.6, 4.5.2, 4.5.4, 4.5.5

PMRA document number	Reference
3066468	2003, Neuromotor Effects of Acute Ethanol Inhalation Exposure in Humans: A Preliminary Study, DACO: 4.2.3
3066469	2016, Alcohol Vapor Inhalation as a Model of Alcohol-Induced Organ Disease, DACO: 4.2.1,4.2.3
3066470	2008, Safety evaluation of topical applications of ethanol on the skin and inside the oral cavity, DACO: 4.2.2,4.2.5,4.2.6
3066471	2001, Fate of ethanol topically applied to skin, DACO: 4.2.2
3066472	1977, Induction of Human Skin Sensitization to Ethanol, DACO: 4.2.6
3066473	1982, Evaluation of the Ocular-Irritation Potential of 56 Compounds, DACO: 4.2.4
3066474	2013, Analysis of Ethanol Effects on Corneal Epithelium, DACO: 4.2.4
3066475	1968, No chemical evidence of hepatic liquid peroxidation in acute ethanol toxicity, DACO: 4.2.1
3066476	1981, Prenatal ethanol exposure permanently reduces the number of pyramidal neurons in rat hippocampus, DACO: 4.5.2
3066477	2016, Prenatal ethanol exposure impairs temporal ordering behaviours in young adult rats, DACO: 4.5.2
3066478	2018, Long-Term Reductions in the Population of Gabaergic Interneurons in the Mouse Hippocampus Following Developmental Ethanol Exposure, DACO: 4.5.2
3066479	2015, Third Trimester-Equivalent Ethanol Exposure Increases Anxiety-like Behavior and Glutamatergic Transmission in the Basolateral Amygdala, DACO: 4.5.2
3066480	2001, Is ethanol genotoxic? A review of the published data, DACO: 4.5.4,4.5.5
3066481	2010, The in vitro genotoxicity of ethanol and acetaldehyde, DACO: 4.5.4,4.5.5
3066493	2019, DACO 4 - Toxicology, DACO: 4.1, 4.6, 4.6.1, 4.6.2, 4.6.3, 4.6.4, 4.6.5, 4.6.6, 4.6.8, 4.7, 4.8
3066494	2019, DACO 5 - Exposure (Occupational and/or Residential/Bystander), DACO: 5.1,5.2
3066495	2019, DACO 6 - Metabolism/Toxicokinetic Studies (Nature of Residue), DACO: 6.1,6.2,6.3,6.4
3066496	2019, DACO 7 - Food Residue - Analytical Methodology, DACO: 7.1, 7.2, 7.2.1, 7.2.2, 7.3, 7.4, 7.4.1, 7.4.2, 7.4.3, 7.4.4, 7.4.5, 7.5, 7.6, 7.8
3066523	2015, Ethylene, CAS Registry Number: 74-85-1, DACO: 4.1,4.7,4.8

PMRA document number	Reference
3066524	2014, Registration Report, Part A, Risk Management (National Assessment), DACO: 4.1,4.6,4.8,7.2.1
3066525	2014, Registration Report, Part B, Section 3: Mammalian Toxicology (Core Assessment), DACO: 4.7
3066526	2001, Priority Substances List Assessment Report, Ethylene Oxide, DACO: 4.8
3066531	2019, PMRA List of Formulants, Single Substance, DACO: 5.1,5.2
3066533	2012, Product Risk Profile, Ethylene, DACO: 5.1,5.2
3066534	2019, Registration Report, Part B, Section 4: Metabolism and Residues (Core Assessment), DACO: 5.1, 5.2, 6.1, 6.2, 6.3, 7.4, 7.4.1, 7.4.2, 7.4.3, 7.4.4, 7.4.5, 7.5, 7.8

3.0 Environment

PMRA document number	Reference
2604633	DACO: 11.1
2952297	DACO: 2.14.10,2.14.12,2.14.13,2.14.8,2.7
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3066454	2019, DACO 9 - Environmental Toxicology/Non-Target Organism Testing, DACO: 9.1, 9.2, 9.2.4, 9.3, 9.3.2, 9.4, 9.4.2, 9.5, 9.5.2.1, 9.5.2.2, 9.5.2.3, 9.5.2.4, 9.5.4, 9.6, 9.8, 9.8.2
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B. Additional Information Considered

i) Published Information

Environment

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