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Proposed Registration Decision

PRD2019-05

1-Octanol and 1,4Zap

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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 1-Octanol

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 1,4Zap Technical, and 1,4Zap, containing the technical grade active ingredient 1-octanol, for post-harvest application on stored potatoes to control emerged sprouts in ventilated storage facilities only.

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 1-octanol and 1,4Zap.

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 acceptable¹ 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 *Pest Control Products Act* also requires that products have value² 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 Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides section of the Canada.ca website at Canada.ca/pesticides.

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 1-octanol and 1,4Zap, 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 Decision⁴ on 1-octanol and 1,4Zap, 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 1-Octanol?

1-octanol is a fatty alcohol compound, which, when applied to potato tubers in storage, controls sprouting, thereby improving tuber longevity and maintaining tuber quality.

Health Considerations

Can Approved Uses of 1-Octanol Affect Human Health?

1,4Zap Technical, containing 1-octanol, is unlikely to affect human health when it is used according to label directions.

Potential exposure to 1-octanol may occur through the diet or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide-containing products are used according to label directions.

In laboratory animals, 1-octanol was of low acute toxicity via the oral, dermal or inhalation routes. It was moderately irritating to the eyes and skin. 1-Octanol is not considered to be a skin sensitizer.

The toxicology profile for 1,4Zap is low acute toxicity via the oral, dermal or inhalations routes, moderately irritating to the eyes and skin and not a predicted dermal sensitizer.

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

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

Information for animal toxicity tests, as well as supplemental data and published scientific literature, were assessed for the potential of 1-octanol to cause short-term toxicity, developmental effects, genotoxicity, and various other effects. Adverse effects in animals given repeated high doses resulted in effects on organs (skin, adrenal) and reduced body weights. There was no indication that the young were more sensitive than the adult animal. There was no evidence that octanol induced mutagenic or genotoxic effects. The risk assessment protects against the finding noted above as well as any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are acceptable.

Dietary exposure to 1-octanol may occur through consumption of treated potatoes; however, given its low toxicity, volatility and natural occurrence in a variety of fruits, vegetables and meats, health risks 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.

There are no residential uses for 1,4Zap, as the product will be applied to potatoes stored in commercial storage facilities. Therefore, risk due to residential and bystander exposure is acceptable.

Occupational Risks From Handling 1,4Zap

Occupational risks are acceptable when 1,4Zap is used according to the label directions, which include protective measures.

During loading and handling, individuals can come in direct contact with 1-octanol by skin or eye contact. For this reason, the label states that handlers and loaders must wear coveralls over long-sleeved shirt, long pants, chemical-resistant gloves, socks and chemical-resistant footwear, and protective eyewear.

Due to the closed and automated nature of the application system, no applicator exposure is expected. Occupational bystander exposure to 1-octanol is also not expected to occur due to the nature of the application. Precautionary and hygiene statements on the label are considered adequate to protect individuals from occupational exposure.

Re-entry activities that take place before the ventilation period is complete are considered to potentially represent a high exposure scenario and the primary routes of exposure would be ocular, inhalation and dermal. Precautionary statements (for example, wearing of personal protective equipment (PPE)), 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

An environmental assessment was not required for the application to register the end-use product as minimal environmental exposure is expected with this use pattern. Therefore, risks to the environment are not expected.

Value Considerations

What Is the Value of 1,4Zap?

1,4Zap is used to manage sprouting in potatoes.

Sprouting of potatoes in storage occurs when dormancy is lost. It occurs earlier in varieties with relatively low dormancy and/or in unrefrigerated or partially refrigerated conditions. Sprouted potatoes are less firm, bruise more easily, are lower in quality and therefore are less marketable as table stock or less desirable for processing.

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 1,4Zap Technical and 1,4Zap to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

The signal words “WARNING – EYE and SKIN IRRITANT” are required on the principal display panels of the labels for both 1,4Zap Technical and 1,4Zap. Standard hazard and precautionary statements are also required on the end-use product labels to inform workers of the irritation potential of the active ingredient to the skin and eyes. Workers handling and loading 1,4Zap will be required to wear standard personal protective equipment including coveralls over long-sleeved shirt, long pants, chemical-resistant gloves, socks and chemical-resistant footwear, and protective eyewear.

A restricted-entry interval (REI) is included on the label for 1,4Zap which specifies that workers are not allowed to enter into the treated area until complete ventilation of the storage facility has occurred with aerosol particles visibly 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, long pants, chemical-resistant gloves, socks and chemical-resistant footwear, goggles, 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.

Next Steps

Before making a final registration decision on 1-octanol and 1,4Zap, 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 1-octanol and 1,4Zap (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

1-Octanol and 1,4Zap

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	1-Octanol
Function	Plant growth regulator
Chemical name	<i>n</i> -Octanol
1. International Union of Pure and Applied Chemistry (IUPAC)	Octan-1-ol
2. Chemical Abstracts Service (CAS)	1-Octanol
CAS number	111-87-5
Molecular formula	C ₈ H ₁₈ O
Molecular weight	130.23
Structural formula	
Purity of the active ingredient	99.0

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

Technical Product—1,4Zap Technical

Property	Result
Colour and physical state	Colourless liquid
Odour	Sweet, orange-rose
Melting range	-17 to -16°C
Boiling point or range	194 to 195°C
Density at 20°C	0.827 g/mL
Vapour pressure at 20°C	10.6 Pa
Ultraviolet (UV)-visible spectrum	No absorption above $\lambda \geq 300$ nm is expected
Solubility in water at 20°C	Insoluble

Solubility in organic solvents	Miscible with ethanol and ethyl ether, soluble in carbon tetrachloride
<i>n</i> -Octanol-water partition coefficient (K_{ow})	Log K_{ow} = 3.0
Dissociation constant (pK_a)	Estimated to be ~ 20 based on the pK_a of other alcohols
Stability (temperature, metal)	Not expected to be susceptible to direct photolysis by sunlight.

End-Use Product—1,4Zap

Property	Result
Colour	Colourless
Odour	Sweet, orange-rose
Physical state	Liquid
Formulation type	Liquid (LI)
Label concentration	99.0%
Container material and description	4–113.5 L plastic bottles, jugs and totes
Density at 20°C	0.827 g/mL
pH of 1% dispersion in water	5.9
Oxidizing or reducing action	This product is not expected to have any oxidizing or reducing action
Storage stability	The product was shown to be stable when stored in HDPE containers at ambient temperature over 1 year.
Corrosion characteristics	Corrosion to HDPE containers was not observed when the product was stored in the containers for 1 year at ambient temperature.
Explosibility	Above 76°C, explosive vapour/air mixtures may be formed

1.3 Directions for Use

1,4Zap is applied to potatoes in enclosed storage facilities by means of thermal aerosol generating equipment at a rate of 0.91 to 2.27 kg product/22680 kg potatoes, equivalent to a 1-octanol concentration of 40–100 ppm on a tuber whole weight basis. 1,4Zap may be reapplied multiple times per season when sprouting reoccurs, up to a maximum cumulative rate of 9.1 kg product/22680 kg potatoes per storage season.

1.4 Mode of Action

The mode of action of 1-octanol is not well understood; however, the 1-octanol vapour acts to desiccate meristematic growth on tubers, including buds (“peeps”) and sprouts thereby causing them to eventually fall off the tubers.

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

2.3 Methods for Residue Analysis

No methods are required to quantify residues of 1-octanol 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 1-octanol was conducted. The registrant submitted acute toxicity studies, prenatal developmental toxicity studies, subchronic toxicity studies, and genotoxicity studies. 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, published clinical trials and available scientific literature were used to supplement the assessment.

Acute studies on 1-octanol found it to be of low toxicity via the oral, dermal and inhalation routes of exposure. 1-Octanol was moderately irritating to the eyes and skin and not a predicted skin sensitizer.

In a short-term (90-day) dermal rat study male and female Sprague-Dawley rats were exposed to a fatty acid blend containing 43% octanol for 13 weeks. Two animal deaths were determined to be unrelated to the study. Dermal symptoms included erythema, edema, desquamation, eschar formation and exfoliation and fissuring (all treated groups). Body weight decreased and adrenal weights increased with higher doses. Some animals receiving the highest dose (1000 mg/kg) displayed vocalization and hypersensitivity to touch. The systemic no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) were set at 300 mg/kg/day fatty acid blend and 1000 mg/kg/day fatty acid blend, respectively, based on the changes in hematology and clinical chemistry parameters as well as decreased body weight. The dermal LOAEL, based on severe irritation, was set at 100 mg/kg of the fatty acid blend. A dermal irritation NOAEL was not established.

In a developmental toxicity study, female Sprague-Dawley rats were orally dosed with a fatty alcohol blend containing 40.7% octanol from gestation day 6 to 16. There were no signs of developmental toxicity and the only clinical sign of maternal toxicity was excess salivation in the highest dosed dams, resulting in a LOAEL of 1000 mg/kg/day of fatty acid blend and a maternal NOAEL of 375 mg/kg/day for the fatty acid blend. A second developmental toxicity study exposed pregnant Sprague-Dawley rats to 1-octanol at a dose of 400 mg/m³ by inhalation for 7 hours per day on gestation days 1–19. The administered dose was the highest dose obtainable due to the volatility of the chemical. There was no evidence of maternal or developmental toxicity, therefore the maternal and developmental NOAELs were 400 mg/m³ for 1-octanol. The final developmental toxicity study gavaged pregnant Wistar rats with n-octanol on gestation days 6–15. Maternal toxicity increased with the dose and clinical signs of toxicity included non-typical lateral and abdominal position, unsteady gait, salivation, piloerection, nasal discharge and pneumonia and incidences of mortality reported at 650 and 1300 mg/kg. The maternal NOAEL was < 130 mg/kg bw/day and the LOAEL was 650 mg/kg bw/day based on mortality. There were no signs of developmental toxicity.

Octanol screened for genotoxicity with and without S9 activation was found to be inactive in both the *Salmonella* mutagenesis (at 2000 µg/plate) and the L5178Y mouse lymphoma (100 µg) assays. A fatty acid blend (40.7% octanol) was screened with and without S9 activation and found to be inactive in *Salmonella* mutagenesis and the L5178Y mouse lymphoma assays. There was no evidence of in vitro genotoxic activity. In a mammalian erythrocyte micronucleus test, mice were dosed by gavage with a fatty alcohol blend (41% octanol) in corn oil once a day for 3 days. There was no resulting animal mortality or signs of cytotoxicity in bone marrow cells, but animals (both sexes) at all doses showed piloerection. Harvested bone marrow cells did not have increased numbers of micronucleated erythrocytes compared to positive control. The highest dose tested was 2000 mg/kg/day. There were no signs of genotoxic effects.

Additional evidence supporting a history of human exposure to 1-octanol was submitted and considered under the scope of this review. Provided information cited 1-octanol as being present in a number of foods and the environment. Studies reported 1-octanol in apricots, peaches, and pears, and as a volatile released from fried bacon, and identified octanol in cooked meat and raw and boiled potatoes. Octanol has a history of use as: an ingredients in perfumes, cosmetics, solvents (industrial and agricultural), and antifoaming agents; as a food additive, food enhancer or flavouring agent; and as an active ingredient in pesticides (tobacco and recently as a sprout inhibitor on potatoes in the United States). Furthermore, 1-octanol can be released into the environment due to the breakdown of foods and plants and as a waste by-product of industry.

There are no data requirements for chronic toxicity, immunotoxicity, or carcinogenicity studies. There is no evidence of carcinogenic potential for 1-octanol in the available published literature. The results of the subchronic toxicity studies and the genotoxicity/mutagenicity studies did not indicate that 1-octanol has carcinogenic potential.

The end-use product has the same toxicity profile as 1,4Zap Technical (1-octanol).

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

Incident Reports

As of 20 September 2018, no human or domestic animal incident reports involving 1-octanol have been submitted to the PMRA.

3.2 Occupational, Residential and Bystander Exposure and Risk Assessment

3.2.1 Dermal Absorption

Although the log K_{ow} of 3.0 suggests the potential for moderate to high absorption; however, due to the high volatility and low toxicity by the dermal route, dermal absorption of 1-octanol is not expected to be of concern.

3.2.2 Use Description

1,4Zap is a commercial end-use product that is applied post-harvest in stored potatoes to inhibit sprouting and encourage dormancy. The end-use product does not require mixing or agitation and is either pumped directly into a thermo-fogger from the product chemical container or poured into a stainless steel tank and then pumped directly from the tank into the fogger. Using thermal aerosol generating equipment (thermal fogger), the liquid is heated and the aerosol is pumped into the ventilation system of a storage area. During application of the product, recirculation fans should be on for at least 1 and up to 24 hours after application of product. The storage area should be closed as long as practical to allow for maximum absorption of the product into the potatoes. Re-entry activities are restricted until after complete ventilation has occurred with aerosol particles visibly settled. Visual inspection of the produce 48–72 hours after application followed by a second inspection of potatoes seven to ten days later is recommended by the manufacturer.

1,4Zap can be applied at the rate of 0.91 to 2.27 kg 1,4Zap per 22680 kg of potato which is equivalent to 40–100 ppm. Lower rates of application can be used on small sprouts, higher rates on larger sprouts and the maximum rate for heavily sprouted potatoes. Reapplication is permissible as necessary with a maximum application of 400 ppm per storage lot per storage season. 1,4Zap is not for seed potatoes.

Workers can be exposed to 1-octanol when handling and loading 1,4Zap into the thermal fogging equipment, or when re-entering a treated area before the ventilation period is complete.

3.2.3 Mixer, Loader, and Applicator Exposure and Risk

Workers can be exposed to 1,4Zap when manually loading (pouring or pumping) the liquid into the fogger or collection tank. There are no mixing activities.

Although the dermal and inhalation toxicity of 1,4Zap is low, the liquid is moderately irritating to the eyes and skin. Therefore, workers are required to wear coveralls over long-sleeved shirt, long pants, chemical-resistant gloves, socks and chemical-resistant footwear, and protective eyewear during all handling and loading activities.

Applicators/workers remain outside the enclosed storage area during the automated fogging application and until the aerosol has settled. Due to the aerosol being pumped into the ventilation system from outside of the building, no exposure to applicators is expected. Also, no cleaning of equipment is required after application of the liquid because of the volatile nature of the end-use product.

Precautionary statements such as the wearing of PPE on the end-use product label aimed at mitigating exposure are considered adequate to protect individuals from any risk due to occupational exposure. Overall, occupational risks for handlers, loaders and applicators are acceptable when label directions are followed which include PPE.

3.2.4 Postapplication Exposure and Risk

There is a potential for postapplication exposure to workers by the dermal, inhalation and ocular routes upon entry into the storage areas that have been treated with 1,4Zap for maintenance activities and for visually inspecting potatoes for the effectiveness of the application.

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, inhalation and ocular 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, respiratory and ocular irritation from vapour exposure. Therefore, workers entering before the end of the ventilation period are required to wear coveralls over a long sleeved shirt and long pants, socks and chemical-resistant footwear, chemical-resistant gloves, goggles, 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 PPE) statements on the end-use product label aimed at mitigating exposure are considered adequate to protect individuals from risk due to postapplication exposure.

3.2.5 Residential and Bystander Exposure and Risk

There are no residential uses of 1,4Zap.

Overall, the PMRA does not expect that residential and bystander exposure will pose a health risk concern on the basis that the end-use product will be applied through the ventilation of commercial storage facilities for potatoes where bystanders are not expected to be present. The storage facilities are to be closed and sealed from all entry during application. Consequently, the health risk to infants and children is acceptable.

3.3 Food Residue Exposure Assessment

3.3.1 Food

While dietary exposure to 1-octanol may occur through consumption of treated potatoes, available toxicology data indicate that 1-octanol is of low acute oral toxicity, unlikely to be toxic via repeated oral exposure, and is not a developmental toxicant or a mutagenic substance. It is naturally present in a variety of regularly consumed fruits, vegetables and meats. Additionally, 1-octanol is a volatile chemical and breaks down rapidly to non-toxic constituents, and therefore it is expected that any remaining residues will further decrease in potato tissue as a result of washing, peeling, and cooking practices.

Considering all available information, no health risks of concern are anticipated from the presence of residues of 1-octanol on food.

3.3.2 Drinking Water

As the end-use product is proposed for indoor, post-harvest use on stored potatoes, 1,4Zap will not come into contact with surface or groundwater. Exposure to 1-octanol in drinking water is expected to be minimal. The label has necessary mitigative measures to prevent contamination of drinking water from the proposed use of 1-octanol. In addition, toxicity to 1-octanol is low. Consequently, no risk due to exposure from drinking water is expected.

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 1-octanol. Based on all the available information and hazard data, this active ingredient is considered to be of low toxicity. Thus, there are no threshold effects of concern. As a result, there is no need to apply uncertainty factors to account for intra- and interspecies variability, or have a margin of exposure required. Further factoring of consumption patterns among infants and children, special susceptibility in these subpopulations to the effects of 1-octanol 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 1-octanol to human health.

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 1-octanol 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 and all other non-occupational exposures (dermal and inhalation) for which there is reliable information.

3.3.5 Cumulative Exposure and Risk

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with a common mechanism of toxicity. Accordingly, a cumulative health assessment was undertaken. While 1-octanol, a C8 straight chain (aliphatic) alcohol may share a common moiety with other registered aliphatic alcohols, the potential health risk from cumulative exposure to aliphatic alcohol-based pest control products is acceptable given that 1-octanol has a low toxicity profile. In addition, 1-octanol is a volatile chemical and breaks down rapidly to non-toxic constituents resulting in minimal dietary risk.

3.3.6 Maximum Residue Limits (MRLs)

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.

Dietary risk to humans from the proposed post-harvest use of 1-octanol on stored potatoes is not of concern because of the low toxicity profile of the active ingredient and the fact that it is a volatile chemical. Therefore, the specification of an MRL, under the *Pest Control Products Act*, will not be required for 1-octanol.

4.0 Impact on the Environment

An environmental assessment was not required for the application to register the end-use product as minimal environmental exposure is expected with this use pattern. Therefore, risks to the environment are not expected.

5.0 Value

Value information was submitted in the form of data generated in efficacy studies as well as information pertaining to history of use in the United States. Results from multiple small-scale and commercial-scale studies collectively demonstrated that a 1-octanol concentration of 40–100 ppm was effective in controlling emerged sprouts, with higher 1,4Zap concentrations within this range being required for the control of longer sprouts. The data demonstrated that the degree of sprout control can be expected to be consistent throughout the potato pile in storage buildings with forced air ventilation systems in which internal air is recirculated during and following application. Documentation from the United States indicated that application of 1,4Zap at 50 ppm controlled sprouts at the peep stage of growth and that control has been observed to be consistent the majority of the time and that sprouts do not regrow for 6–8 weeks after treatment. This record of use is consistent with the submitted efficacy data.

1,4Zap is a non-conventional pest control product, which may serve as an alternative to registered conventional products for the management of sprouting in potatoes. Additionally, 1,4Zap may be acceptable for use on potatoes for export to countries that do not permit or otherwise restrict the importation of chlorpropham-treated potatoes.

1,4Zap is compatible with an integrated pest management program in that it may be used in conjunction with other pest control products that are applied prior to or after harvest to manage sprouting and diseases that may occur on potatoes during storage.

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, in other words, 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, 1,4Zap Technical and 1,4Zap were assessed in accordance with the PMRA Regulatory Directive DIR99-03⁵ and evaluated against the Track 1 criteria. 1,4Zap Technical and its end-use product 1,4Zap did not meet TSMP criteria.

6.2 Formulants and Contaminants of Health Concern

During the review process, contaminants in the technical as well as 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*.⁶ The list is used as described in the PMRA Notice of Intent NOI2005-01⁷ and is based on existing policies and regulations including Regulatory Directives DIR99-03 and DIR2006-02,⁸ and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act*, 1999 (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

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

⁶ SI/2005-114

⁷ NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*

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

- Technical grade 1,4Zap Technical and its associated end-use product 1,4Zap, do not contain 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 DIR2006-02.

7.0 Summary

7.1 Human Health and Safety

The available information for 1-octanol is adequate to qualitatively identify the toxicological hazards that may result from human exposure to 1-octanol. It is of low acute toxicity, moderately irritating to the eyes and skin, and it is not a predicted skin sensitizer. In a subchronic dermal toxicity study in the rat, a fatty acid blend containing 43% octanol caused skin irritation in all treated animals, and vocalization and hypersensitivity to touch in some of the highest dosed animals. Three developmental toxicity studies in the rat did not show signs of developmental toxicity. Available evidence suggests that 1-octanol is not mutagenic, genotoxic, or carcinogenic. The end-use product has the same toxicological profile as the technical grade active ingredient.

Workers can be exposed to 1-octanol when manually loading the liquid product into the fogging unit, and thus, are required to wear coveralls over long-sleeved shirt, long pants, chemical-resistant gloves, socks and chemical-resistant footwear, and protective eyewear 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. Postapplication exposure will occur mainly by the dermal, inhalation and ocular routes. If re-entry into treated areas is required during fogging application or prior to ventilation or settling of aerosol fog, there is a potential for dermal, respiratory and ocular 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 risk due to occupational exposure.

Residential and bystander exposure is minimal and not of concern since there are no residential uses for 1,4Zap, and the product is used in commercial potato storage facilities where bystanders are not expected to be present.

1,4Zap 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 due to its volatility and from washing, peeling and cooking practices. Dietary risk to humans from the proposed uses of 1,4Zap in food and drinking water will be acceptable when the product is used according to label instructions. Consequently, the specification of an MRL under the *Pest Control Products Act* is not being recommended.

7.2 Value

The information submitted to register 1,4Zap is adequate to demonstrate value, including efficacy, of its use to control sprouts on potato tubers in storage.

8.0 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 1,4Zap Technical and 1,4Zap, containing the technical grade active ingredient 1-octanol, for post-harvest application on stored potatoes to control emerged sprouts in ventilated storage facilities only.

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

List of Abbreviations

♀	female
λ	wavelength
μg	micrograms
ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
CAS	Chemical Abstracts Service
cm	centimetres
d	day
DACO	data code
DER	Data Evaluation Report
EP	end-use product
EPA	Environmental Protection Agency
g	gram
GLP	Good Laboratory Practice
HDPE	High density polyethylene
hr(s)	hour(s)
HSDB	Hazardous Substances Database
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{ow}	<i>n</i> -octanol-water partition coefficient
L	litre
LC ₅₀	lethal concentration 50%
LD ₅₀	lethal dose 50%
LI	liquid
LOAEL	lowest observed adverse effect level
m ³	cubic metre
mg	milligram
mL	millilitre
MAS	maximum average score
MIS	maximum irritation score
MRL	maximum residue limit
NIOSH	The National Institute for Occupation Safety and Health
nm	nanometre
NOAEL	no observed adverse effect level
Pa	Pascal
p <i>K</i> _a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
REI	restricted entry interval
TSMP	Toxic Substances Management Policy
US	United States

USEPA	United States Environmental Protection Agency
UV	ultraviolet
WHO	World Health Organization

Appendix I Tables and Figures

Table 1 Toxicity Profile of 1-octanol (Technical Grade Active Ingredient and End-Use Product)

(Effects are known or assumed to occur in both sexes unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Rat, Sprague-Dawley, ♀ PMRA # 2801786	LD ₅₀ > 5000 mg/kg bw Low toxicity
Acute dermal toxicity Rat, Sprague-Dawley PMRA # 2801787	LD ₅₀ > 5000 mg/kg bw Low toxicity
Acute inhalation toxicity Rat, Sprague-Dawley PMRA # 2801788	LC ₅₀ > 5.10 mg/L Low toxicity
Eye irritation Rabbit, New Zealand albino, ♀ PMRA # 2801789	MAS ^a = 28.12/110 MIS ^b = 33.34/110 (1 hr) Moderately irritating
Dermal irritation Rabbit, New Zealand albino, ♀ PMRA # 2801790	MAS = 4.56/8 MIS = 4.67/8 (48 hr) Moderately irritating
Dermal sensitization (Local Lymph Node Assay) Mouse, CBA/J, ♀ PMRA # 2801791, 2798939	Positive (Q)SAR results: Predicted non-sensitizer
Short-term oral toxicity Waiver rationale PMRA # 2718710, 2850873, 2850886	Based on a published developmental oral toxicity study (Maternal LOEL 650 mg/kg bw/d based on mortality and NOAEL was < 130 mg/kg bw/d), and due to the fact that 1-octanol is ubiquitous in food and the environment and that it has been registered by the EPA for post-harvest application to stored potatoes, waivers were requested and granted.

Short-term dermal toxicity Waiver rationale Rat, Sprague-Dawley PMRA # 2718710, 2850873	Supplemental short-term dermal study (LOAEL 43 mg/kg bw/d and NOAEL not established) was submitted and accepted.
Short-term inhalation toxicity (90 days) Waiver rationale PMRA # 2718710, 2718711, 2850873, 2850885	Based on a published developmental inhalation toxicity study (Maternal NOAEL 400 mg/ m ³ /d), the fact that 1-octanol is ubiquitous in crops and the environment and due to the fact that the end-use product will be applied through the ventilation system and re-entry will be restricted until the vapour has settled limiting inhalation exposure, waivers were requested and were granted.
Prenatal developmental toxicity Waiver rationale PMRA # 2718710, 2718711, 2850873, 2850886, 2850885	No signs of fetal toxicity in three developmental studies. 1)The maternal NOAEL was < 130 mg/kg bw/day and the LOAEL was 650 mg/kg bw/day was based on mortality (gavage). 2)Maternal NOAEL was 400 mg/m ³ (inhalation). 3)Maternal NOAEL was 153 mg/kg/day and LOAEL was 407 mg/kg/day (oral).
Gene mutations in bacteria Waiver rationale PMRA # 2718710, 2850873, 2891885	Negative for gene mutations in <i>Salmonella</i> assays.
Gene mutations in mammalian cells (in vitro) Waiver rationale PMRA # 2718710, 2850873, 2891885	Negative for gene mutations in mouse lymphoma assays.
Erythrocyte micronucleus test (in vivo) Waiver rationale PMRA # 2718710, 2850873	No genotoxic response in mammalian erythrocyte micronucleus test.

^a MAS = Maximum Average Score for 24, 48, and 72 hrs

^b MIS = Maximum Irritation Score (average)

References

A. List of Studies/Information Submitted by Registrant

PMRA Document Number	References
1.0 Chemistry	
2718706	2013, Product Chemistry for 1,4Zap(R) Technical, DACO: 2.11.1,2.11.2,2.11.3,2.11.4,2.12.1,2.13.1,2.13.2,2.13.3,2.13.4,2.14.1,2.14.12,2.14.13,2.14.14,2.14.15,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.7,2.14.8,2.14.9,2.4,2.5,2.6,2.7,2.8,2.9,830.7000 CBI
2718707	2014, Supplemental Product Chemistry for 1,4Zap Technical, DACO: 2.13.1,2.14.11,2.3.1 CBI
2815495	2017, Detailed Production Process Description, DACO: 2.11.3 CBI
2745000	2015, Characterization of 1,4ZAP(R) Lot Number 1844171, DACO: 2.13.2 CBI
2745001	2017, 1,ZAP(R): Determination of Acid Value, DACO: 2.13.3 CBI
2815496	2014, Specifications, DACO: 2.12 CBI
2815497	2014, Specifications, DACO: 2.12 CBI
2815498	2014, Specifications, DACO: 2.12 CBI
2815499	2014, Specifications, DACO: 2.12 CBI
2815500	2014, Specifications, DACO: 2.12 CBI
2814921	2016, Corrosion Characteristics, DACO: 3.5.10,3.5.14 CBI
2814920	2015, Enforcement Analytical Method, DACO: 3.4.1 CBI
2.0 Human and Animal Health	
2718708	2015, Octanol/Water Partition Coefficient, DACO: 2.14.11 CBI
2718710	2013, Response to Tier 1 Biochemical Pesticide Data Requirements for 1,4Zap Technical, DACO: 4.2.1,4.2.2,4.2.3,4.2.4,4.2.5,4.2.6,4.3.1,4.3.2,4.3.6,4.5.2,4.5.4,4.5.5,4.5.6,9.2.7,9.3.2,9.5.2.3,9.6.2.3,9.6.2.6,9.8.6
2718711	2014, Supplemental Response to Tier 1 Biochemical Pesticide Data Requirements for 1,4Zap, DACO: 4.2.6,4.3.1,4.3.4,4.5.2
2718712	2013, Petition for an exemption from the requirement of a tolerance for residues of products containing the active ingredient "1- octanol" in and on all post-harvest food commodities, DACO: 7.8
2719428	2017, Use Description, DACO: 5.2
2801786	2012, 1,4PEEP Acute Oral Toxicity Up and Down Procurement in Rats, DACO: 4.2.1
2801787	2012, 1,4PEEP Acute Dermal Toxicity Study in Rats - Limit test, DACO: 4.2.2
2801788	2013, 1,4PEEP Acute Inhalation Toxicity Study in Rats, DACO: 4.2.3
2801789	2012, 1,4PEEP Primary Eye Irritation Study in Rabbits, DACO: 4.2.4
2801790	2012, 1,4PEEP Primary Skin Irritation Study in Rabbits, DACO: 4.2.5
2801791	2013, 1,4PEEP Local Lymph Node Assay (LLNA) in Mice, DACO: 4.2.6

- 2850873 2018, Waiver Rationale, DACO: 4.3.4,4.5.2,4.5.4,4.5.5,4.5.6
- 2850874 Burdock, G.A., 2010, Fenaroli's Handbook of Flavor Ingredients, Sixth Edition, DACO: 4.3.4,4.5.2,4.5.4,4.5.5,4.5.6
- 2850875 Ho, C. T., Lee, K.N., and Jin, Q.Z., 1986, Isolation and Identification of Volatile Flavor Compounds in Fried Bacon, Journal of Agriculture and Food Chemistry 31:336-342, DACO: 4.3.4,4.5.2,4.5.4,4.5.5,4.5.6
- 2850876 Shahidi, F., Rubin, L.J. and D'Souza, A., 1986, Meat Flavor Volatiles: A Review of the Composition, Techniques of Analysis, and Sensory Evaluation, CRC Critical Reviews of Food Science 24(2):141-243, DACO: 4.3.4,4.5.2,4.5.4,4.5.5,4.5.6
- 2850878 Dresow, J.F. and Bohm, H., 2009, The influence of volatile compounds of the flavor of raw, boiled, and baked potatoes, VTI Agriculture and Forestry Research, 4:309-338, DACO: 4.3.4,4.5.2,4.5.4,4.5.5,4.5.6
- 2850879 US FDA, 2018, Code of Regulations Synthetic Flavoring Substances and adjuvant, Volume 21, Section 172.515, DACO: 4.3.4,4.5.2,4.5.4,4.5.5,4.5.6
- 2850881 World Health Organization (WHO), 1999, Technical Report Series 884, Evaluation of Certain Food Additives and Contaminants, DACO: 4.3.4,4.5.2,4.5.4,4.5.5,4.5.6
- 2850882 World Health Organization (WHO), 1998, International Programme on Chemical Safety, Safety Evaluation of Certain Food Additives and Contaminants. WHO Food Additive Series 40, DACO: 4.3.4,4.5.2,4.5.4,4.5.5,4.5.6
- 2850885 Nelson, B., Brightwell, W., Khan, A., and Hoberman, A., 1990, Developmental Toxicity Assessment of 1-Octanol, 1-Nonanol, and 1-Decanol Administered by Inhalation to Rats, Journal of the American College of Toxicology. 9:93-97, DACO: 4.3.4,4.5.2,4.5.4,4.5.5,4.5.6
- 2850886 Hellwig, J. and Jackh, R., 1997, Differential Prenatal Toxicity of One Straight Chain and Five Branched-Chain Primary Alcohols, Food and Chemical Toxicology 35:489-500, DACO: 4.3.4,4.5.2,4.5.4,4.5.5,4.5.6
- 2850889 ClinicalTrials.gov, 2015, Treatment Efficacy of 1-Octanol Compared to Placebo in Adults with Essential Tremor, DACO: 4.3.4,4.5.2,4.5.4,4.5.5,4.5.6
- 2850890 Nahab, F.B., Wittevrongel, L, Ippolito, D., Toro, C., Grimes, G.J., Starling, J., Poti, G., Haubenberger, D., Bowen, D., Buchwalk, P., Dong, C., Kalowitz, D., Hallet, M., 2011, An Open-Label, Single Dose, Crossover Study of the Pharmacokinetics and Metabolism of Two oral Formulations of 1-Octanol in Patients with Essential Tremor, Neurotherapeutics 8:753-762, DACO: 4.3.4,4.5.2,4.5.4,4.5.5,4.5.6
- 2850891 Haubenberger, D., Nahab, F.B., Voller, G., and Hallett, M., 2014, Treatment of Essential Tremor with Long-Chain Alcohols: Still Experimental or Ready for Prime Time?, Tremor and Other Hyperkinetic Movements 4:1-9, DACO: 4.3.4,4.5.2,4.5.4,4.5.5,4.5.6
- 2891880 Riu-Aumatell, M., Lopez-Tamames, E., and Buxaderas, S., 2005, Assessment of the Volatile Composition of Juices of Apricot, Peach, and Pear, Journal of Agricultural and Food Chemistry 53:7837-7843, DACO: 4.2.1,4.2.2,4.2.3,4.2.4,4.2.5,4.2.6,4.3.4,4.5.2
- 2891885 Heck, J., Vollmuth, T., Cifone, M., Jagannath, D.R., Myhr, B, and Curren, R.D., 1989, An Evaluation of Food Flavoring Ingredients in a Genetic Toxicity Screening Battery, Toxicologist. 9:257, DACO: 4.5.4

- 2923331 Narotsky, M.G., Francis, E.A. and Kavlock, R.J., 1994, Developmental Toxicity and Structure-Activity Relationships of Aliphatic Acids, Including Dose-Response Assessment of Valproic Acid in Mice and Rats, *Fundamental and Applied Toxicology*. 22:251-265., DACO: 7.8
- 2923333 Voller, B., Lines, E., McCrossin, G., Tinaz, S., Lungu, C., Grimes, G., Starling, J., Potti, G., Buchwald, P., Haubenberger, D. and Hallett, M., 2016, Dose-escalation study of octanoic acid in patients with essential tremor, *The Journal of Clinical Investigation*. 126(4):1451-1457, DACO: 7.8

3.0 Value

- 2719430 2014, Evaluation of 1,4PEEP & 1,4ZAP 10 & 14 Days after Treatment, DACO: 10.2.3
- 2719431 2017, Use History Table, DACO: 10.2.4
- 2719433 2016, Use History Table, DACO: 10.2.4
- 2814097 2015, Optimization of the Application of 1,4ZAP to Stored Potatoes, DACO: 10.2.3.3
- 2825708 2015, Optimization of the Application of 1,4ZAPTM to Stored Potatoes, DACO: 10.2,10.2.3.3

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

- 2935372 Centre for Disease Control and Prevention (CDC) NIOSH, 2018, International Chemical Safety Card for 1-Octanol, DACO: 12.5
- 2935376 Deutsche Forschungsgemeinschaft, 2012, Documentations and Methods, 1-Octanol [MAK Value Documentation, 2003], DACO: 4.2.6
- 2935380 vanThriel, C., Kiesswetter, E., Blaszkewicz, M. Golka, K., Seeber, A., 2003, *Scandinavian Journal of Work and Environmental Health*, Neurobehavioral Effects During Experimental Exposure to 1-Octanol and Isopropanol, DACO: 4.2.3
- 2935381 Seeber, A., vanThriel, C, Haumann, K., Kiesswetter, E., Blaszkewicz, M., and Golka, K., 2002, *International Archive of Occupational and Environmental Health*, Psychological Reactions Related to Chemosensory Irritation, DACO: 4.2.3