Proposed Registration Decision PRD2020-12

Racemic camphor, eucalyptus oil, l-menthol and thymol and Api Life VAR

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Overview

Proposed Registration Decision for Racemic Camphor, Eucalyptus Oil, *l*-Menthol and Thymol

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 Api Life VAR Technical and Api Life VAR, containing the technical grade active ingredients racemic camphor, eucalyptus oil, *l*-menthol and thymol, for suppression of varroa mite in honey bee hives.

Thymol is currently registered against varroa mites on bees. For details, see Proposed Registration Decision PRD2010-18, *Thymol*, and Registration Decision RD2016-16, *Thymol*. Use in beehives is a proposed new use for eucalyptus oil. Racemic camphor and *l*-menthol are proposed new active ingredients, not currently registered in Canada.

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 racemic camphor, eucalyptus oil, *l*-menthol and thymol and Api Life VAR.

What Does Health Canada Consider When Making a Registration Decision?

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

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment.

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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."

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 racemic camphor, eucalyptus oil, *l*-menthol and thymol and Api Life VAR, 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 racemic camphor, eucalyptus oil, *l*-menthol and thymol and Api Life VAR, 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 Are Racemic Camphor, Eucalyptus Oil, *l* -Menthol and Thymol?

Racemic camphor, eucalyptus oil, *l*-menthol and thymol are essential oils. These are the active ingredients used to formulate Api Life VAR, which is used to suppress varroa mites in honey bee hives. Api Life VAR consists of tablets made of an inert matrix impregnated with racemic camphor, eucalyptus oil, *l*-menthol and thymol. Api Life VAR is applied to the brood chamber of a honey bee hive by breaking up one tablet into four pieces and placing the pieces on the top bars of the brood frames. The mode of action of racemic camphor, eucalyptus oil, *l*-menthol and thymol in killing varroa mites is not known; however, it has been observed that application of this product increases grooming behaviour in adult bees, leading to increased rates of varroa mite removal.

Health Considerations

Can Approved Uses of Thymol, Eucalyptus Oil, Racemic Camphor, and *l*-Menthol Affect Human Health?

Thymol, Eucalyptus Oil, Racemic Camphor, and *l*-Menthol are unlikely to affect human health when it is used according to label directions.

Potential exposure to thymol, eucalyptus oil, racemic camphor, and *l*-menthol may occur when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed.

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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*.

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.

Based on registrant-supplied published scientific literature and publicly available information, the technical grade active ingredient, Api Life VAR Technical, containing a mixture of thymol, eucalyptus oil, racemic camphor, and *l*-menthol, is slightly acutely toxic via the oral route, corrosive to the eyes, extremely irritating to the skin, and is a dermal sensitizer. The end-use product, Api Life VAR, is also considered to be of slight acute oral toxicity, corrosive to the eyes, extremely irritating to the skin, and a dermal sensitizer.

Requests to waive acute oral, dermal, and inhalation toxicity, skin and eye irritation, and dermal sensitization testing for Api Life VAR were accepted in lieu of actual test data. Thymol, eucalyptus oil, racemic camphor, and *l*-menthol are not expected to cause adverse health effects when used according to label instructions.

Registrant-supplied scientific rationales, as well as information from the published scientific literature, were assessed for the potential of thymol, eucalyptus oil, racemic camphor, and *l*-menthol to cause short-term toxicity, developmental toxicity, and genotoxicity. Adverse effects in animals given repeated high doses of eucalyptus oil included increased liver and kidney weights. Treatment related adverse effects in animals administered repeated high doses of thymol, racemic camphor, or *l*-menthol were not observed. There was no indication of prenatal developmental toxicity or genotoxicity for thymol, eucalyptus oil, racemic camphor, or *l*-menthol.

Residues in Water and Food

Dietary risks from food and water are acceptable.

Dietary exposure to thymol, eucalyptus oil, racemic camphor, and *l*-menthol to humans is unlikely since application of Api Life VAR is not to be used during honey flow or when surplus honey supers are installed in the hives. Also, users are not to collect honey or wax from the treated brood chambers and to further reduce any potential residues in the honey or wax collected from the surplus honey supers, the proposed label specifies a preharvest interval (PHI) of 30 days following the removal of the Api Life VAR tablets. It is expected that the proposed use of thymol, eucalyptus oil, racemic camphor, and *l*-menthol will not pose a health risk to any segment of the population, including infants, children, adults and seniors, from consumption of honey or wax from treated beehives.

Exposure to thymol, eucalyptus oil, racemic camphor, and *l*-menthol from drinking water will be negligible. Consequently, the dietary risk from drinking water is acceptable.

Occupational Risks From Handling Api Life VAR

Occupational risks are acceptable when Api Life VAR is used according to the label directions, which include protective measures.

To protect workers from exposure to Api Life VAR, the label states that applicators must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes, and goggles or face shield. The occupational risks are acceptable when the precautionary statements on the label are observed.

Risks in Residential and Other Non-Occupational Environments

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

Api Life VAR is proposed as a commercial product that will not be marketed to residential users, but it could be used in beehives near residential areas. Bystander and residential exposure to thymol, eucalyptus oil, racemic camphor, and *l*-menthol is not expected due to the direct application of the tablets to beehives. Thus, the health risk to residents and the general public is acceptable when Api Life VAR is used according to label directions.

Environmental Considerations

Due to lack of environmental exposure, an environmental assessment was not required for Api Life VAR Technical and Api Life VAR.

Value Considerations

What Is the Value of Api Life VAR?

Api Life VAR provides suppression of varroa mites, the most important pest of honey bees, and offers users new active ingredients for use against this pest.

Varroa mites are the most important parasitic pest of honey bees, and have a severe economic impact on the Canadian beekeeping industry. Significant varroa mite infestation in a honey bee colony will cause the loss of the infested colony. Varroa mites are an important cause of honey bee colony loss in Canada. Based on the mode of action of Api Life VAR, varroa mites are not expected to develop resistance, which is a problem with some other varroa mite control products.

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 Api Life VAR Technical and Api Life VAR to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

The signal words “CAUTION POISON”, “DANGER – CORROSIVE TO EYES”, “DANGER SKIN IRRITANT”, and “POTENTIAL SKIN SENSITIZER” are required on the principal display panels of the labels for Api Life VAR Technical and Api Life VAR tablets. 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 acute oral toxicity, skin irritation, eye irritation, and skin sensitization of the product.

Workers handling packages, as well as the individual tablets of Api Life VAR, will be required to wear standard personal protective equipment including long-sleeved shirt, long pants, chemical-resistant gloves, socks, shoes, and goggles or face shield.

Next Steps

Before making a final registration decision on racemic camphor, eucalyptus oil, *l*-menthol and thymol and Api Life VAR, 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 Health Canada makes its registration decision, it will publish a Registration Decision on racemic camphor, eucalyptus oil, *l*-menthol and thymol and Api Life VAR (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).

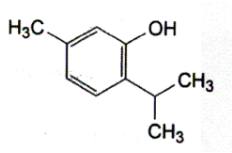
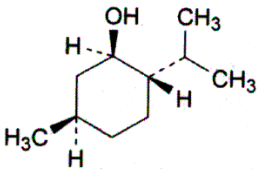
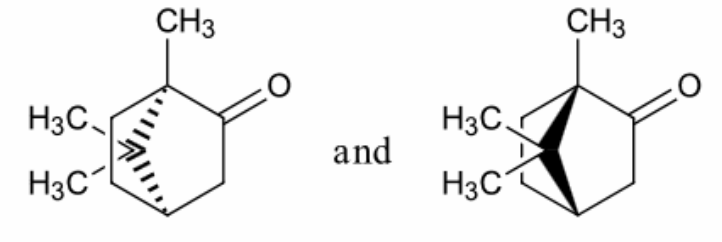
Science Evaluation

Racemic camphor, eucalyptus oil, *l*-menthol and thymol and Api Life VAR

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substances	Thymol Eucalyptus oil Racemic camphor *l*-Menthol
Function	Acaricides
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	Thymol: 5-Methyl-2-(propan-2-yl)phenol *l*-menthol: (1R,2S,5R)-2-isopropyl-5-methylcyclohexanol Racemic camphor: (1*RS*,4*RS*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one or (±)-bornan-2-one or *rac*-(1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (PIN) Eucalyptus oil : N/A
2. Chemical Abstracts Service (CAS)	Thymol : 2-Isopropyl-5-methylphenol *l*-Menthol: (1R,2S,5R)-5-methyl-2-(1-methylethyl)cyclohexanol Racemic camphor: 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one[1] Eucalyptus oil : N/A
CAS number	Not applicable, the product is a complex mixture of thymol (CAS # 89-83-8), eucalyptus oil (CAS # 8000-48-4), racemic camphor(CAS # 76-22-2), and *l*-menthol (CAS # 2216-51-5)

Molecular formula	Thymol:  *l*-Menthol:  Racemic camphor  Eucalyptus oil: N/A
Molecular weight	Thymol : 150.22 *l*-Menthol: 156.27 Racemic camphor: 152.24 Eucalyptus oil : N/A
Structural formula	Thymol : $C_{10}H_{14}O$ *l*-Menthol: : $C_{10}H_{20}O$ Racemic camphor : $C_{10}H_{16}O$ Eucalyptus oil : N/A
Purity of the active ingredient	Thymol at 76 % *l*-Menthol at 3.8 % Racemic camphor at 3.8 % Eucalyptus oil at 16.4 %

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

Technical Product—Api Life VAR Technical

The technical product is a complex mixture of thymol, eucalyptus oil, racemic camphor and *l*-menthol in a liquid form.

End-use Product—Api Life VAR

Property	Result
Colour	Green
Odour	Characteristic
Physical state	Solid mass
Formulation type	Impregnated fabric (IF)
Label concentration	Thymol……. 8.0 g/tablet Eucalyptus Oil……...…1.72 g/tablet Racemic camphor…….……0.39 g/tablet *l*-Menthol…….....0.39 g/tablet
Container material and description	Bag constituted of different layers of materials: First layer: polyester (PET), second layer: paper/polyethylene (CRTC PE), third layer: aluminum (ALU) and fourth layer: polypropylene (OPP CAST)
Density	0.6 g/mL
pH of 1% dispersion in water	Not applicable, the product is a tablet.
Oxidizing or reducing action	The product does not contain reducing or oxidizing agents.
Storage stability	The product was stable after 24-month storage at 25 ºC and 60% relative humidity. It was also stable after 12-month storage at 30 ºC and 65% relative humidity.
Corrosion characteristics	No effects were observed on the bag after 24-month storage at 25 ºC and 60% relative humidity.
Explodability	The product does not present an explosion hazard.

1.3 Directions for Use

Api Life VAR provides suppression of varroa mites in honey bee hives. One treatment of Api Life VAR mites consists of 3 applications, re-applied at 7–10 day intervals, with each application consisting of one tablet of Api Life VAR broken into 4 pieces and placed in the corners of the brood box on top of the brood frame top bars. Remove the previous tablet before applying the next tablet. The last (3rd) tablet of the treatment should be left in the hive for 12 days, then removed from the hive. Do not apply when honey supers are in place. Apply when daytime temperature highs are between 18 °C and 35 °C. Two treatments, consisting of three applications each, may be applied per year. Applications may be made in any season (spring, summer, fall, or winter).

1.4 Mode of Action

The mode of action of thymol, eucalyptus oil, racemic camphor, and *l*-menthol in killing varroa mites is not known. These active ingredients are active through volatilisation in the hive. Application of Api Life VAR has been observed to increase grooming behaviour in adult bees, leading to increased rates of varroa mite removal by bees.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

Since the product is a mixture of essential oils, which meet the Food Chemical Codex (FCC) requirements (thymol, eucalyptus oil and *l* -menthol) or the European Union (EU) pharmacopeia requirements (racemic camphor), no analytical method is required.

2.2 Method for Formulation Analysis

Since the product is a mixture of essential oils, which meet the FCC requirements (thymol, eucalyptus oil and *l*-menthol) or the EU pharmacopeia requirements (racemic camphor), no analytical method is required.

2.3 Methods for Residue Analysis

No methods are required to quantify residues of thymol, eucalyptus oil, racemic camphor, and *l*-menthol.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological information was conducted in support of Api Life VAR Technical and Api Life VAR. The data package for Api Life VAR Technical and Api Life VAR is considered acceptable to assess the toxic effects that may result from exposure to thymol, eucalyptus oil, racemic camphor, and *l*-menthol. 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, dermal sensitization, short-term toxicity, prenatal developmental toxicity, and genotoxicity testing of Api Life VAR Technical and scientific rationales to waive acute toxicity studies for Api Life VAR (acute oral, dermal, and inhalation toxicity, skin and eye irritation, and dermal sensitization).

Based on a review of the registrant-supplied published scientific literature and publicly available information, Api Life VAR Technical (a mixture of thymol, eucalyptus oil, racemic camphor, and *l*-menthol) was found to be of slight acute oral toxicity (LD_{50} of 1203 mg/kg bw in rats), corrosive to the eyes, extremely irritating to the skin, and a dermal sensitizer.

Registrant-supplied scientific rationales, as well as information from the published scientific literature, were assessed for the potential of thymol, eucalyptus oil, racemic camphor, and *l*-menthol to cause short-term toxicity, developmental toxicity, and genotoxicity. Adverse effects in animals given repeated high doses of eucalyptus oil included increased liver and kidney weights. Treatment-related adverse effects in animals administered repeated high doses of thymol, racemic camphor, or *l*-menthol were not observed. There was no indication that the young were more sensitive to thymol, eucalyptus oil, racemic camphor, or *l*-menthol than the adult animal.

There was no evidence that thymol, eucalyptus oil, racemic camphor, or *l*-menthol induced mutagenic or genotoxic effects. The risk assessment protects against these findings 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.

Requests to waive acute oral, dermal, and inhalation toxicity, primary skin and eye irritation, and dermal sensitization testing for Api Life VAR were accepted. Api Life VAR is considered to be of slight acute oral toxicity, corrosive to the eyes, extremely irritating to the skin, and a dermal sensitizer.

Incident Reports

Api Life VAR Technical is a new active ingredient mixture pending registration for use in Canada, and as of 13 January 2020, no incident reports had been submitted to the PMRA.

3.2 Occupational, Residential and Bystander Exposure and Risk Assessment

3.2.1 Dermal Absorption

No information on dermal absorption of thymol, eucalyptus oil, racemic camphor, and *l*-menthol from Api Life VAR was provided, however, dermal absorption is expected to be limited when the precautionary statements on the label are observed.

3.2.2 Use Description

Api Life VAR is proposed for use in beehives. The method of application is by applying foamed phenolic resin tablets (each tablet cut into four pieces) impregnated with the technical grade active ingredient, Api Life VAR Technical, containing thymol, eucalyptus oil, racemic camphor, and *l*-menthol as the active ingredients, on top of the frames and around the edges of each hive. Tablets are replaced twice (seven to 10 day interval) per treatment. Api Life VAR tablets may be applied up to a maximum of two treatments per year. Api Life VAR tablets are not to be used during honey flow or when surplus honey supers are installed on the hives. Honey or wax is not to be harvested from the brood chambers or the colony feed supers. The maximum amount of active ingredient handled by one individual treating 500 hives per day is 4.0 kg thymol/day, 860 g eucalyptus oil/day, 195 g of racemic camphor/day, and 195 g of *l*-menthol/day.

3.2.3 Mixer, Loader and Applicator Exposure and Risk

When Api Life VAR is used according to label directions, occupational exposure is characterized as short- to intermediate-term in duration and is primarily by the dermal route, but incidental inhalation and ocular exposure is also possible while applying the product, as well as during clean-up and repair. To protect applicators from exposure to Api Life VAR, the label states to wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks, shoes, and wear goggles or face shield.

Precautionary statements such as the wearing of personal protective equipment (PPE) on the end-use product label aimed at mitigating exposure are adequate to protect individuals from any risk due to occupational exposure. Overall, occupational risks to workers are acceptable when the precautionary statements on the label are followed which include PPE.

3.2.4 Postapplication Exposure and Risk

Post-application activities include integrated pest management (IPM) scouting, harvesting honey, splitting hives, the removal of spent Api Life VAR tablets, re-queening the hives, removal of queen cells, managing colony growth, and providing bees protein and sugar feed supplements. Given the nature of the post-application activities, dermal contact with the treated tablets is expected, but the wearing of bee keeping equipment (in other words, gloves, jacket, pants, and boots) is expected to mitigate the exposure. A restricted-entry interval was not specified on the proposed label and is not required. Consequently, the health risks to individuals involved in postapplication activities are considered acceptable.

3.2.5 Residential and Bystander Exposure and Risk

As Api Life VAR tablets are to be applied directly to beehives and do not involve outdoor spraying, bystander exposure due to drift is not expected. Consequently, the health risks to bystanders are acceptable.

Api Life VAR is a commercial product and is not to be marketed to residential users, but could be used in beehives near residential areas. The direct application of Api Life VAR to beehives is such that exposure to humans and companion animals in residential areas is unlikely. Consequently, the health risks to individuals in residential areas are acceptable.

3.3 Food Residue Exposure Assessment

3.3.1 Food

Api Life VAR is not to be used during honey flow or when surplus honey supers are installed on the hives and workers are not to harvest honey or wax from the brood chambers. In addition and to further reduce any potential residues in the honey or wax collected from the surplus honey supers, the proposed label specifies a preharvest interval of 30 days following the removal of the Api Life VAR tablets. Based on this along with noting that thymol, eucalyptus oil, racemic camphor, and *l*-menthol have long histories of use in foods, the dietary risk from exposure to thymol, eucalyptus oil, racemic camphor, and *l*-menthol from honey and wax harvested from treated hives is acceptable.

3.3.2 Drinking Water

Api Life VAR is proposed for use inside the beehives and is not subject to agricultural run-off during application, post-application activities, or due to inclement weather. Exposure to thymol, eucalyptus oil, racemic camphor, and *l*-menthol from drinking water is expected to be negligible and health risks from residues in drinking water are acceptable due to the limited exposure following application of Api Life VAR.

3.3.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

Acute reference doses (ARfDs) and acceptable daily intakes (ADIs) are not required for thymol, eucalyptus oil, racemic camphor, and *l*-menthol. Based on all the available information and hazard data, these active ingredients are considered to be of low toxicity to all sub-populations including infants and children. The consumption patterns (for example, among infants and children) along with the potential susceptibility in all subpopulations to the effects of thymol, eucalyptus oil, racemic camphor, and *l*-menthol including developmental effects from pre- or post-natal exposures are also taken into consideration. Overall, there are no threshold effects of concern and thus, there is no need to apply uncertainty factors to account for intra- and interspecies variability, or have a margin of exposure required. As a result, the PMRA has not used a margin of exposure (safety) approach to account for intra- and inter-species variability or have a margin of exposure given that a threshold for potential effects is not required.

3.3.4 Aggregate Exposure and Risk

Based on the relevant information, there is reasonable certainty that no harm will result from aggregate exposure of residues of thymol, eucalyptus oil, racemic camphor, and *l*-menthol to the general Canadian population, including infants and children, when Api Life VAR 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 Assessment

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pest control products with a common mechanism of toxicity. For the current evaluation, the PMRA did not identify the potential for dietary or residential exposure for thymol, eucalyptus oil, racemic camphor, and *l*-menthol. Therefore, there is no requirement for a cumulative health risk assessment at this time.

3.3.6 Maximum Residue Limits

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine 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 an 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.

The dietary risks from food and drinking water are acceptable given that Api Life VAR is proposed for use in brood chambers and not honey supers; honey or wax are not to be harvested from the brood chambers; and thymol, eucalyptus oil, racemic camphor, and *l*-menthol have long histories of use in foods. Furthermore, there is a PHI of 30 days following the removal of the Api Life VAR tablets. Consequently, the specification of an MRL under the *Pest Control Products Act* is not required.

4.0 Value

Value information reviewed in support of Api Life VAR consisted of efficacy data from 10 trials. Results from these trials were variable, with Api Life VAR demonstrating product performance consistent with a claim of control in some trials and suppression in others. Taking all submitted information into consideration, the weight of evidence demonstrated product performance consistent with a claim of suppression of varroa mite. The treatment consisting of three applications at 7–10 day intervals was supported based on bee and mite biology: mites reproduce in sealed bee brood, and bee brood takes on average 21 (workers) to 24 (drones) days to emerge from brood cells. As mites are difficult to control in sealed brood, mite control treatments generally must be long enough to span at least one brood cycle. The value information was sufficient to support a label claim that Api Life VAR, when applied with three applications at a rate of 1 tablet per hive, and an application interval of 7–10 days, will suppress varroa mite in honey bee hives.

Tolerance of honey bees to Api Life VAR was supported based on observations of adverse effects in the submitted trials. No trials reported any adverse effects on worker or queen bees. Some trials reported a reduction in the amount of sealed brood in hives treated with Api Life VAR when sealed brood was present. A warning on the Api Life VAR label regarding this effect on brood is required.

Alternative active ingredients registered to treat honey bee hives infested with varroa mites include oxalic acid, formic acid, hop beta acids (present as potassium salts), amitraz, thymol, fluvalinate-tau, coumaphos, and flumethrin. Varroa mites have historically developed resistance to conventional miticides such as fluvalinate-tau and coumaphos, resulting in difficulty in controlling this pest. Based on the mode of action of Api Life VAR, varroa mites are unlikely to develop resistance to this product.

Api Life VAR has value for suppressing varroa mites in honey bee hives with a mode of action which is unlikely to lead to resistance. Api Life VAR is compatible with current management practices and would be a useful addition to the integrated pest management of varroa mites and aid in the control of resistant mites.

5.0 Pest Control Product Policy Considerations

5.1 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, 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, thymol, eucalyptus oil, racemic camphor, and *l*-menthol and their transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the conclusion that thymol, eucalyptus oil, racemic camphor, and *l*-menthol and their transformation products do not meet all of the Track 1 criteria.

5.2 Formulants and Contaminants of Health or Environmental 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 NOI2005-01[7] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act*, 1999 (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade Api Life VAR Technical and its end-use product, Api Life VAR, 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.

6.0 Summary

6.1 Human Health and Safety

The toxicology data package for thymol, eucalyptus oil, racemic camphor, and *l*-menthol is adequate to qualitatively identify the toxic effects that may result from exposure to thymol, eucalyptus oil, racemic camphor, and *l*-menthol. Based on published scientific literature and other publicly available information, the active ingredient, a mixture of thymol, eucalyptus oil, racemic camphor, and *l*-menthol, is of slight acute toxicity by the oral route, corrosive to the eyes, extremely irritating to the skin, and is a dermal sensitizer. As information provided for the technical grade active ingredient acted as surrogate data for Api Life VAR, the end-use product is considered to be toxicologically equivalent to the technical grade active ingredient.

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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 Concernt.

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

Applicators and postapplication workers will not be exposed to unacceptable levels of thymol, eucalyptus oil, racemic camphor, and *l*-menthol when Api Life VAR tablets are used according to label directions.

Bystander and residential exposure during application of Api Life VAR tablets are not expected. Consequently, the health risk to bystanders and residents is acceptable.

Exposure to thymol, eucalyptus oil, racemic camphor, and *l*-menthol from food and drinking water will be negligible. Consequently, the dietary risk from food and drinking water is acceptable.

The specification of an MRL under the *Pest Control Products Act* is not required.

6.2 Value

Varroa mites are the most important parasitic pest of honey bees, and have a severe economic impact on the Canadian beekeeping industry. Significant varroa mite infestation in a honey bee colony will cause the loss of the infested colony. Varroa mites are an important cause of honey bee colony loss in Canada. Based on the mode of action of Api Life VAR, varroa mites are not expected to develop resistance, which is a problem with some other varroa mite control products. Api Life VAR provides suppression of varroa mites in honey bee hives when applied as a treatment consisting of three applications of 1 tablet per hive, with an application interval of 7–10 days.

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 Api Life VAR Technical and Api Life VAR, containing the technical grade active ingredients racemic camphor, eucalyptus oil, *l*-menthol and thymol, for suppression of varroa mite in honey bee hives.

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

ADI	acceptable daily intake
ARfD	acute reference dose
atm	atmosphere
bw	body weight
CAS	Chemical Abstracts Service
DF	dry flowable
DNA	deoxyribonucleic acid
FCC	Food Chemical Codex
g	gram
IPM	integrated pest management
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
LD_{50}	lethal dose 50%
mg	milligram
mL	millilitre
MRL	maximum residue limit
N/A	not applicable
PHI	preharvest interval
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency

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A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

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2.0 Human and Animal Health

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