Proposed Registration Decision PRD2010-18

Thymol

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Table of Contents

Overview

Proposed Registration Decision for Thymol

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Thymol E_9509758 and Thymovar, containing the technical grade active ingredient thymol, to control Varroa mites (*Varroa destructor*) in honeybee hives.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of thymol and Thymovar.

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 (e.g. children) as well as organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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 thymol, the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on thymol, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

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

What Is Thymol?

Thymol is a volatile oil which is found in oil of thyme. While the mode of action of thymol is not known, it is believed that the site of action is the nervous system in insects. Thymol vapourizes at varying rates, depending on temperature. Thymovar is a product containing thymol for control of varroa mite (*Varroa destructor*) in honeybee hives. Through volatilization from the Thymovar wafers, thymol vapours build up in the hive. Varroa mites are more sensitive to thymol than bees; therefore, the thymol vapours are at a high enough concentration to be toxic to varroa mites but are not high enough to harm bees. Thymol is not effective on mites within brood cells; therefore, the treatment period must be long enough to ensure that the brood in cells which are capped at the onset of treatment have time to emerge.

Health Considerations

- **Can Approved Uses of Thymol Affect Human Health?**

Thymol is unlikely to affect your health when used according to label directions.

Exposure to thymol may occur when handling and applying the end-use product, Thymovar. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g., children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

The technical grade active ingredient, Thymol E_9509758, is of moderate acute toxicity by the oral route, slight acute toxicity by the dermal route, and low acute toxicity by inhalation. Thymol is corrosive to the eyes and extremely irritating to the skin. Additionally, it is a known respiratory irritant and a dermal sensitizer. Based on available information and a long history of safe use as a food additive, cosmetics ingredient, and its presence in foods and beverages, exposure to thymol is unlikely to result in any short-term toxicity, prenatal developmental toxicity or genotoxicity.

[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*.

- **Residues in Water and Food**

Dietary risks from food and water are not of concern.

The amount of thymol present as residue in honey following the application of Thymovar in beehives is not expected to exceed natural or artificial amounts typically used to flavour foods and beverages. Therefore, the direct application to beehives with wafers impregnated with thymol is not expected to result in any dietary risk due to exposure from food or water.

- **Occupational Risks From Handling Thymovar**

Occupational risks are not of concern, when Thymovar is used according to label directions, which include protective measures.

Pesticide applicators can come into direct contact with thymol when handling and applying Thymovar to beehives. Potential exposure routes include direct contact with the skin and indirect contact of thymol vapour with the eyes and lungs. Although thymol is known for its corrosive and irritating properties, the product label contains a number of mitigative measures to limit potential exposure to the applicators.

As Thymovar is a Commercial class product that requires direct application inside beehives, bystander exposure is expected to be negligible and therefore not of concern.

Environmental Considerations

- **What Happens When Thymol Is Introduced Into the Environment?**

Thymol is a naturally occurring essential oil that transforms rapidly under environmental conditions. During the use of Thymovar for control of varroa mite in beehives, exposure of the chemical to the environment is expected to be limited. The product is applied as textile wafers containing the active ingredient thymol, which evaporates into the closed beehives. Environmental exposure would occur primarily through leakage during application or from improper disposal of used wafers. Based on limited environmental exposure, the chemical's natural occurrence and the likelihood for relatively rapid transformation under environmental conditions, the proposed use of thymol is not expected to pose a significant risk to the environment. Therefore, further review of the environmental chemistry, fate, and toxicology of thymol was not considered necessary.

Value Considerations

What Is the Value of Thymovar?

Thymovar controls varroa mite (*Varroa destructor*) in honeybee hives.

Efficacy studies from various locations, including Quebec, Switzerland, Portugal, Turkey, Italy, Germany, Greece, and the Netherlands, were reviewed in support of Thymovar. These studies found that Thymovar generally provided control of varroa mites in excess of 90% when applied according to label directions, with no significant adverse effects. Thymovar is used for control of varroa mite in honeybee hives by applying 2 consecutive applications of ½ a wafer in nucleus hives, 1 wafer in 1 storey hives, or 2 wafers in 2 storey hives. Applications are left in the hive for 3-4 weeks. Applications must only be made when temperatures are above 12°C and below 30°. No significant adverse effects are expected provided that the Thymovar wafers are not placed directly over brood and temperatures do not exceed 30°C.

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 Thymovar to address the potential risks identified in this assessment are as follows.

Human Health

The statements, “WARNING – POISON”, “DANGER – CORROSIVE TO EYES”, and “DANGER – SKIN IRRITANT” have been included on the principal display panel of the general label and "Harmful or Fatal if swallowed", “CORROSIVE to the eyes”, “CORROSIVE to the skin”, “DO NOT get on skin, eyes or clothing, “Avoid inhaling the vapour” and “Handle Thymovar in a well-ventilated area" have been included in the Precautions section of the secondary display panel of the general label. Furthermore, the product label instructs applicators to wear chemical resistant gloves, long-sleeved shirt and pants, shoes and socks, and eye goggles or a face shield when handling Thymovar.

The Thymovar product label requires that all of the honey supers are removed prior to treatment and that the product be applied before the honey flow or after all surplus honey has been removed. Additionally, the label also instructs beekeepers not to extract honey from treated combs of the brood chambers in the following spring.

Next Steps

Before making a final registration decision on thymol, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

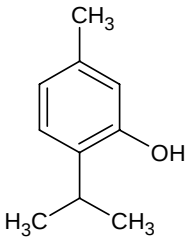
When the PMRA makes its registration decision, it will publish a Registration Decision on thymol (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's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

Science Evaluation

Thymol

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Thymol
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	5-Methyl-2-(propan-2-yl)phenol
2. Chemical Abstracts Service (CAS)	Phenol, 5-Methyl-2-(1-methylethyl)
CAS number	89-83-8
Molecular formula	$C_{10}H_{14}O$
Molecular weight	150.2
Structural formula	
Purity of the active ingredient	99.9%

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

Technical Product: Thymol E_9509758

Property	Result
Colour and physical state	White
Odour	Characteristic pungent
Melting point	49°C
Boiling point or range	N/A
Density	0.97 g/cm^3
Vapour pressure at 20°C	Not provided
Henry's law constant at 20°C	N/A
Ultraviolet (UV)-visible spectrum	Does not absorb at $\lambda > 300$ nm
Solubility in water at 20°C	Slightly soluble in water.

Property	Result
Solubility in organic solvents at 20°C	Highly soluble in alcohols
n-Octanol-water partition coefficient (K_{ow})	3.28+/- 0.20 (calculated)
Dissociation constant (pK_a)	10.8 (calculated)
Stability (temperature, metal)	Stable under normal conditions

End-Use Product—Thymovar

Property	Result
Colour	Yellow
Odour	Aromatic/Thymol odour
Physical state	Solid
Formulation type	Impregnated fabric
Guarantee	15 g per wafer
Container material and description	Flexible plastic bags
Density	0.97 g/cm^3 (for active ingredient)
pH of 1% dispersion in water	N/A
Oxidizing or reducing action	Not available
Storage stability	The product is stable at ambient temperature. Storage in plastic sachets for 12 months results in a drop in active ingredient content by approximately 2.3%, which is within standard limits.
Corrosion characteristics	There was no observable change in the physical characteristics of the product.
Explodability	The product does not contain ingredients which are potentially explosive.

1.3 Directions for Use

For control of varroa mite (*Varroa destructor*) in honeybee hives, apply 2 consecutive applications of Thymovar. Thymovar is applied at a rate of a ½ a wafer for nucleus hives, 1 wafer for single brood chamber hives, or 2 wafers for double brood chamber hives. Thymovar wafers are left in the hive for a 3-4 week treatment period. Immediately following the first application, remove the used wafer(s) and apply a second application of Thymovar. The second application of wafer(s) is also left in the hive for 3-4 weeks. All wafers should be used immediately after opening the sealed sachet. Remove all wafer(s) from the hive after each application period.

Prior to Thymovar treatment, remove all honey supers and close or replace open or screened hive floors with solid floors, and reduce the hive entrance to normal size. If bees are fed and varroa infestation levels and temperatures allow, it is recommended that part of the feeding be carried out before treatment with Thymovar.

For 1 wafer applications in single brood chamber hives, cut the wafer in half. For 2 wafer applications in double brood chamber hives, use uncut wafers. The cut or uncut wafer(s) are placed on top of the combs of the top brood chamber on either side of the edge of the brood, close to but not directly over open or sealed brood. Wafers are preferably placed a minimum of 4 cm from brood. Close the hive, leaving a space (about 5 mm) between the wafers and the hive covers, to improve the evaporation of thymol. Do not place plastic cover foils directly on the wafers.

Thymovar must only be used when honey supers are not present on the hive. Applications may be made in the spring before honey flow or in the late summer to early autumn after all surplus honey has been removed. Apply when maximum daily temperatures are above 12°C and below 30°C. Temperatures below 12°C will reduce the effectiveness of the treatment, while temperatures above 30° will cause increased stress and mortality of adult bees and brood.

1.4 Mode of Action

Thymol is a volatile oil which is found in oil of thyme. While the mode of action of thymol is not known, it is believed that the site of action is the insect nervous system. Thymol vapourizes at varying rates, depending on temperature. Thymovar is used for control of varroa mites (*Varroa destructor*) in honeybee hives. Each Thymovar wafer contains 15 g of the volatile oil thymol. Through volatilization from the wafers, thymol vapours build up in the hive. Varroa mites are more sensitive to thymol than bees; therefore, the vapours are at a high enough concentration to be toxic to varroa mites but are not high enough to harm bees. Thymol is not effective on mites within brood cells; therefore, the treatment period must be long enough to ensure that the brood in cells which are capped at the onset of treatment have time to emerge.

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 the impurities in Thymol E_9509758 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

Thymol residue in honey and beeswax may be analyzed using a gas chromatography or a gas chromatography-mass spectrometry method.

3.0 Impact on Human and Animal Health

3.1 Metabolism

Thymol is readily absorbed in the gastrointestinal tract and approximately 50% is excreted via the kidney, either unconjugated or as a glucuronide or sulphate conjugate within 24 hours of administration. Investigations in rabbits and humans have confirmed the formation of glucuronide and sulphate conjugates and their excretion in urine. Upon single oral administration of 500 mg thymol/kg bw in rabbits, a marked increase in glucuronide and sulphate conjugates was seen in the urine over a period of 24 hours. In 24-hour urine samples obtained from human subjects, the metabolite thymohydroquinone was also detected in addition to the glucuronide and sulphate conjugates of thymol.

Similar findings were also reported in male albino rats (Wistar strain derived). The animals were administered a single dose of 1 mmol (approximately 150 mg) of thymol/kg bw. The study found that most of the administered thymol was excreted within 24 hours. In a clinical trial in humans, healthy volunteers were given 1.08 mg of thymol in the form of a tablet (containing primrose and thyme dry extracts). No thymol could be detected in plasma or urine. The metabolites, thymol sulphate and thymol glucuronide, were found in urine and elimination half-life in plasma was determined to be 10.2 hours.

3.2 Toxicology Assessment

A detailed review of the toxicological database for thymol was conducted. This review also took into consideration the evaluation summaries prepared by regulatory authorities with equivalent health assessment criteria and standards. The review relied, in part, on test data summaries in the U.S. Environmental Protection Agency's Biopesticide Registration Action Document for thymol as well as the European Agency for the Evaluation of Medicinal Products' Committee for Veterinary Medicinal Products summary report on thymol.

The applicant provided information consisting of reviews of published studies on thymol to support the required assessment for acute oral, dermal and inhalation toxicity as well as irritation, sensitization, short-term toxicity, prenatal developmental toxicity and genotoxicity. Also submitted were data waiver requests based on literature reviews in lieu of providing product-specific data. The PMRA normally requires acute toxicity and irritation studies on both the technical grade active ingredient (TGAI) and the end-use product (EP). Given that the end-use product contains no formulants of toxicological concern, the information used to assess the toxicological hazards of the TGAI (Thymol E_9509758) was also utilized to assess the toxicological hazards of the associated EP (Thymovar). The overall scientific quality of the toxicology information is considered sufficient (see Appendix I) for characterizing the toxicity of the TGAI and EP for the purposes of conducting a human health risk assessment when thymol is used to control varroa mites on honey bees.

3.2.1 Acute Toxicity

Acute oral toxicity studies indicate that thymol is of moderate toxicity with an LD_{50} of 640 mg/kg bw in mice. The oral LD_{50} of thymol has been reported to be 980 and 880 mg/kg bw in rats and guinea pigs, respectively. Toxicity signs observed in these studies included depression, ataxia, irritated gastrointestinal tract, tremors, coma and respiratory failure.

The dermal LD_{50} of thymol has been reported to be 1049 mg/kg bw in mice and greater than 2000 mg/kg bw in rats according to different studies. Thymol is classified as slightly acutely toxic via the dermal route of exposure.

Although there are a limited number of available inhalation toxicity studies, thymol is an approved ingredient for use in over-the-counter drugs including nasal decongestant drug products. There have been no known reports of adverse effects relating to the inhalational use of thymol in humans treated for respiratory disorders. Based on the long history of use and a lack of reported incidents, thymol is expected to be of low acute toxicity when inhaled.

According to the open scientific literature, thymol is corrosive to the eyes and extremely irritating to the skin. Contact dermatitis has been reported for consumer products containing thymol, such as douches, personal dental products and topical anesthetics. Based on available information, thymol is expected to be a dermal sensitizer.

3.2.2 Short-term Toxicity

Only one study was available in the open scientific literature that addressed the short-term toxicity of thymol. In a 19-week study, groups of five male and five female weanling Osborne-Mendel rats were fed 0 (control), 1000 or 10,000 ppm of food grade thymol in the diet. Body weights, food intake and general condition were recorded weekly. Hematological parameters and organ weights for liver, kidneys, spleen, heart, and testes were assessed at study termination. The tissues of all rats were examined macroscopically at death. There were no growth, hematological or macroscopic changes in the tissues noted in either dose group, compared with the control group. In addition, microscopic analysis of tissues was performed only for rats in the high-dose group and no changes were noted. Based on the long history of use of synthetic thymol in foods, cosmetics and human drugs and the fact that thymol has been part of the human diet for centuries, short-term toxicity is not expected to be of concern.

3.2.3 Prenatal Developmental Toxicity

The prenatal developmental toxicity of thymol was investigated using developing chicken embryos. Thymol was injected into chicken embryos via the air cell and the yolk. Each injection group was treated at two stages of incubation: pre-incubation (0 h) and on the fourth day (96 h of incubation). At pre-incubation, thymol caused 0% to 36.13% and 1.73% to 15.65% of embryos to develop abnormally when treated via the air cell and the yolk sac, respectively. At 96 h of incubation, thymol caused 0% to 13.57% and 0.90% to 6.36% of embryos to develop abnormally when treated via the air cell and the yolk sac, respectively. The incidence of abnormal embryo

development was statistically significant compared to controls for the air cell treatment, but not for the yolk treatment with thymol.

Although this test system may be useful for screening large numbers of compounds, it is not recognized internationally as a standard animal model for conducting developmental toxicity studies. Given the differences in developmental physiology and anatomy between avian and mammalian species, it is not possible to extrapolate effects observed in chicken embryos to mammalian, including human, developmental effects. With the long history of use of thymol in the human diet and a lack of reports of adverse effects (incidents), exposure to thymol is unlikely to result in prenatal developmental toxicological effects.

3.2.4 Genotoxicity

A number of in vivo and in vitro studies were available to assess the genotoxic potential of thymol. However, mixed findings have been reported. Thymol (99.73% pure) was tested for mutagenic potential in the Salmonella/microsome assay (standard plate incorporation test) using *Salmonella typhimurium* strains TA 98, TA 100, TA1535 and TA 1537. The tests were carried out in the presence and absence of metabolic activation (S-9 mix from Aroclor 1254-induced rat liver). The test concentrations ranged from 6 to 5000 µg/plate. At higher concentrations, thymol showed varying degrees of bacterial toxicity, depending on the strain. Thymol was not observed to produce any genotoxic effects in this test system. Negative findings were also reported in similar studies.

Thymol (99.5% purity) was investigated for its genotoxic potential using V79 Chinese hamster lung fibroblast cells. The cells were treated with 1, 5 or 25 µM thymol for 30 minutes. The comet assay with formamido pyrimidine glycosylase protein was used. The results showed a lack of clastogenic activity for thymol at biologically relevant concentrations.

In addition, according to a recent in vivo genotoxicity study, groups of four Sprague-Dawley rats (two male and two female) were intraperitoneally treated with thymol (99.6% purity) at doses of 40, 60, 80 and 100 mg/kg bw for 6, 12 and 24 h. Significant induction of structural and total chromosome abnormalities was observed in bone marrow cells of rats in all the concentrations and treatment times. Cytotoxicity from a decrease in the mitotic index was also observed at all test concentrations and treatment times. Although genotoxicity was observed in this study, these effects were noted at cytotoxic doses.

The genotoxic effects of thymol were also investigated using sister chromatid exchange, chromosome aberration, and micronucleus tests in human peripheral lymphocyte cells. The cells were treated with 25, 50, 75 and 100 µg/mL concentrations of thymol (99.6% purity) for 24 h and 48 h treatment periods. Induction of sister chromatid exchange, structural chromosome aberration and frequency of micronucleus were observed in all treatment groups and times, as were cytoxic effects measured by decreases in the replication, mitotic and nuclear division indices.

Further, groups of 15 A/He mice per sex per dose received intraperitoneal injections of thymol three times a week for eight weeks. The total thymol dose per mouse was 1.2 or 6.0 g/kg bw. The results reported that thymol was negative for inducing primary lung tumours in mice. Overall, the weight of evidence suggests that thymol is not genotoxic or mutagenic at non-cytotoxic doses.

3.2.5 Chronic Toxicity

Based on a critical review of published scientific literature on the acute and short-term toxicity of thymol, coupled with a long history of use of thymol as a food additive, and as an active ingredient in pharmaceutical, cosmetic and disinfectant products, there is no conclusive evidence to suggest that thymol is carcinogenic, genotoxic, neurotoxic, or a developmental/reproductive toxicant.

3.3 Occupational/Bystander Exposure and Risk Assessment

While Thymol E_9509758 is considered a new technical grade active ingredient for use in pest control products in Canada, it is a chemical that is widely used as an ingredient in the food, beverage, cosmetics and dental industries. It is also a main ingredient found in surface disinfectants that are intended for use in homes, hospitals, food processing plants and farms. A number of disinfectants as well as human and veterinary drug products containing thymol of synthetic or natural origin have been approved for sale in Canada.

3.3.1 Occupational

There is no mixing required for applying Thymovar as the product is a ready-to-use wafer and exposure is limited to the number of applications performed by the applicator. Possible user contact is limited to applying and removing Thymovar from the beehives. Since Thymovar is designed to slowly release thymol vapour, significant exposure from applications to thymol is unlikely.

Based on the proposed use scenario, if all hives are of the double-storey type, an applicator could use a maximum of roughly 2900 to 5800 wafers of Thymovar over an eight-hour shift per day. In Canada, commercial beekeepers in the Prairies maintain 500 to 13,000 hives per beekeeper with an average of 2,000 hives whereas those in the eastern Canada and British Columbia, commercial beekeepers operate 50 to 5,000 hives with an average of 600 hives (Canadian Honey Council, 2010). It is expected that most apiaries will have more than one applicator working during the varroa mite treatment season. Assuming a single applicator is required to treat an apiary of 13,000 hives (a maximum use scenario), the maximum number of wafers that an applicator may use will be approximately 52,000 for the entire treatment season (two applications), if all are double-storey hives. In turn, it may take two to four weeks for one operator or one to two weeks for two operators to complete each application, a duration that can be much shorter if more operators are involved in product application.

Applicators of Thymovar may be exposed to thymol by dermal and inhalation routes. Due to thymol's corrosive nature, potential for skin sensitization and repeated dermal exposure scenario, there are toxicological concerns from its dermal exposure. Therefore, the label will instruct applicators to wear chemically resistant gloves and protective clothing during handling and application of Thymovar in order to mitigate any potential risk relating to dermal exposure.

Thymol is a known respiratory irritant. Based on the proposed use scenario, applicators could be expected to experience respiratory irritation from exposure to high localized concentrations of thymol vapour, when Thymovar is first taken out of the packaging (sachets). Thymol has a very pungent odour which serves as a warning sign to those working with it to avoid taking a deep breath and avoid prolonged exposures when thymol concentrations are potentially high. In light of the repeated exposure scenario for using Thymovar, the label will advise applicators to "Avoid inhaling the vapour" and "Handle Thymovar in a well-ventilated area" in order to mitigate unnecessary risk due to inhalation exposure.

Moreover, thymol vapour is known to be corrosive to the eyes and is extremely irritating. As a mitigative measure, the product label will instruct applicators to wear safety goggles or a face shield while handling Thymovar wafers to minimize eye exposure to the vapour.

Finally, post application exposure is expected to be minimal as it only involves the removal of used Thymovar wafers from beehives for disposal. Because the thymol concentration in used or spent wafers will be significantly lower at three to four weeks post application, post-application exposure is expected to be minimal and not of concern.

3.3.2 Bystander

As Thymovar is a Commercial class product that requires direct application inside beehives, bystander exposure is expected to be negligible and therefore not of concern.

3.4 Dietary Exposure and Risk Assessment

3.4.1 Food

Thymol (CAS #89-83-8), an alkyl derivative of phenol, is found in essential oils of many plants, particularly in thyme (*Thymus vulgaris* and *Thymbra spicata*). It has a characteristic phenol-like, aromatic odour with a sweet, medicinal, spicy flavour. The taste threshold for thymol is reported to be between 1.1 and 1.3 mg/kg (ppm) in honey. Studies have shown that the general consumer can distinguish the "medicinal" taste of thymol once the residue level of thymol in honey exceeds the taste threshold.

In lime blossom honey, thymol is a natural component occurring at a measured value of 0.16 mg/kg. Synthetic thymol is used as a flavouring and food additive. The reported inclusion limits for thymol in foods are outlined in the table below according to the Flavour and Extract Manufacturers Associations.

Food Category	Usual (ppm)	Max (ppm)
Alcoholic beverages	2.13	5.78
Baked goods	17.35	23.24
Frozen Dairy	10.70	14.94
Gelatins, puddings	15.62	19.38
Hard candy	78.05	78.05
Nonalcoholic beverages	3.79	5.94
Soft candy	10.71	15.68

As demonstrated in a Canadian field study using Thymovar as a fall treatment, the thymol residue level was found to be 0.009 ppm in honey. Based on available information, the reported levels of thymol residues in honey ranged from 0.009 to 0.600 ppm when honey samples were measured after recommended and modified treatments.

In addition, as illustrated in a Thymovar study conducted in the Netherlands, even when Thymovar was applied immediately before honey flow, which represents a worst case scenario for potential residue exposure, the thymol residue did not exceed the taste threshold of 1.1 to 1.3 ppm honey. The measured thymol residue level in honey derived from treated hives had an average of 0.384 ppm (0.270 to 0.600 ppm) whereas that from the control hives had an average of 0.036 ppm (0.02 to 0.06 ppm). Therefore, in order to limit the thymol residue at a minimum level, the Thymovar product label requires the removal of all honey supers during treatment.

Furthermore, according to another Thymovar residue study conducted in Switzerland, thymol residue in honey is not expected to accumulate or increase over time when Thymovar is used according to label instructions. This finding was based upon analysis of honey samples collected from a residue study which monitored Thymovar treatment in Swiss hives between August 1998 and 2002. The highest thymol residue value reported from the long-term study was 0.26 ppm, which is well below the taste threshold of 1.1 to 1.3 ppm for thymol in honey. Similar findings were also reported by a residue trial conducted in Switzerland on Apilife Var, a product comparable to Thymovar with respect to formulation and thymol content. The highest concentration of thymol residue in honey was reported to be 0.48 ppm from treated hives.

With respect to thymol residues in beeswax, the residues in wax could be much higher compared to those found in honey because of the lipophilic properties of thymol. As reported in the residue study for Apilife Var, approximately 500 ppm of thymol was found in the wax of brood combs and approximately 22 ppm of thymol was found in the wax of honey combs over years of repeated thymol application. To minimize the level of thymol residues where it could alter the natural sweetness of honey, the label instructs beekeepers to not extract honey from combs of the brood chambers in the following spring. In Canada, comb honey is defined by the Canadian Food Inspection Agency as honey stored by bees in cells of freshly built broodless combs, which is sold in sealed whole comb or sections of comb. The edible combs in this marketed product are likely from the hive supers and not potentially treated brood combs which are of poorer visual quality and more likely to contain substances to off-flavour the honey.

3.4.2 Drinking Water

The application of Thymovar to beehives should not result in exposure to sources of drinking water. Therefore, the use of thymol is not expected to result in a dietary risk from drinking water.

3.4.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

When used according to label directions, Thymovar is not expected to result in thymol residues at concentrations of toxicological concern and the potential levels are well below that found in foods and beverages. Additionally, thymol residues from Thymovar use are not expected to result in environmental residues of any kind. Currently, there are no other registered pesticidal uses of thymol. Exposure of the general population and potentially sensitive subpopulations, including infants and children, to thymol residues above levels found naturally in lime blossom honey and in other foods is not expected to occur as a result of the proposed use of Thymovar.

3.5 Maximum Residue Limits (MRL)

Thymol is present naturally in a number of plants and in lime blossom honey. Its presence and levels in honey depends and varies with the floral sources that the honey bees visit. To distinguish between thymol levels in honey attributed to endogenous versus treatment sources is not feasible. Residue data derived from studies conducted in Canada and in Europe have demonstrated that the residue levels in honey from Thymovar treatment are expected to be well below the thymol concentrations found in foods and beverages. In addition, based on published studies in rats and in humans, thymol is readily metabolized and eliminated by the gastrointestinal tract.

Moreover, the establishment of a tolerance concentration of 0.8 ppm in honey in Switzerland was to prevent potential thymol residues from exceeding concentrations which could alter the original sweet taste of honey. In the EU, Thymol is considered to be a non-toxic veterinary drug and is listed in Annex II of Council Regulation (EEC) No. 2377/90; in turn, it does not require an MRL. The USEPA exempted thymol from the requirement of a tolerance for residues on honey, honey comb and honeycomb with honey, when it is used as a treatment to control varroa mites in honey bees. Recently, a review by the Joint Expert Committee on Food Additives on thymol concluded that thymol's use is acceptable and supports the designation of thymol as a "generally regarded as safe" substance for use in bees.

Furthermore, the low taste threshold of 1.1 to 1.3 ppm for thymol will likely reduce consumption of honey with higher residue levels because of its medicinal taste. This in turn will limit the potential dietary exposure to honey with thymol residues exceeding the taste threshold. Therefore, in light of the aforementioned, the establishment of an MRL will not be required for thymol and the use of Thymovar (containing thymol) to control varroa mites in beehives is not expected to result in unacceptable dietary risks when the product is used according to label instructions.

3.6 Aggregate Exposure

The potential for dietary exposure of the general public to thymol residues resulting from its use in beehives for the control of varroa mites is not expected to be of concern, considering the background levels found in foods of other sources. Exposure via drinking water is not expected to occur from this use because use in beehives is not expected to result in environmental residues of any sort. Non-occupational (i.e., residential) exposure is not expected to occur as a result of this use because there are no residential or any other pesticide uses registered for thymol.

The general public is exposed to thymol by virtue of its natural occurrence in lime blossom honey and other foods. Given that no appreciable increase in dietary or residential exposure relative to background levels is expected to occur from this use, there is no unacceptable risk of harm expected from aggregate exposure to thymol residues.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Thymol is a natural occurring substance in many plant species and is rapidly degraded upon entry into the environment. Additionally, the substance is only to be applied in closed beehives. The major fraction of the product Thymovar is the essential oil thymol, which will evaporate. The proposed use pattern of thymol is not expected to contribute substantially to the exposure of the aquatic and terrestrial compartments. The use of Thymovar will not alter the concentration and distribution of thymol in the environment. Used product containing the remaining amount of active ingredient can be disposed of in the household waste stream, which will minimize the spread of the active ingredient into the environment.

4.2 Risk characterization

Based on limited exposure, the chemical's natural occurrence and the likelihood for relatively rapid transformation under environmental conditions, the proposed use of thymol is not expected to pose a significant risk to the environment. Therefore, further review of the environmental chemistry, fate, and toxicology of thymol was not required.

5.0 Value

5.1 Effectiveness Against Pests

A total of 18 studies and foreign reviews were reviewed in support Thymovar. These studies were from various locations, including Quebec, Switzerland, Portugal, Turkey, Italy, Germany, Greece, and the Netherlands. Most studies found that Thymovar provided control of varroa mite in excess of 90% when applied according to label directions, with no significant adverse effects. The information and data reviewed for Thymovar support a claim that it provides control of varroa mite in honeybee hives with 2 consecutive applications of ½ a wafer in nucleus hives, 1 wafer in one storey hives, or 2 wafers in 2 storey hives. Thymovar applications are left in the

hive for 3-4 weeks, and must only be made when temperatures are above 12°C and below 30°. A follow-up treatment of a non-thymol based product, such as oxalic acid, may be applied if monitoring indicates treatment is necessary. No significant adverse effects are expected provided that the Thymovar wafers are not placed directly over brood and temperatures do not exceed 30°C.

5.1.1 Acceptable Efficacy Claims

Control of varroa mite (*Varroa destructor*) in honeybee hives with 2 consecutive applications of ½ a wafer in nucleus hives, 1 wafer in 1 storey hives, or 2 wafers in 2 storey hives has been demonstrated. Thymovar applications are left in the hive for 3-4 weeks. Applications are made when temperatures are above 12°C and below 30°C.

5.2 Sustainability

5.2.1 Survey of Alternatives

Alternative active ingredients for control of varroa mite in honeybee hives include formic acid, oxalic acid, coumaphos, and fluvalinate-tau.

5.2.2 Compatibility with Current Management Practices Including Integrated Pest Management

Use of Thymovar is compatible with current integrated pest management practices for varroa mites in honeybee hives.

5.2.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

While varroa mites have developed resistance to some available control products, there are no published reports of resistance to thymol. Due to its complex mode of action, varroa mites are not likely to develop resistance to thymol.

5.2.4 Contribution to Risk Reduction and Sustainability

Thymovar has the potential to contribute to sustainable management of varroa mites in honey bee colonies, as it is a new mode of action for control of this pest and varroa mites are unlikely to develop resistance to thymol.

6.0 Pest Control Product Policy Considerations

6.1 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 [those that meet all four criteria outlined in the policy, i.e., persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, thymol 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 following conclusions:

- Thymol does not meet the Track 1 criteria and will not form any transformation products which meet the Track 1 criteria. Thymol is a naturally occurring substance and is not expected to be persistent or bioaccumulative in the environment.

6.2 Formulants and Contaminants of Health or Environmental Concern

Thymol E_9509758 and the end-use product Thymovar do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02[6].

7.0 Summary

7.1 Human Health and Safety

Metabolism studies in rats and in humans showed that thymol is readily absorbed in the gastrointestinal tract.

The available toxicological information on thymol is of sufficient quality to identify the majority of toxic effects that could result from exposure to the active ingredient. Thymol is corrosive and extremely irritating to the eyes and skin, and its vapour is a known respiratory irritant. It has also been identified as a potential skin sensitizer. It is of moderate acute oral toxicity and slight acute dermal toxicity. Available short-term toxicity data were limited to only one non-guideline study, which did not report any effects on animal growth or hematological and histologic parameters at sublethal dietary doses. No chronic toxicity studies were submitted or found in the published scientific literature, but given the long history of use of thymol as a food additive and an active

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

[6] DIR2006-02, PMRA Formulants Policy.

ingredient in a wide variety of pharmaceutical, cosmetic and disinfectant products, there is no evidence to suggest that thymol is carcinogenic, genotoxic, neurotoxic, or a developmental/reproductive toxicant.

Pesticide applicators can come into direct contact with thymol when handling and applying Thymovar to beehives. Potential exposure routes include direct contact with the skin and indirect contact of thymol vapour with the eyes and lungs. Although thymol is known for its corrosive and irritating properties, the product label contains a number of mitigative measures to limit potential exposure to the applicators.

The establishment of an MRL was not required for thymol, as the increase in residues in honey from pesticidal applications to beehives is expected to be negligible compared to levels found in foods and beverages.

7.2 Environmental Risk

Based on limited exposure, the chemical's natural occurrence and the likelihood for relatively rapid transformation under environmental conditions, the proposed use of thymol is not expected to pose a significant risk to the environment.

7.3 Value

Thymovar provides control of varroa mite in honeybee hives with 2 consecutive applications of ½ a wafer in nucleus hives, 1 wafer in one storey hives, or 2 wafers in 2 storey hives. Thymovar applications are left in the hive for 3-4 weeks, and must only be made when temperatures are above 12°C and below 30°. No significant adverse effects are expected provided that the Thymovar wafers are not placed directly over brood and outside temperatures do not exceed 30°C.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Thymol E_9509758 and Thymovar, containing the technical grade active ingredient thymol, to control Varroa mites (*Varroa destructor*) in honey bee (*Apis mellifera*) hives.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	microgram(s)
bw	body weight
CAS	Chemical Abstracts Service
cm	centimetre(s)
EEC	estimated environmental exposure concentration
EP	end-use product
F	female
g	gram(s)
h	hour(s)
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{ow}	*n*-octanol-water partition coefficient
LD_{50}	lethal dose 50%
M	male
mg	milligram(s)
mL	millilitre(s)
mmol	millimole
MRL	maximum residue limit
nm	nanometre(s)
N/A	not applicable
PCPA	*Pest Control Product Act*
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency

Appendix I Tables and Figures

Table 1 Acute Toxicity of Thymol E_9509758 and Its Associated End-use Product (Thymovar)

Study Type	Species	Result	Comment	Reference
Acute Toxicity of Thymol E_9509758				
Oral	Mice	LD_{50} = 640 mg/kg bw	Moderately acute toxicity	1690185 1890186 1894311
Dermal	Mice and Rats	LD_{50} ranges between 1049 mg/kg bw in mice and 2000 mg/kg bw in rats	Slightly acute toxicity	1690185 1894312
Inhalation	Based on known clinical use of thymol in humans.		Low toxicity	1894312
Skin irritation	Thymol is known for its corrosiveness based on published literatures.		Extremely irritating	1690185 1894312 1894320
Eye irritation			Extremely irritating	
Skin sensitization	Based on published studies, thymol is a known sensitizer.		Potential skin sensitizer	1894312 1902319 1902320 1902321
Acute Toxicity of End-Use Product – Thymovar				
Oral	Mice	LD_{50} = 640 mg/kg bw	Moderately acute toxicity	1690185 1890186 1894311
Dermal	Mice and Rats	LD_{50} ranges between 1049 mg/kg bw in mice and 2000 mg/kg bw in rats	Slightly acute toxicity	1690185 1894312 1894320
Inhalation	Based on known clinical use of thymol in humans.		Low toxicity	1894312
Skin irritation	Thymol is known for its corrosiveness based on published literatures.		Extremely irritating	1690185 1894312
Eye irritation			Extremely irritating	
Skin sensitization	Based on published studies, thymol is a known sensitizer.		Potential skin sensitizer	1894312 1902319 1902320 1902321

Table 2 Short-term and Chronic Toxicity Profile of Thymol E_9509758

Study Type	Species	Results (mg/kg/day in M/F)	Reference
Short-term oral toxicity	The request to waive this data requirement was accepted based on available published information.		1690185 1690197 1690202 1894311 1894312
Prenatal developmental toxicity	The request to waive this data requirement was accepted based on available published information.		
Reverse gene mutation assay	The request to waive this data requirement was accepted based on available published information.		
Gene mutations in mammalian cells in vitro	The request to waive this data requirement was accepted based on available published information.		

Table 3 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Proposed label claim	VSAD supported use claim
Control of varroa mites in honeybee hives with 2 consecutive applications of ½ a wafer in nucleus hives, 1 wafer in one storey hives, and 2 wafers in 2 storey hives. Applications are left in the hive for 3-4 weeks, and are applied when temperatures are above 12°C and below 30°C.	Accepted as proposed

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Number	Reference
1690166	2008, Technical Data Sheet, DACO: 1.1.1, 2.2, and 2.3
1690168	2008, Thymol Technical PMRA Dossier 2008, DACO: 2.1 **CBI**
1690169	2001, Flow Chart of the synthesis of Thymol Mane, DACO: 2.11, 2.11.1 C**BI**
1690171	2001, Flow chart of the synthesis of Thymol, DACO: 2.11.3 **CBI**
1690172	2003, Analysis Certificate of Thymol, DACO: 2.11.4, 2.12.1 **CBI**
1690176	Thymol, DACO: 2.13.2 **CBI**
1690178	2006, Batch Analysis by Mane fils, DACO: 2.13.3 **CBI**
1776602	Chromatophic analysis of vaporised Thymol, DACO: 2.13.1 **CBI**
1776603	Analysys certificate, DACO: 2.13.2 **CBI**
1778938	Chromatophic analysis of vaporised Thymol, DACO: 2.13.1 **CBI**
1690476	Flow Chart of in process control of the manufacturing process, DACO: 3.2.1 **CBI**
1690482	3.2.2 Description of the Formulation Process, DACO: 3.2.2 **CBI**
1690483	2005, GMP Certificate, DACO: 3.2.2 **CBI**
1690488	Validation Report on the Determination of Thymol in Foam Sheets, DACO: 3.4.1 **CBI**
1690490	METHOD OF ANALYSIS Determination of Thymol, DACO: 3.4.1 **CBI**
1690506	Storage Stability Tables, DACO: 3.5.10 **CBI**

2.0 Human and Animal Health

PMRA Number	Reference
1690165	Material Safety Data Sheet – Thymol, DACO 0.9, 2.14.1, 2.14.14, 2.14.3, 2.14.6, 2.15
1690168	Registration summary for Thymol technical, DACO 2.1
1690185	Toxicological evaluation – Thymol (No. 259), BG Chemie, 2000, DACO 4.1, 4.2, 4.2.2, 4.2.5, 4.2.6, 4.2.7, 4.8
1690186	2000, IUCLID Datasheet, authored by the European commission, European Chemicals Bureau, February 19, 2000, DACO 4.1
1690187	1996, EMEA summary report - thymol, EMEA/MRL/075/96-Final, March 1996, DACO 4.1
1690191	Kohlert et al., 2002, Systemic availability and pharmacokinetics of thymol in humans, J. Clin Pharmacol. 42: 731-737, DACO 4.2.9

PMRA Number	Reference
1690192	Verrett *et al.*, 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo, Toxicology and applied pharmacology 56: 265-273, DACO 4.2.9
1690194	Bogdanov *et al*., 1998, Residues in wax and honey after Apilife Var treatment, Apidologie 29: 513-524, DACO 6.4
1690197	Part I C 3.2 Expert report on safety and residues –Thymovar, DACO 6.4
1690202	Part III, Safety and Residue documentation – Thymovar, DACO M12.5.8, M12.5.9, M12.7
1690437	Material Safety Data Sheet – Thymovar, DACO 0.9
1690444	Final efficacy study report – Canadian field study
1690452	Part IV, Efficacy documentation, DACO 10.3.1
1690462	Part I C3.1, Expert report on the Chemical, pharmaceutical and biological documentation of Thymovar, DACO 12.5.3
1690463	Part I C3.4, Summary on the ecotoxicity and consumer safety of Thymovar, DACO 12.5.3, 12.5.4, 12.5.5, 12.5.8, 12.5.9
1690516	2004, Residue analysis in honey after a spring treatment with Thymovar and formic acid, Applied Plant Research (The Netherlands), DACO 7.8
1690519	2004, Residues in honey after Thymovar treatments, Internal Andermatt BioVet AG report, DACO 7.8
1737615	Draft label for Thymovar, DACO 1.2.1
1776602	GC Chromatographic analyses of N-thymol, DACO 2.13.1
1896101	Response to e-mail clarification request, DACO 5.2

3.0 Value

1690444	2008, Évaluation de l'efficacité de trois traitements en fin d'été combinés a un traitement automnal a l'aide d'acide oxalique en novembre contre *Varroa destructor* dans ruchers en Montérégie, DACO: 10.2.3
1690447	2004, Projets de recherche sur la lutte intégrée contre le parasite Varroa destructor dans les ruchers du Québec, DACO: 10.2.3.2
1690448	Imdorf, A., V. Kilchenmann, C. Maquelin and S. Bogdanov. 1994. Optimisation of the application of Apilife Var for the control of *Varroa* jacobsoni Oud in bee colonies, Apidologie 25: 49-60. DACO: 10.2.3.2
1690449	Thymovar for the control of *Varroa jacobsoni*, DACO: 10.2.3.2
1690452	2006, Andermatt Biocontrol, DACO: 10.3.1
1690453	Use of Different Formulated (*sic*) with thymol for summer treatment antivarroa (*sic*) in a Mediterranean Environment, DACO: 10.3.2
1690454	Bogdanov, S., A. Imdorf and V. Kilchenmann. 1998. Residues in wax after Apilife Var treatment. Apidologie 29: 513-524. DACO: 10.3.2
1690455	Expert Report Part IV, DACO: 10.3.2

1690456 Imdorf, A., V. Kilchenmann, S. Bogdanov, B. Bachofen and C. Beretta. 1995. Toxicity of Thymol. Camphor, Menthol and Eucalyptol on *Varroa jacobsoni* Oud and *Apis mellifera* L. in a laboratory test, Apidologie 26: 27-31. DACO: 10.5.1

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1690459 2005, Summer treatment against the Varroosis with preparations of thymol, DACO: 10.5.1

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1732080 Valuation de l'efficacité de 3 traitements *Varroa destructor*, DACO: 10.2.3.3

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

PMRA Number	Reference
1894294	Dr. E. Guzman, Research project SR9172 – Pathogen's resistance to current chemical treatments, novel control agents, and chemical residues in honey of Ontario's honey bee colonies, University of Guelph, DACO 7.8
1894295	Bogdanov, et al., 1999, Influence of organic acids and components of essential oils on honey taste, Swiss Bee Research Centre, DACO 7.8
1894296	2009, Joint FAO/WHO Expert committee on food additives (JECFA), Seventieth meeting (residue of veterinary drugs) held on October 21-29, 2008, Summary and Conclusions – Corrected, published on March 10, 2009, DACO 7.8
1894299	Lazaro et al., 2005, Evaluation of residues of essential oil components in honey after different anti-varroa treatments, Journal of Agric. Food Chem. 53: 10085-10090, DACO 7.8
1894300	2000, Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives, DACO 7.8
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1894312	U.S. EPA Registration Action Document for Thymol (PC code 080402), DACO 4.8

PMRA Number	Reference
1894314	Jenner et al., 1964, Food flavourings and compounds of related structure, I. Acute oral toxicity, Fd Cosmet. Toxicol. 2: 327-343, DACO 4.2.1
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1894319	Stammati et al., 1999, Toxicity of selected plant volatiles in microbial and mammalian short-term assays, Food and Chemical Toxicology 37: 813-823, DACO 4.8
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1894322	E. Rencuzogullari, 2009, The effects of thymol on sister chromatid exchange, chromosome aberration and micronucleus in human lymphocytes, Ecotoxicology and environmental safety 72: 943-947, DACO 4.8
1894323	Rencuzogullari et al., 2008, The *in vivo* genotoxic effects of carvacrol and thymol in rat bone marrow cells, Environmental Toxicology 728-735, DACO 4.8
1894325	N. Basaran et al., 2009, Antioxidant activities of major thyme ingredients and lack of (oxidative) DNA damage in V79 Chinese hamster lung fibroblast cells at low levels of carvacrol and thymol, Food and chemical toxicology 47: 2037-2043, DACO 4.8
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1902318	Susan D. Shaw and Monona Rossol, 1991, Overexposure, Health Hazards in Photography, DACO 4.8
1902319	Robert L. Rietschel, Joseph F. Fowler, Alexander A. Fisher, 2008,
1902320	Fisher's Contact Dermatitis, DACO 4.8
1902321	

2.0 Value

PMRA Number	Reference
1902050	2004, First European Conference of Apidology, Out of control? *Varroa destructor* in Europe, DACO: 10.6
1902052	CONTROLLO DELLA VARROA CON TIMOLO, Studio comparativo su sei formulati contenenti timolo nel controllo di *Varroa destructor* (Anderson & Trueman) in Grecia, DACO: 10.6

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