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Proposed Registration Decision

PRD2020-12

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

(publié aussi en français)

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

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

Canada 

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Overview

Proposed Registration Decision for 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 acceptable¹ if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value² when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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

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 Decision⁴ 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.

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

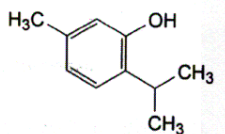
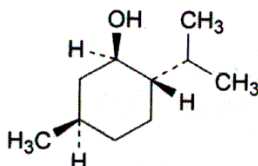
1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

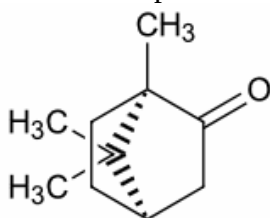
Active substances	Thymol Eucalyptus oil Racemic camphor <i>l</i> -Menthol
Function	Acaricides
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	Thymol: 5-Methyl-2-(propan-2-yl)phenol <i>l</i> -menthol: (1R,2S,5R)-2-isopropyl-5-methylcyclohexanol Racemic camphor: (1R,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one or (±)-bornan-2-one or <i>rac</i> -(1R,4R)-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 <i>l</i> -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 <i>l</i> -menthol (CAS # 2216-51-5)

Molecular formula

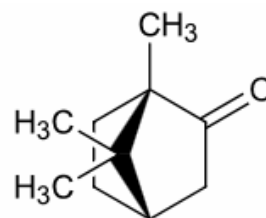
Thymol:

*l*-Menthol:

Racemic camphor



and



Eucalyptus oil: N/A

Molecular weight

Thymol : 150.22

l-Menthol: 156.27

Racemic camphor: 152.24

Eucalyptus oil : N/A

Structural formulaThymol : C₁₀H₁₄O*l*-Menthol: : C₁₀H₂₀ORacemic camphor : C₁₀H₁₆O

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 <i>l</i> -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 °C and 60% relative humidity. It was also stable after 12-month storage at 30 °C and 65% relative humidity.
Corrosion characteristics	No effects were observed on the bag after 24-month storage at 25 °C and 60% relative humidity.
Explosibility	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 (LD₅₀ 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 DIR99-03⁵ 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 NOI2005-01⁷ 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.

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

⁶ SI/2005-114

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

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

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

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2864945	2014, (Product chemistry document & manufacturing process) Api Life-Var Chemical, Pharmaceutical And Biological Documentation Of Api Life Var Part II 10-2014, DACO: 2.0, 2.1, 2.11.1, 2.11.2, 2.11.3, 2.12, 2.13, 2.13.1, 2.13.2, 2.13.3, 2.13.4, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.1.1, 3.1.2, 3.1.3, 3.2, 3.2.1, 3.2.2, 3.3.1, 3.4, 3.5 CBI
2891133	2018, DACO 3 overview and waiver requests, DACO: 3.1, 3.1.1, 3.1.2, 3.1.3, 3.1.4, 3.2, 3.2.1, 3.2.2, 3.3.1, 3.4.1, 3.5.10, 3.5.11, 3.5.12, 3.5.13, 3.5.14, 3.5.15, 3.5.2, 3.5.4, 3.5.5, 3.5.6, 3.5.7, 3.5.8, 3.5.9
2891148	2009, Certificate of Analysis - Thymol, DACO: 2.12,2.13,2.14,2.16,3.5,3.7
2891149	2009, Certificate of Analysis - Thymol, DACO: 2.12,2.13,2.14,2.16,3.5,3.7
2938850	2018, Food Chemicals Codex compliance - Certificate of Analysis - Camphor, DACO: 2.13 CBI
2938851	2018, Food Chemicals Codex compliance - Certificate of Analysis - Thymol, DACO: 2.13
2938852	2018, Food Chemicals Codex compliance - Certificate of Analysis - Menthol, DACO: 2.13
2938853	2018, Food Chemicals Codex compliance - Certificate of Analysis - Eucalyptus Oil, DACO: 2.13
2938854	2018, Food Chemicals Codex compliance - Certificate of Analysis - Camphor (additional data), DACO: 2.13
2938855	2018, Food Chemicals Codex compliance - Certificate of Analysis - Thymol (additional data), DACO: 2.13
2938856	2018, Food Chemicals Codex compliance - Certificate of Analysis - Menthol (additional data), DACO: 2.13

2.0 Human and Animal Health

PMRA Document Number	Reference
2864937	2018, Api Life VAR DACO overview EP and TGAI, DACO: 10.1,2.0,3.0,4.1
2864946	2007, Toxicology - detailed report - Api Life Var Part IIIA+CV+Expert Report 09-11-07, DACO: 4.1,4.2,4.5.2,4.5.4,4.5.5,4.6.1,4.6.2,4.6.3,4.6.5,4.6.6
2864947	2007, Report on Residue in Honey - Api Life Var Part IIIB, DACO: 4.8

- 2864956 2016, DACO walkthrough for tox and rationale for tox data waiver – camphor technical, DACO: 4.1, 4.2.1, 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.2.6, 4.2.9, 4.3.1, 4.3.8, 4.4.2, 4.5.2, 4.5.3, 4.5.4, 4.5.5, 4.5.6, 4.5.7, 4.5.8
- 2864957 European Chemicals Agency, 2016, ECHA summary - Shika Gakuho 1975, DACO: 4.2.1
- 2864958 Siegel E, Wason S, 1986, Camphor toxicity (Pediatric Clinics of North America 33(2): 375-379), DACO: 4.2.1
- 2864959 European Chemicals Agency, 2016, ECHA summary - Unnamed 2003(a), DACO: 4.2.1
- 2864960 Wickstrom E, National Poison Center, 1988, Camphor (PIM 095), DACO: 12.5.4,4.2.1,4.5.3
- 2864961 European Chemicals Agency, 2016, ECHA summary - Unnamed 2003(c), DACO: 4.2.2
- 2864963 European Chemicals Agency, 2016, ECHA summary - Unnamed 2003(b), DACO: 4.2.3
- 2864964 European Chemicals Agency, 2016, ECHA summary - Volkova et al 1998, DACO: 4.2.3
- 2864965 International Programme on Chemical Safety / Chemical Safety and the European Commission, 2003, Camphor ICSC: 1021, DACO: 4.2.3,4.2.4,4.2.5
- 2864966 European Chemicals Agency, 2016, ECHA summary - Unnamed 2003(e), DACO: 4.2.4
- 2864967 European Chemicals Agency, 2016, ECHA summary - QSAR toolbox v.3.0 2012(a), DACO: 4.2.4
- 2864968 European Chemicals Agency, 2016, ECHA summary - Toolbox v.3.0 2012, DACO: 4.2.5
- 2864969 European Chemicals Agency, 2016, ECHA summary - Unnamed 2003(d), DACO: 4.2.5
- 2864970 European Chemicals Agency, 2016, ECHA summary - QSAR toolbox v.3.0 2012(b), DACO: 4.2.6
- 2864971 European Chemicals Agency, 2016, ECHA summary - Unnamed 2003(j), DACO: 4.2.6
- 2864972 European Chemicals Agency, 2016, ECHA summary - Unnamed 2003(f), DACO: 4.3.1
- 2864973 European Chemicals Agency, 2016, ECHA summary - Unnamed 1998(a), DACO: 4.3.4
- 2864974 European Chemicals Agency, 2016, ECHA summary - Unnamed 1998(b), DACO: 4.3.4
- 2864975 European Chemicals Agency, 2016, ECHA summary - Unnamed 2003(g), DACO: 4.3.7,4.3.8
- 2864976 Cherneva E, Pavlovic V, Smelcerovic A, Yancheva D, 2012, The Effect of Camphor and Borneol on Rat Thymocyte Viability and Oxidative Stress, DACO: 4.3.8
- 2864977 LeuschnerJ, 1997, Reproductive toxicity studies of *d*-camphor in rats and rabbits (Arzneimittel-Forschung 47(2):124-128), DACO: 4.5.2,4.5.3
- 2864978 European Chemicals Agency, 2016, ECHA summary - Unnamed 1992(a), DACO: 4.5.2

- 2864979 Weiss J, Catalano P, 1973, Camphorated oil intoxication during pregnancy (Pediatrics 52(5):713-4), DACO: 4.5.3
- 2864980 European Chemicals Agency, 2016, ECHA summary - Unnamed 1992(b), DACO: 4.5.3
- 2864981 European Chemicals Agency, 2016, ECHA summary - Unnamed 1998(c), DACO: 4.5.4
- 2864982 European Chemicals Agency, 2016, ECHA summary - Unnamed 2003(h), DACO: 4.5.4
- 2864983 European Chemicals Agency, 2016, ECHA summary - Unnamed 2013, DACO: 4.5.5
- 2864984 European Chemicals Agency, 2016, ECHA summary - Unnamed 1999, DACO: 4.5.7
- 2864985 European Chemicals Agency, 2016, ECHA summary - Unnamed 2003i, DACO: 4.5.7
- 2864986 Center for Disease Control and Prevention (CDC), 1994, Camphor (synthetic), DACO: 12.5.4,4.2.3
- 2864987 McCrea S, National Poisons Information Service (London Centre), 1996, Monograph for UKPID: Camphor, DACO: 12.5.4,4.3.1,4.5.3,4.5.6,4.8
- 2864988 European Chemicals Agency (website: <https://echa.europa.eu>), 2016, Toxicological Summary - Bornan-2-one, DACO: 12.5.4,4.1
- 2864989 Committee for Veterinary Medicinal Products, Veterinary Medicines Evaluation Unit, The European Agency for the Evaluation of Medicinal Products, 1999, Camphora (use in veterinary homeopathy) summary report, DACO: 12.5.4,4.2.1,4.3.1
- 2864990 RTECS - Registry of Toxic Effects of Substances, 2003, Camphor, DACO: 12.5.4,4.5.6,4.8
- 2864992 TOXNET database - US National Library of Medicine <https://toxnet.nlm.nih.gov>, 2016, Camphor CASRN: 76-22-2, DACO: 4.2.1,4.2.3,4.2.4,4.2.5,4.2.9,4.3.3,4.3.8,4.4.2,4.5.2,4.5.3,4.5.4,4.5.6,4.8
- 2864993 2016, DACO walkthrough for tox and rationale for tox data waiver - Eucalyptus oil technical, DACO: 4.1, 4.2.1, 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.2.6, 4.2.9, 4.3.1, 4.3.8, 4.4.2, 4.5.2, 4.5.3, 4.5.4, 4.5.5, 4.5.6, 4.5.7, 4.5.8
- 2864995 Brownlee, George, 1940, A pharmacological examination of cineole and phellandrene (Q.J. Pharm. Pharmac. 13, 130-137), DACO: 4.2.1
- 2864997 European Chemicals Agency, 2016, ECHA summary - Ohsumi et al 1984, DACO: 4.2.1
- 2864998 Shalaby SE, El-Din MM, Abo-Donia SA, Mettwally M, Attia ZA, 2011, Toxicological effects of essential oils from Eucalyptus globules and Clove Eugenia caryophyllus on albino rats (Polish J Environ Stud.20:429-434), DACO: 4.2.1
- 2865000 European Chemicals Agency, 2016, ECHA summary - vonSkramlik 1959, DACO: 4.2.1
- 2865001 Jenner PM, Hagan EC, Taylor JM, Cook EL, Fitzhugh OG, 1964, Food Flavourings and compounds of related structure I. Acute oral toxicity (Fd. Cosmet. Toxicol. 2, 327-343), DACO: 4.2.1

- 2865003 Saeed MA, Sabir AW, 1998, Studies on the contact dermatitic properties of indigenous Pakistani medicinal plants. Dermal irritating properties of Eucalyptus oil constituents (Acta Pharmaceutica Turcica. 40: 21-25), DACO: 4.2.2
- 2865004 European Chemicals Agency, 2016, ECHA summary - Unnamed 1973(a), DACO: 4.2.2
- 2865005 European Chemicals Agency, 2016, ECHA summary - Unnamed 1973(b), DACO: 4.2.2
- 2865007 European Chemicals Agency, 2016, ECHA summary - Unnamed 1991(c), DACO: 4.2.2
- 2865008 European Chemicals Agency, 2016, ECHA summary - Unnamed 1991(d), DACO: 4.2.4
- 2865009 European Chemicals Agency, 2016, ECHA summary - Unnamed 2012(a), DACO: 4.2.4
- 2865010 European Chemicals Agency, 2016, ECHA summary - Unnamed 2013(f), DACO: 4.2.4
- 2865011 European Chemicals Agency, 2016, ECHA summary - Unnamed 2012(b), DACO: 4.2.5
- 2865013 Dharmagunawardena B, Takwale A, Sanders KJ, Cannan S, Rodger A and Ilchyshyn A, 2002, Gas Chromatography: An Investigative Tool in Multiple Allergies to Essential Oils (Contact Dermatitis. 47(5): 288-292), DACO: 4.2.6
- 2865015 Klecak G, 1985, The Freunds Complete Adjuvant Test and the Open Epicutaneous Test. A Complementary Test Procedure for Realistic Assessment of Allergenic Potential (Curr. Probl. Derm. 14: 152-171), DACO: 4.2.6
- 2865016 European Chemicals Agency, 2016, ECHA summary - Peltonen et al 1985, DACO: 4.2.6
- 2865017 European Chemicals Agency, 2016, ECHA summary - Unnamed 2013(g), DACO: 4.2.6
- 2865018 European Chemicals Agency, 2016, ECHA summary - Unnamed 2012(c), DACO: 4.3.1,4.3.8
- 2865019 European Chemicals Agency, 2016, ECHA summary - Unnamed 2013(h), DACO: 4.3.1,4.3.3,4.3.8
- 2865020 European Chemicals Agency, 2016, ECHA summary - Unnamed 2010, DACO: 4.3.1,4.3.8
- 2865021 European Chemicals Agency, 2016, ECHA summary - Unnamed 2013(a), DACO: 4.3.8
- 2865022 Sipes IG, 2004, WHO FOOD ADDITIVES SERIES: 52 Aliphatic and aromatic ethers, DACO: 12.5.4,4.2.1,4.3.8,4.4.2,4.5.2,4.8
- 2865023 Roe FJ, Field WE, 1965, Chronic toxicity of essential oils and certain other products of natural origin (Food and cosmetics toxicology 3:311-23), DACO: 4.4.2
- 2865024 Roe FJ, Palmer AK, Worden AN, Van Abb NJ., 1979, Safety evaluation of toothpaste containing chloroform: I. Long-term studies in mice, DACO: 4.4.2
- 2865025 European Chemicals Agency, 2016, ECHA summary - Unnamed 2002, DACO: 4.4.2
- 2865026 Jori A, Briatico G, 1973, Effect of eucalyptol on microsomal enzyme activity of foetal and newborn rats (Biochem Pharmacol 22(4):543-4), DACO: 4.5.2

- 2865027 European Chemicals Agency, 2016, ECHA summary - Unnamed 2013(b), DACO: 4.5.2
- 2865028 European Chemicals Agency, 2016, ECHA summary - Unnamed 2013(i), DACO: 4.5.2
- 2865029 World Health Organization, 2004, WHO Monographs on Selected Medicinal Plants Volume 2: Aetheroleum Eucalypti, DACO: 4.5.2
- 2865030 Gomes-Carneiro M, Felzenszwalb I, Paumgarten FJ., 1998, Mutagenicity testing (+/-)-camphor, 1,8-cineole, citral, citronellal, (-)-menthol and terpineol with the Salmonella/microsome assay (Mutation Research 416(1-2): 129-136), DACO: 4.5.4
- 2865032 Haworth S, Lawlor T, Mortelmans K, Speck W, Zeiger E, 1983, Salmonella Mutagenicity Test Results for 250 Chemicals (Environ Mutagen 5 Suppl 1:1-142), DACO: 4.5.4
- 2865033 European Chemicals Agency, 2016, ECHA summary - Unnamed 1991(a), DACO: 4.5.4
- 2865034 European Chemicals Agency, 2016, ECHA summary - Unnamed 1998, DACO: 4.5.4
- 2865035 European Chemicals Agency, 2016, ECHA summary - Unnamed 2013(d), DACO: 4.5.4
- 2865036 European Chemicals Agency, 2016, ECHA summary - Unnamed 2013(c), DACO: 4.5.5
- 2865037 European Chemicals Agency, 2016, ECHA summary - Unnamed 1993, DACO: 4.5.7
- 2865038 Galloway SM, Armstrong MJ, Reuben C, Colman S, Brown B, Cannon C, Bloom AD, Nakamura F, Ahmed M, Duk S, Rimpo J, 1987, Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals (Environ Mol Mutagen. 1987;10 Suppl 10:1-175., DACO: 4.5.6,4.8
- 2865039 Sasaki YF, Imanishi H, Ohta T, Shirasu Y, 1989, Modifying effects of components of plant essence on the induction of sister-chromatid exchanges in cultured Chinese hamster ovary cells (Mutat Res. 1989 Jun;226(2):103-10., DACO: 4.5.6,4.8
- 2865040 European Chemicals Agency, 2016, ECHA summary - Unnamed 1987(a), DACO: 4.5.6,4.8
- 2865041 European Chemicals Agency, 2016, ECHA summary - Unnamed 1987(b), DACO: 4.5.6,4.8
- 2865042 European Chemicals Agency, 2016, ECHA summary - Unnamed 2013(e), DACO: 4.5.6,4.8
- 2865043 Yoo YS, 1986, Mutagenic and antimutagenic activities of flavoring agents used in foodstuffs (Osaka City Med J 34(3-4):267-88), DACO: 4.5.8,4.8
- 2865044 European Chemicals Agency (website: <https://echa.europa.eu>), 2016, Cineole Toxicological Summary, DACO: 12.5.4,4.1
- 2865045 European Chemicals Agency (website: <https://echa.europa.eu>), 2016, Eucalyptus globulus, ext. Toxicological Summary, DACO: 12.5.4,4.1
- 2865046 James Magarey, 1997, Eucalyptus oil, International Programme on Chemical Safety, Poisons Information Monograph 031, Pharmaceutical, DACO: 12.5.4,4.2.3

- 2865047 Committee for Veterinary Medicinal Products, Veterinary Medicines Evaluation Unit, The European Agency for the Evaluation of Medicinal Products, 1998, *Eucalypti aetheroleum*: summary report, DACO: 12.5.4,4.5.2
- 2865048 Committee for Veterinary Medicinal Products, Veterinary Medicines Evaluation Unit, The European Agency for the Evaluation of Medicinal Products, 1999, *Eucalyptus globulus* (use in veterinary homeopathy) summary report, DACO: 12.5.4
- 2865049 TOXNET database - US National Library of Medicine <https://toxnet.nlm.nih.gov>, 2016, Cineole CASRN: 470-82-6, DACO: 12.5.4, 4.2.1, 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.3.1, 4.3.8, 4.5.2, 4.5.4, 4.5.6, 4.8
- 2865051 2016, DACO walkthrough for tox and rationale for tox data waiver - thymol technical, DACO: 12.5.4, 4.1, 4.2.1, 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.2.6, 4.2.9, 4.3.1, 4.3.8, 4.4.2, 4.5.2, 4.5.3, 4.5.4, 4.5.5, 4.5.6, 4.5.7, 4.5.8, 4.8
- 2865054 J. Bailenger, B. Amyot, 1967, Etude experimentale du pouvoir antihelminthique de nouveaux derives du diphenyl-methane (Therapie 22(2):285-296), DACO: 4.2.1
- 2865056 Hasegawa R , Nakaji Y , Kurokawa Y , Tobe M, 1989, Acute toxicity tests on 113 environmental chemicals (The Science Reports of the Research Institutes, Tohoku University. Ser. C, Medicine. Tohoku Daigaku [1989, 36(1-4):10-16]), DACO: 4.2.1
- 2865058 Izeki, Motohachi, 1956, Studies on antiseptics - In the toxicity of 3-Methyl-4-isopropylphenol (Osaka Shiritsu Daigaku Igaku Zasshi 5, p.111 -118), DACO: 4.2.1,4.2.9
- 2865063 Livingston AE, 2016, The comparative toxicity of thymol and carvacrol (isothymol) (Jour of Pharm and Exper Therap 17, 261-275), DACO: 4.2.1
- 2865066 W. A. McOmie, Hamilton H. Anderson, F. M. Estess, 1949, Comparative Toxicity of Certain t-Butyl Substituted Cresols and Xylenols (Journal of the American Pharmaceutical Association 38.7 (1949): 366-369), DACO: 4.2.1, 4.2.4,4.2.5
- 2865069 Oelkers HA, 1940, Ueber die Giftigkeit von Wurmmitteln in oeliger Loesung oder waessriger Emulsion (Muench Med Wschr 38, 1026-1028), DACO: 4.2.1
- 2865070 Cosmetic Ingredient Review (CIR) Expert Panel, 2006, Final Report on the Safety Assessment of Sodium *p*-Chloro-*m*-Cresol, *p*-Chloro-*m*-Cresol, Chlorothymol, Mixed Cresols, *m*-Cresol, *o*-Cresol, *p*-Cresol, Isopropyl Cresols, Thymol, *o*-Cymen-5-ol, and Carvacrol (International Journal of Toxicology, 25(Suppl. 1):29-127, 2006), DACO: 4.2.1,4.2.9,4.3.8,4.5.3,4.5.5
- 2865071 European Chemicals Agency, 2016, ECHA summary - Bomhard (Bayer AG) 1986, DACO: 4.2.2
- 2865072 Gerhard Buchbauer et al., 1993, Fragrance Compounds and Essential Oils with Sedative Effects upon Inhalation (Journal of Pharmaceutical Sciences Vol. 82, No. 6, June 1993), DACO: 4.2.3
- 2865073 U.S. Food and Drug Administration, 1997, Anada 200200 Halothane, USP original approval, DACO: 4.2.3
- 2865074 European Chemicals Agency, 2016, ECHA summary - Ruf (Bayer AG) 1986, DACO: 4.2.4
- 2865076 European Chemicals Agency, 2016, ECHA summary - Ruf (Bayer) 1986, DACO: 4.2.5

- 2865078 J. J. Hostynek and P. S. Magee, 1997, Fragrance allergens: Classification and ranking by QSAR (Toxicology in vitro 11.4 (1997): 377-384), DACO: 4.2.6
- 2865079 Berova N, Stransky L, Krasteva M, 1990, Studies on contact dermatitis in stomatological staff (Dermatol Monatsschr. 1990;176(1):15-18), DACO: 4.2.6
- 2865080 Ishihara M, Itoh M, Nishimura M, Kinoshita M, Kantoh H, Nogami T, Yamada K, 1986, Closed epicutaneous test, DACO: 4.2.6
- 2865083 G. Klecak , H. Geleick , J. R. Frey, 1977, Screening of fragrance materials for allergenicity in the guinea pig I. Comparison of four testing methods (J Soc Cosmet Chem 28, 53-64), DACO: 4.2.6
- 2865089 Wahlberg and Boman 1985, 1985, Guinea Pig Maximization Test (Curr Probl Dermatol 14, 59-106), DACO: 4.2.6
- 2865092 Roger James, John B. Glen, 1980, Synthesis, biological evaluation, and preliminary structure-activity considerations of a series of alkylphenols as intravenous anesthetic agents (J. Med. Chem., 1980, 23 (12), pp 1350-1357), DACO: 4.2.9
- 2865093 European Chemicals Agency, 2016, ECHA summary - Lewis 2000, DACO: 4.2.9
- 2865096 Verrett MJ, Scott WF, Reynaldo EF, Alterman EK, Thomas CA, 1980, Toxicity and Teratogenicity of Food Additive Chemicals in the Developing Chicken Embryo (Toxicology and applied pharmacology 56(2):265-73), DACO: 4.2.9,4.5.3
- 2865097 G. S. B. Viana, F. F. Matos, W. L. Araujo, F. J. A. Matos & A. A. Craveiro, 1981, Essential Oil of Lippia grata: Pharmacological Effects and Main Constituents (Quart J Drug Res 19(1), 1-10) , DACO: 4.2.9
- 2865098 European Chemicals Agency, 2016, ECHA summary - Caujolle and Franck 1948, DACO: 4.2.9
- 2865099 European Chemicals Agency, 2016, ECHA summary - Davis et al 1959, DACO: 4.2.9
- 2865101 European Chemicals Agency, 2016, ECHA summary - Izeki 1956(b), DACO: 4.2.9
- 2865103 Hagan EC, Hansen O, Fitzhug OG, Jenner PM, Jones WI, Taylor JM, Long EL, Nelson AA, Brouwer JB, 1967, Food Flavours and compounds of related structure. II. Subacute and Chronic Toxicity (Fd Cosmet Toxicol 5, 141-157), DACO: 4.3.1,4.4.5
- 2865106 Alexander Haselmeyer, Jurgen Zentek and Remigius Chizzola, 2014, Effects of thyme as a feed additive in broiler chickens on thymol in gut contents, blood plasma, liver and muscle, DACO: 4.3.8
- 2865107 European Chemicals Agency, 2016, ECHA summary - Hergt 1930, DACO: 4.3.8
- 2865109 Gary D. Stoner, Michael B. Shimkin, Alexis J. Kniazeff, John H. Weisburger, Elizabeth K. Weisburger, and Gio B. Gori, 1973, Test for Carcinogenicity of Food Additives and Chemotherapeutic Agents by the Pulmonary Tumor Response in Strain A Mice (Cancer Research 33, 3069-3085, December 1973), DACO: 4.3.8,4.4.2
- 2865110 R. K. Boutwell and Dorothy K. Bosch, 1959, The Tumor-promoting Action of Phenol and Related Compounds for Mouse Skin (Cancer Research 19:413-424), DACO: 4.4.2
- 2865111 European Chemicals Agency, 2016, ECHA summary - Boutwell and Bosch 1959, DACO: 4.4.2

- 2865113 Ikuo Matsuura (Study director), Yukari Taya, Minoru Tsuchitani, Yumi Wako, Naoto Toyota, Katsuyo Takano, 2016, Combined Repeat Dose and Reproductive/ Developmental Toxicity Screening Test of Thymol by Oral Administration in Rats, DACO: 4.5.2
- 2865114 European Chemicals , 2016, ECHA summary - Savignoni and Maria 1933, DACO: 4.5.2
- 2865115 European Chemicals Agency, 2016, ECHA summary - Unnamed 1996(e), DACO: 4.5.2
- 2865116 European Chemicals Agency, 2016, ECHA summary - Unnamed 1996(f), DACO: 4.5.2
- 2865121 Diether Neubert, Robert J. JKavlock, Hans-Joachim Merker, Jane Klein (eds), 1992, Risk Assessment of Prenatally-Induced Adverse Health Effects, DACO: 4.5.3
- 2865122 Skofitsch, G, 1989, From dog to egg? Large and small laboratory animals in: Scientific alternatives to animal experiments / editor, Fred Lembeck ; translator, Jacqui Welch ; translation editor, John Francis, DACO: 4.5.3
- 2865126 A. Azizan, R. D. Blevins, 1995, Mutagenicity and Antimutagenicity Testing of Six Chemicals Associated with the Pungent Properties of Specific Spices as Revealed by the Ames Salmonella/Microsomal Assay A. (Arch. Environ. Contain. Toxicol. 28,248-258), DACO: 4.5.4
- 2865127 Blevins RD, Azizan A, 1989, Mutagenicity and Antimutagenicity Testing of Six Chemicals Associated with the Pungent Properties of Specific Spices (Environ Mol Mutagen 14, Suppl. 15, 24/abstract no 63), DACO: 4.5.4
- 2865130 Maria LLana-Ruiz-Cabello, Sara Maisanaba, Maria Puerto, Ana I. Prieto, Silvia Pichardo, Angeles Jos, Ana M. Camean, 2014, Evaluation of the mutagenicity and genotoxic potential of carvacrol and thymol using the Ames Salmonella test and alkaline, Endo IIIand FPG-modified comet assays with the human cell line Caco-2 (Food and Chemical Toxicology 72 (2014) 122-128), DACO: 4.5.4,4.5.8,4.8
- 2865131 European Chemicals Agency, 2016, ECHA summary - Herbold (Bayer AG) 1989, DACO: 4.5.4
- 2865132 A. Stamatii, P. Bonsi, F. Zucco, R. Moezelaar, H.-L. Alakomi, A. von Wright, 1999, Toxicity of Selected Plant Volatiles in Microbial and Mammalian Short-term Assays, DACO: 4.5.4
- 2865133 European Chemicals Agency, 2016, ECHA summary - Unnamed 1996(b), DACO: 4.5.4
- 2865134 F. Zani, G. Massimo, S. Benvenuti, A. Bianchi, A. A Ibasini, M. Melegari, G. Vampa, A. Bellotti, and P. Mazza, 1991, Studies on the Genotoxic Properties of Essential Oils with *Bacillus subtilis* rec-Assay and Salmonella/Microsome Reversion Assay, DACO: 4.5.4,4.5.8,4.8
- 2865135 European Chemicals Agency, 2016, ECHA summary - Unnamed 2010 and unnamed 2010, DACO: 4.5.5
- 2865137 Azirak S, Rencuzogullari E, 2008, The in vivo genotoxic effects of carvacrol and thymol in rat bone marrow cells (Environ Toxicol 23, 728-735), DACO: 4.5.7

- 2865138 Kusakabe H, Yamakage K, Wakuri S, Sasaki K, Nakagawa Y, Watanabe M, Hayashi M, Sofuni T, Ono H, Tanaka N, 2002, Relevance of chemical structure and cytotoxicity to the induction of chromosome aberrations based on the testing results of 98 high production volume industrial chemicals (Mutation Research 517 (2002) 187-198), DACO: 4.5.7
- 2865140 Someya H, Higo Y, Ohno M, Tsutsui TW, Tsutsui T, 2008, Clastogenic activity of seven endodontic medications used in dental practice in human dental pulp cells (Mutat Res 650, 39-47), DACO: 4.5.7
- 2865143 European Chemicals Agency, 2016, ECHA summary - Unnamed 1996d, DACO: 4.5.7
- 2865145 Hirohito Hikiba, Eiko Watanabe, J. Carl Barrett, and Takeki Tsutsui, 2005, Ability of Fourteen Chemical Agents Used in Dental Practice to Induce Chromosome Aberrations in Syrian Hamster Embryo Cells (J Pharmacol Sci 97, 146-152), DACO: 4.5.7
- 2865146 W.R. Lee, S. Abrahamson, R. Valencia, E.S. von Halle, F.E. Wurgler and S. Zimmering, 1983, The sex-linked recessive lethal test for mutagenesis in *Drosophila melanogaster*: A report of the U.S. Environmental Protection Agency Gene-Tox Program (Mutation Research, 123 (1983) 183-279, DACO: 4.5.8,4.8
- 2865147 Fukuda S, 1987, Assessment of the carcinogenic hazard of 6 substances used in dental practices. (1) Morphological transformation, DNA damage and sister chromatid exchanges in cultured Syrian hamster embryo cells induced by carbol camphor, eugenol, thymol, EDTA, benzalkonium chloride and benzethonium chloride (Shigaku 74, 1365-1384), DACO: 4.5.6,4.5.8,4.8
- 2865148 Evrim Ipek, Berrin Ayaz Tuylu and Hulya Zeytinoglu, 2003, Effects of carvacrol on sister chromatid exchanges in human lymphocyte cultures (Cytotechnology 43: 145-148, 2003), DACO: 4.5.6,4.8
- 2865150 Aydin S , Basaran AA, Basaran N, 2004, Effects of major ingredients of oregano on oxidative DNA damage (Toxicol Appl Pharmacol 197, 258), DACO: 4.5.8,4.8
- 2865152 Aydin S, Basaran A, Basaran N, 2005, The effects of thyme volatiles on the induction of DNA damage by the heterocyclic amine IQ and mitomycin C (Mutat Res 581, 43-53), DACO: 4.5.8,4.8
- 2865154 Freese E, Levin BC, Pearce R, Sreevalsan T, Kaufman JJ, Koski WS, Semo NM, 1979, Correlation between the growth inhibitory effects, partition coefficients and teratogenic effects of lipophilic acids (Teratology 20, 413-440), DACO: 4.5.8,4.8
- 2865159 William F. Grant, 1982, Chromosome aberration assays in *Allium*: A report of the U.S. Environmental Protection Agency Gene-Tox Program (Mutation Research, 99 (1982) 273-291), DACO: 4.5.8,4.8
- 2865160 Kramers PG , Burm AG, 1979, Mutagenicity studies with halothane in *Drosophila melanogaster* (Anesthesiology 50, 510-513), DACO: 4.5.8,4.8
- 2865162 Albert Levan, Joe Hin Tijo, 1948, Induction of chromosome fragmentation by phenols (Hereditas 34(4):453-484), DACO: 4.5.8,4.8
- 2865163 Albert Levan, 1947, Studies on the camphor reaction of yeast (Hereditas Volume 33, Issue 4 May 1947 Pages 457-514), DACO: 4.5.8,4.8
- 2865164 J. F . Nunn, J. D. Lovis and K. L. Kimball, 1971, Arrest of mitosis by halothane (Br. J. Anaesth. (1971) 43 (6): 524-530), DACO: 4.8

- 2865166 Berufsgenossenschaft Rohstoffe und chemische Industrie (Institution for Statutory Accident Insurance and and Prevention in the Chemical Industry), 2000, Toxicological Evaluation: Thymol No. 259 CAS No. 89-83-8, DACO: 12.5.4,4.2.1,4.2.2,4.2.4,4.2.6,4.2.9,4.4.2,4.5.3,4.5.6,4.5.7,4.5.8,4.8
- 2865167 US Environmental Protection Agency, Office of Pesticide Programs, 2006, Biopesticide registration Action Document [BRAD] Thymol 5-methyl-2-isopropyl-1-phenol (PC Code 080402), DACO: 12.5.4,4.2.1,4.2.2,4.2.3,4.2.4,4.2.5,4.2.6,4.4.5,4.5.4,4.5.6,4.5.7,4.5.8,4.8
- 2865168 Rapporteur Member State (RMS) the United Kingdom, 2011, Draft Assessment Report (DAR) - public version - THYMOL, DACO: 12.5.4,4.2.3,4.5.2,4.5.4,4.5.7
- 2865169 European Chemicals Agency (website: <https://echa.europa.eu>), 2016, Thymol Toxicological Summary, DACO: 12.5.4,4.1
- 2865170 European Food Safety Authority, 2012, Conclusion on the peer review of the pesticide risk assessment of the active substance thymol (EFSA Journal 2012;10(11):2916), DACO: 12.5.4,4.2.1,4.2.2,4.2.3,4.2.4,4.2.5,4.2.6,4.5.2,4.5.7
- 2865171 Committee for Veterinary Medicinal Products, Veterinary Medicines Evaluation Unit, The European Agency for the Evaluation of Medicinal Products, 1996, Thymol Summary Report, DACO: 12.5.4,4.2.1
- 2865172 RTECS - Registry of Toxic Effects of Substances, 2003, Thymol, DACO: 12.5.4,4.2.1,4.2.4,4.2.5
- 2865173 TOXNET database - US National Library of Medicine <https://toxnet.nlm.nih.gov>, 2016, Thymol CASRN: 89-83-8, DACO: 12.5.4,4.2.1,4.2.2,4.2.4,4.2.5,4.2.6,4.2.9,4.3.1,4.3.8,4.5.3,4.5.4,4.5.6,4.5.7,4.5.8,4.8
- 2865176 Genevieve Marchand, 2016, Household products - US and Canada, DACO: 4.1,4.2.1,4.2.2,4.2.3,4.2.4,4.2.5,4.2.6,4.3.1,4.5.2,4.5.4,4.5.5
- 2865177 Joint FAO/WHO Expert Committee on Food Additives, 1967, Toxicological Evaluation of some flavouring substances and non-nutritive sweetening agents, DACO: 4.1,4.2.1
- 2865178 Joint FAO/WHO Expert Committee on Food Additives, 1976, Toxicological Evaluation of certain food additives, DACO: 4.2.1
- 2865181 European Chemicals Agency, 2016, ECHA summary - Unnamed 1974(a), DACO: 4.2.1
- 2865182 European Chemicals Agency, 2016, ECHA summary - Unnamed 1974(b), DACO: 4.2.1
- 2865183 European Chemicals Agency, 2016, ECHA summary - Unnamed 1974(c), DACO: 4.2.1
- 2865184 European Chemicals Agency, 2016, ECHA summary - Unnamed 1980(a), DACO: 4.2.1
- 2865185 European Chemicals Agency, 2016, ECHA summary - Unnamed 1980(b), DACO: 4.2.1
- 2865186 European Chemicals Agency, 2016, ECHA summary - Unnamed 1980(c), DACO: 4.2.1
- 2865187 European Chemicals Agency, 2016, ECHA summary - Wokes 1932, DACO: 4.2.1
- 2865188 Bhatia SP, McGinty D, Letizia CS, Api AM, 2008, Fragrance material review on menthol, DACO: 4.2.1, 4.2.4, 4.2.5, 4.2.6, 4.3.3, 4.3.8, 4.4.5, 4.5.2, 4.5.3, 4.5.4, 4.5.5, 4.5.6, 4.5.7, 4.5.8, 4.8

-
- 2865189 Joint FAO/WHO Expert Committee on Food Additives (JECFA), 1999, Safety Evaluation of certain food additive, DACO: 12.5.4, 4.2.1, 4.3.1, 4.3.3, 4.3.8, 4.5.3, 4.5.7
- 2865190 European Chemicals Agency, 2016, ECHA summary - Unnamed 1974(d), DACO: 4.2.2
- 2865191 European Chemicals Agency, 2016, ECHA summary - Unnamed 2012, DACO: 4.2.3
- 2865192 Carpenter CP, Smyth HF, 1946, Chemical burns of the rabbit cornea (American journal of ophthalmology 29(11):1363-72), DACO: 4.2.4
- 2865193 European Chemicals Agency, 2016, ECHA summary - Unnamed 1989(b), DACO: 4.2.4
- 2865194 European Chemicals Agency, 2016, ECHA summary - Unnamed 1989(c), DACO: 4.2.4
- 2865195 Barratt MD, 1997, QSARS for the eye irritation potential of neutral organic chemicals (Toxicol In Vitro 11(1-2):1-8), DACO: 4.2.4
- 2865196 Valosen JM, Hayes BB, Howell MD, Manetz TS, Woolhiser MR, Meade BJ, 1999, Evaluation of human irritants and weak to moderate sensitizers using a modified LLNA and an irritancy/phenotyping bioassay (Toxicologist), DACO: 4.2.5
- 2865197 European Chemicals Agency, 2016, ECHA summary - Unnamed 1989(a), DACO: 4.2.5
- 2865198 Baer RL, Serri F, and Weissenbach-Vial CH, 1955, Studies on allergic sensitization to certain topical therapeutic agents, DACO: 4.2.6
- 2865199 Blondeel A, Oleffe J, Achten G, 1978, Contact allergy in 330 dermatological patients, DACO: 4.2.6
- 2865200 Kligman AM, Epstein W, 1975, Updating the maximization test for identifying contact allergens (Contact Dermatitis 1(4):231-9), DACO: 4.2.6
- 2865201 Morton CA, Garioch J, Todd P, Lamey PJ, Forsyth A., 1995, Contact sensitivity to menthol and peppermint in patients with intra-oral symptoms (Contact Dermatitis. 1995 May;32(5):281-4), DACO: 4.2.6
- 2865202 Rudzki E, Kleniewska D, 1970, The epidemiology of contact dermatitis in Poland (Br J Dermatol. 1970 Nov;83(5):543-5) , DACO: 4.2.6
- 2865203 Santucci B, Cristaudo A, Cannistraci C, Picardo M, 1987, Contact dermatitis to fragrances (Contact Dermatitis. 1987 Feb;16(2):93-5), DACO: 4.2.6
- 2865204 Sharp DW, 1978, The sensitization potential of some perfume ingredients tested using a modified draize procedure (Toxicology. 1978 Mar;9(3):261-71), DACO: 4.2.6
- 2865205 European Chemicals Agency, 2016, ECHA summary - Unnamed 1974(e), DACO: 4.2.6
- 2865206 European Chemicals Agency, 2016, ECHA summary - Unnamed 1978, DACO: 4.2.6
- 2865207 European Chemicals Agency, 2016, ECHA summary - Unnamed 1991(a), DACO: 4.2.6
- 2865208 European Chemicals Agency, 2016, ECHA summary - Unnamed 1995, DACO: 4.2.6
- 2865209 European Chemicals Agency, 2016, ECHA summary - Macht and Phar1939, DACO: 4.2.9
-

- 2865210 European Chemicals Agency, 2016, ECHA summary - Unnamed 1979(a), DACO: 4.3.1
- 2865211 European Chemicals Agency, 2016, ECHA summary - Unnamed 1979(b), DACO: 4.3.1
- 2865212 European Chemicals Agency, 2016, ECHA summary - Unnamed 1979(c), DACO: 4.3.1,4.4.1,4.4.3,4.4.4
- 2865213 European Chemicals Agency, 2016, ECHA summary - Unnamed 1979(d), DACO: 4.3.1,4.4.1,4.4.2,4.4.4
- 2865214 National Cancer Institute, 1979, Bioassay of *dl*-Menthol for possible carcinogenicity CAS No. 89-78-1, DACO: 4.3.1,4.4.1,4.4.2,4.4.3,4.4.4
- 2865216 Gaworski CL, Oldham MJ, Wagner KA, Coggins CR, Patskan GJ, 2011, An evaluation of the toxicity of 95 ingredients added individually to experimental cigarettes: approach and methods (Inhal Toxicol. 2011 Jun;23 Suppl 1:1-12. doi: 10.3109/08958378.2010.543187. Epub 2011 Mar 22., DACO: 4.3.6
- 2865218 Rakieten N, Rakieten ML, Boykin M, 1954, Effects of menthol vapor on the intact animal with special reference to the upper respiratory tract (J Am Pharm Assoc 43(7), 390-392), DACO: 4.3.6
- 2865219 Gaworski CL, Dozier MM, Gerhart JM, Rajendran N, Brennecke LH, Aranyi C, Heck JD, 1997, 13-week inhalation toxicity study of menthol cigarette smoke (Food Chem Toxicol 35(7):683-92), DACO: 4.3.6,4.4.2
- 2865220 Imaizumi K, Hanada K, Mawatari K, Sugano M, 1985, Effect of Essential Oils on the Concentration of Serum Lipids and Apolipoproteins in Rats (Agricultural and Biological Chemistry 49(9):2795-6), DACO: 4.3.3,4.3.8
- 2865221 Madsen C, Wurtzen G, Carstensen J, 1986, Short-term toxicity study in rats dosed with menthone (Toxicol Lett. 1986 Jul-Aug;32(1-2):147-52), DACO: 4.3.3,4.3.8
- 2865222 Thorup I, Wurtzen G, Carstensen J, Olsen P, 1983, Short term toxicity study in rats dosed with pulegone and menthol (Toxicol Lett 19(3):207-10), DACO: 4.3.3,4.3.8
- 2865223 Thorup I, Wurtzen G, Carstensen J, Olsen P, 1983, Short term toxicity study in rats dosed with peppermint oil (Toxicol Lett. 1983 Dec;19(3):211-5), DACO: 4.3.3,4.3.8
- 2865224 European Chemicals Agency, 2016, ECHA summary - Unnamed 1983, DACO: 4.3.3,4.3.8
- 2865225 Haseman JK, Huff JE, Rao GN, Arnold JE, Boorman GA, McConnell EE, 1985, Neoplasms observed in untreated and corn oil gavage control groups of F344/N rats and (C57BL/6N X C3H/HeN)F1 (B6C3F1) mice (J Natl Cancer Inst 75(5):975-84), DACO: 4.4.2
- 2865226 Haseman JK, Tharrington EC, Huff JE, McConnell EE., 1986, Comparison of site-specific and overall tumor incidence analyses for 81 recent National Toxicology Program carcinogenicity studies (Regul Toxicol Pharmacol. 1986 Jun;6(2):155-70), DACO: 4.4.2
- 2865227 Jones MR, Tellez-Plaza M, Navas-Acien A, 2013, Smoking, Menthol Cigarettes and All-Cause, Cancer and Cardiovascular Mortality: Evidence from the National Health and Nutrition Examination Survey (NHANES) and a Meta-Analysis (PLoS One. 2013; 8(10): e77941), DACO: 4.4.2
- 2865228 Kabat GC, Hebert JR, 1991, Use of mentholated cigarettes and lung cancer risk (Cancer Res. 1991 Dec 15;51(24):6510-3), DACO: 4.4.2

- 2865229 European Chemicals Agency, 2016, ECHA summary - Unnamed 1979(e), DACO: 4.4.2,4.4.4
- 2865230 European Chemicals Agency, 2016, ECHA summary - Unnamed 1979(f), DACO: 4.4.2,4.4.4
- 2865231 European Chemicals Agency, 2016, ECHA summary - Unnamed 1979(g), DACO: 4.5.1
- 2865232 European Chemicals Agency, 2016, ECHA summary - Unnamed 1979(h), DACO: 4.5.1
- 2865233 European Chemicals Agency, 2016, ECHA summary - Unnamed 1973(b), DACO: 4.5.2
- 2865234 European Chemicals Agency, 2016, ECHA summary - Unnamed 1973(c), DACO: 4.5.2
- 2865235 European Chemicals Agency, 2016, ECHA summary - Unnamed 1973(d), DACO: 4.5.2
- 2865236 European Chemicals Agency, 2016, ECHA summary - Unnamed 1973(a), DACO: 4.5.2
- 2865238 Andersen PH, Jensen NJ, 1984, Mutagenic investigation of peppermint oil in the Salmonella/mammalian-microsome test (Mutat Res 138(1):17-20), DACO: 4.5.4
- 2865240 Gomes-Carneiro MR, Felzenszwalb I, Paumgartten FJ, 1998, Mutagenicity testing (+/-)-camphor, 1,8-cineole, citral, citronellal, (-)-menthol and terpineol with the Salmonella/microsome assay (Mutat Res 416(1-2):129-36), DACO: 4.5.4
- 2865242 Ishidate M Jr, Sofuni T, Yoshikawa K, Hayashi M, Nohmi T, Sawada M, Matsuoka A, 1984, Primary mutagenicity screening of food additives currently used in Japan (Food Chem Toxicol 22(8):623-36), DACO: 4.5.4,4.5.6,4.8
- 2865244 Miller JE, Vlasakova K, Glaab WE, Skopek TR, 2005, A low volume, high-throughput forward mutation assay in *Salmonella typhimurium* based on fluorouracil resistance (Mutat Res 578(1-2):210-24) , DACO: 4.5.4
- 2865245 European Chemicals Agency, 2016, ECHA summary - Unnamed 1988, DACO: 4.5.4
- 2865246 European Chemicals Agency, 2016, ECHA summary - Unnamed 1992, DACO: 4.5.4
- 2865248 European Chemicals Agency, 2016, ECHA summary - Unnamed 1975(c), DACO: 4.5.4,4.5.6,4.8
- 2865249 European Chemicals Agency, 2016, ECHA summary - Unnamed 1991(c), DACO: 4.5.5
- 2865250 Myhr BC, Caspary WJ, 1991, Chemical mutagenesis at the thymidine kinase locus in L5178Y mouse lymphoma cells: results for 31 coded compounds in the National Toxicology Program (Environ Mol Mutagen 18(1):51-83), DACO: 4.5.5,4.8
- 2865251 Shelby MD, Erexson GL, Hook GJ, Tice RR, 1993, Evaluation of a three-exposure mouse bone marrow micronucleus protocol: results with 49 chemicals (Environ Mol Mutagen 21(2):160-79), DACO: 4.5.7
- 2865252 European Chemicals Agency, 2016, ECHA summary - Unnamed 1975(b), DACO: 4.5.7
- 2865253 European Chemicals Agency, 2016, ECHA summary - Unnamed 1993 , DACO: 4.5.7

- 2865257 Ivett JL, Brown BM, Rodgers C, Anderson BE, Resnick MA, Zeiger E, 1989, Chromosomal aberrations and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. IV. Results with 15 chemicals (Environ Mol Mutagen. 1989;14(3):165-87), DACO: 4.5.6,4.8
- 2865258 Murthy PB, Ahmed MM, Regu K, 1991, Lack of genotoxicity of menthol in chromosome aberration and sister chromatid exchange assays using human lymphocytes in vitro (Toxicol In Vitro 5(4):337-40), DACO: 4.5.6,4.8
- 2865259 European Chemicals Agency, 2016, ECHA summary - Unnamed 1975(a), DACO: 4.5.6,4.8
- 2865260 European Chemicals Agency, 2016, ECHA summary - Unnamed 1991(b), DACO: 4.5.6,4.8
- 2865261 European Chemicals Agency, 2016, ECHA summary - Unnamed 1998(a), DACO: 4.5.6,4.8
- 2865262 Foureman P., Mason JM, Valencia R, Zimmering S, 1994, Chemical Mutagenesis Testing in *Drosophila*. IX. Results of 50 Coded Compounds Tested for the National Toxicology Program (Environmental and Molecular Mutagenesis 2351-63), DACO: 4.5.8,4.8
- 2865263 European Chemicals Agency, 2016, ECHA summary - Unnamed 1975(d), DACO: 4.5.8,4.8
- 2865264 European Chemicals Agency, 2016, ECHA summary - Unnamed 1998(b), DACO: 4.5.6,4.8
- 2865265 Hartmann A, Speit G, 1997, The contribution of cytotoxicity to DNA-effects in the single cell gel test (comet assay) (Toxicol Lett. 1997 Feb 7;90(2-3):183-8), DACO: 4.5.8,4.8
- 2865266 Hilliard CA, Armstrong MJ, Bradt CI, Hill RB, Greenwood SK, Galloway SM, 1998, Chromosome aberrations in vitro related to cytotoxicity of non-mutagenic chemicals and metabolic poisons (Environ Mol Mutagen 31(4):316-26), DACO: 4.5.8,4.8
- 2865267 Matsuoka A, Hayashi M, Sofuni T, 1998, In vitro clastogenicity of 19 organic chemicals found in contaminated water and 7 structurally related chemicals (Environ Mutagen Res 1998 Oct 31;20(3):159-65., DACO: 4.5.8,4.8
- 2865269 Storer RD, McKelvey TW, Kraynak AR, Elia MC, Barnum JE, Harmon LS, Nichols WW, DeLuca JG, 1996, Revalidation of the in vitro alkaline elution/rat hepatocyte assay for DNA damage: improved criteria for assessment of cytotoxicity and genotoxicity and results for 81 compounds (Mutat Res. 1996 Jun 12;368(2):59-101), DACO: 4.5.8,4.8
- 2865270 European Chemicals Agency (website: <https://echa.europa.eu>), 2016, *l*-Menthol - Toxicological Summary, DACO: 12.5.4,4.1
- 2865271 Committee for Veterinary Medicinal Products, The European Agency for the Evaluation of Medicinal Products, 1995, Menthol Summary Report, DACO: 12.5.4, 4.2.9
- 2865272 Opdyke DLJ, 1976, Fragrance raw materials monographs: Menthol Racemic (Food and Cosmetics Toxicology, 14(5), 473-474), DACO: 12.5.4, 4.2.1, 4.2.2, 4.2.5, 4.2.6, 4.2.9, 4.3.8
- 2865273 Opdyke DLJ, 1976, Fragrance raw materials monographs: *l*-menthol (Food and Cosmetics Toxicology, 14(5), 471-472), DACO: 12.5.4,4.2.2,4.2.5,4.2.6

2865275	TOXNET database - US National Library of Medicine https://toxnet.nlm.nih.gov , 2016, <i>l</i> -Menthhol CASRN: 2216-51-5, DACO: 12.5.4, 4.2.1, 4.2.3, 4.2.4, 4.2.5, 4.2.6, 4.2.9
2865276	TOXNET database - US National Library of Medicine https://toxnet.nlm.nih.gov , 2016, Menthol CASRN: 1490-04-6, DACO: 4.2.1, 4.2.2, 4.2.4, 4.2.5, 4.2.6, 4.2.9, 4.3.1, 4.3.3, 4.3.6, 4.3.8, 4.4.2, 4.4.3, 4.5.2, 4.5.3, 4.5.4, 4.5.5, 4.5.7, 4.8
2865274	OECD SIDS, 2003, Menthols CASN: 2216-51-5, 15356-60-2, 89-78-1, 1490-04-6 / SIDS Initial Assessment Report For SIAM 16, DACO: 12.5.4, 4.2.1, 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.2.6, 4.3.1, 4.3.3, 4.3.6, 4.3.8, 4.4.1, 4.4.2, 4.4.3, 4.4.4, 4.5.2, 4.5.3, 4.5.4, 4.5.5, 4.5.7, 4.8
2865175	2016, DACO walkthrough for tox and rationale for tox data waiver - levomenthol technical, DACO: 4.1,4.2.1,4.2.2,4.2.3,4.2.4,4.2.5,4.2.6,4.2.9,4.3.1,4.3.6,4.3.8, 4.4.1,4.4.2,4.4.3,4.4.4,4.4.5,4.5.1,4.5.2,4.5.3,4.5.4,4.5.5,4.5.6,4.5.7,4.5.8,4.8
2891134	2018, Use description scenario, DACO: 5.2

3.0 Value

PMRA

Document

Number

Reference

2864905	2018, Api Life VAR DACO overview EP and TGAI, DACO: 10.1, 2.0, 3.0, 4.1
2864906	2014, Clinical Documentation of Apilife VAR, DACO: 10.1, 10.2, 10.2.1, 10.2.2, 10.2.3, 10.3
2864907	2018, List of other products registered in Canada for Varroa mite, DACO: 10.5.1
2864909	2014, Varroa mite - Biology and Diagnosis, DACO: 10.2.2
2864913	2010, Comparative Effectiveness of Some Acaricides used to Control <i>Varroa destructor</i> (Mesostigmata: Varroidae) in Algeria, DACO: 10.2.3
2864914	2003, Comparison Between Two Thymol Formulations in the Control of <i>Varroa destructor</i> : Effectiveness, Persistence, and Residues, DACO: 10.2.3
2864915	2013, Efficacy of Apilife Var and Thymovar against <i>Varroa destructor</i> as an autumn treatment in a cool climate, DACO: 10.2.3
2864916	2001, Efficacy of a Bottom Screen Device, Apistan, and Apilife VAR, in Controlling <i>Varroa destructor</i> , DACO: 10.2.3
2864917	2001, Comparison of Two Thymol-Based Acaricides, Apilife VAR and Apiguard, for the Control of Varroa Mites, DACO: 10.2.3
2864918	1999, Use of different formulated with thymol for summer treatment antivarroa in a mediterranean enviroment (sic), DACO: 10.2.3
2864919	2004, Evaluation of Selected Biopesticides for the Late Fall Control of Varroa Mites in a Northern Temperate Climate, DACO: 10.2.3
2864920	2008, Comparison of the acaricides BAYVAROL (i.a. flumetrine) and Apilife Var (i.a. menthol, thymol, alcanphor y eucalyptol) for the spring control of <i>Varroa destructor</i> Anderson and Trueman (Spanish), DACO: 10.2.3

- 2864921 2001, Evaluation of honey bee miticides, including temporal and thermal effects on formic acid gel vapours, in the central south-eastern USA, DACO: 10.2.3
- 2864922 2016, Two commercial formulations of natural compounds for *Varroa destructor* (Acari: Varroidae) control on Africanized bees under tropical climatic conditions, DACO: 10.2.3
- 2864923 2018, Excel summary spreadsheet, DACO: 10.2.3.1