Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Proposed Regulatory Decision Document PRDD2002-02

p-Menthane-3,8-diol

The active ingredient, p-menthane-3,8-diol, and the associated end-use product, OFF! Botanicals Lotion Insect Repellent 1, containing p-menthane-3,8-diol, for use as a personal insect repellent against mosquitoes and black flies are proposed for registration under Section 13 of the Pest Control Products Regulations (PCPR).

This Proposed Regulatory Decision Document provides a summary of data reviewed and the rationale for the proposed full registration of these products. The Pest Management Regulatory Agency (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 the Publications Coordinator at the address listed below.

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Foreword

The PMRA has reviewed the submission for the full registration of the active ingredient p-menthane-3,8-diol and the end-use product OFF! Botanicals Lotion Insect Repellent 1, by S.C. Johnson & Son, Limited, as a personal insect repellent for use against mosquitoes and blackflies.

p-Menthane-3,8-diol is a synthetic analogue of a compound derived from the lemon eucalyptus plant (*Eucalyptus maculata citriodon*) and was recently registered as a biopesticide personal insect repellent in the United States (U.S.). p-Menthane-3,8-diol is a metabolite of menthol, which is used as a food additive and is also present in a number of pharmaceutical preparations.

The PMRA has carried out an assessment of available information in accordance with Section 9 of the PCPR and has found it sufficient pursuant to Section 18.b to allow a determination of the safety, merit and value of the active ingredient p-menthane-3,8-diol and the end-use product OFF! Botanicals Lotion Insect Repellent 1. The PMRA has concluded that the use of the active ingredient p-menthane-3,8-diol and the end-use product OFF! Botanicals Lotion Insect Repellent 1 in accordance with the label has merit and value consistent with section 18.c of the PCPR and does not entail an unacceptable risk of harm pursuant to Section 18.d. Therefore, based on the considerations outlined above, the use of the active ingredient p-menthane-3,8-diol and the end-use product OFF! Botanicals Lotion Insect Repellent 1 for use as an insect repellent against mosquitoes and blackflies is proposed for full registration, pursuant to Section 13 of the PCPR.

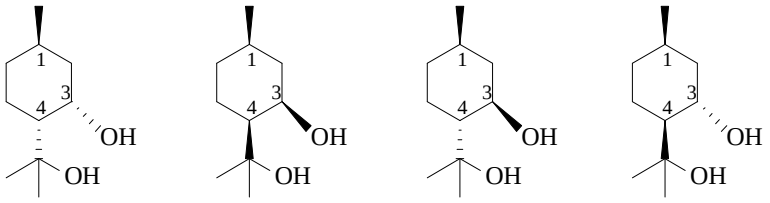
The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

Table of Contents

1.0 The active substance, its properties and uses

1.1 Identity of the active substance and impurities

Table 1.1-1 TGAI Identification

Active substance	p-Menthane-3,8-diol
Function	Insect repellent
Chemical name: International Union of Pure and Applied Chemistry: Chemical Abstracts Service (CAS)	 2-(2-hydroxy-2-methyl)-5-methyl-cyclohexanol Cyclohexanemethanol, 2-hydroxy-alpha,alpha,4-trimethyl-
CAS registry number	42822-86-6
Molecular formula	$C_{10}H_{20}O_2$
Molecular weight	172
Structural formula	 (+) cis 1R;3S;4R (-) cis 1R;3R;4S (-) trans 1R;3R;4R (+) trans 1R;3S;4S
Purity of active	99.0% nominal (upper certified limit [UCL] = 100.0%, lower certified limit [LCL] = 96.0%) cis/trans isomers ratio: min. 60% (±)cis and max. 40% (±) trans
Identity of relevant impurities of toxicological, environmental and/or other significance	Based on the starting material and the manufacturing process used, Toxic Substances Management Policy (TSMP) Track 1 substances as identified in Appendix II of Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, are not expected to be present in the product.

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

Table 1.2-1 Technical product: p-menthane-3,8-diol

Property	Result	Comment
Colour and physical state	Opaque, white solid	
Odour	Faint mint	
Melting point	34.5˚C	
Boiling point/range	N/A	
Density	0.989 g/mL at 24˚C	
Vapour pressure	0.00136 mm Hg at 25˚C	
Henry's Law Constant at 25°C	$K_H = 4.342 \times 10^{-5}$ $1/K_H = 2.303 \times 10^4$	U.S. Environmental Protection Agency (EPA) classification: low volatility
Ultraviolet (UV)/visible spectrum	Not expected to absorb UV at $\lambda >$ 350 nm	
Water solubility (g/L) at 25ºC	0.29	Very soluble in water.
Solubility in organic solvents at 25˚C	Soluble up to at least a 10% in the following solvents: ethanol, isopropanol, octyl dodecanol, ethylene glycol, isoparaffinic solvents, mineral oil, vegetable oils isopropyl myristate and isopropyl palmitate	
n-Octanol/water partition coefficient K_{ow} at room temperature	Not required	The product is intended for use as a personal insect repellent.
Dissociation constant	N/A	

Property	Result	Comment
Stability (temperature, metal)	Stable to exposure to sunlight, heat (54˚C), metals (iron, aluminium) and metal ions (iron (II) acetate, aluminium acetate)	

Table 1.2-2 End-use product: OFF! Botanicals Lotion Insect Repellent 1

Property	Result
Colour	Off-white
Odour	Fresh scent
Physical state	Liquid
Formulation type	Emulsion
Guarantee	10.0% nominal (UCL = 10.49%, LCL = 9.5%)
Formulants	The product does not contain any U.S. EPA List 1 formulants or formulants known to be TSMP Track 1 substances.
Container material	Plastic resealable bottle 10–175 mL
Density	0.978 g/mL at 24˚C
pH	7.3 (5% in deionized water)
Oxidizing or reducing action	None
Storage stability	Stable when stored for 12 months at 20–25˚C and 25–75% relative humidity in commercial packaging.
Explodability	N/A

1.3 Details of uses

OFF! Botanicals Lotion Insect Repellent 1 is proposed for use as a domestic class personal insect repellent containing 10.0% p-menthane-3,8-diol to repel mosquitoes and black flies.

The U.S. EPA registered the proposed S.C. Johnson & Son, Limited product in March 2000 as a biopesticide, with the label claims that this product repels mosquitoes, black flies, gnats and no-see-ums.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

Table 2.1 Method for analysis of the active substance as manufactured

Product	Analyte	Method type	Analytical range g/mL	Mean recovery	Relative standard deviation (%)	Method
Technical	Active	GC/FID*	0.029–0.087	Not required	±0.46	Acceptable
	Major impurities		0.015–0.045		0.46–0.85	Acceptable

*Gas chromatography/flame ionization detector

2.2 Method for formulation analysis

Table 2.2 Method for formulation analysis

Product	Analyte	Method	Linearity range (%)	Recovery range (%) (nominal [n])	Standard deviation (n)	Method
OFF! Botanicals Lotion Insect Repellent 1	Active	GC/FID	5–25	97.8–102 (5)	±0.32 (6)	Acceptable

2.3 Methods for residue analysis

Not applicable

3.0 Impact on human and animal health

3.1 Integrated toxicological summary

The submitted toxicology package for p-menthane-3,8-diol was consistent with that required by the U.S. EPA for biopesticides. The data package included five acute studies (waiver request for an acute inhalation study), a 90-day dermal toxicity study in rats, a

dermal immunotoxicity screening study in mice, a dermal developmental toxicity study in rats, and a battery of mutagenicity studies performed with p-menthane-3,8-diol and identified in the toxicity studies as Granola 97. The registrant referenced published information on menthol, citing similarity in chemical structure to p-menthane-3,8-diol, in order to address the remaining toxicology data requirements.

Absorption, distribution, metabolism and excretion

p-Menthane-3,8-diol has been reported to be a major urinary metabolite in rats after oral exposure to menthol; therefore, menthol was cited as a suitable predictor of the toxicological behaviour of p-menthane-3,8-diol. The structure of p-menthane-3,8-diol suggests that it is more polar and more accessible to conjugation; thus, more rapidly eliminated than menthol. After an oral dose of 500 mg/kg body weight (bw) of menthol to Fischer rats (intact or bile duct cannulated), 71% of the dose was excreted in 48 hours with equal amounts in urine and feces. The majority of the fecal excretion occurred in 24 hours. In bile duct cannulated rats, 74% of dose was excreted, 67% in the bile and 7% in the urine. No unchanged menthol could be detected in the urine, feces or bile. There was a significant difference in the metabolites found in the urine and bile, with menthol glucuronide dominating in the bile but with a variety of oxidation products in the urine. A number of products of oxidation of the methyl and isopropyl groups were found to be major urinary metabolites after the daily administration of menthol to rats for up to 20 days. The urinary metabolites from hydroxylation at the C-7 methyl group or C-8 and C-9 in the isopropyl moiety, resulting in a series of mono- and dihydroxylmenthols and carboxylic acids, some of which are excreted in part as glucuronic acid conjugates. Menthol glucuronide is also found in urine. This information has enabled the construction of a metabolic map for menthol in rats that provides the basis for structure-metabolism relationships describing the fate of numerous menthol congeners.

Acute toxicity

Technical p-menthane-3,8-diol was of low toxicity via the oral and dermal routes of exposure. It was severely irritating to the eyes, but only mildly irritating to the skin. It did not show dermal sensitization potential when tested in guinea pigs using the modified Buehler method. The requirement for an acute inhalation study was waived since the product is a solid at room temperature and the material is intended for formulation use only; thus, inhalation is not an expected route of exposure.

The end-use product, Off! Botanicals Lotion Insect Repellent 1, was of low toxicity following acute oral and dermal dosing. Due to formulation type, the requirement for acute inhalation toxicity was waived. Off! Botanicals Lotion Insect Repellent 1 was a mild and slight irritant for eyes and skin, respectively. When tested in human volunteers, Off! Botanicals Lotion Insect Repellent 1 did not induce skin irritation or sensitization. Formulants contained in the end-use product are on the U.S. EPA Inerts List 3, 4A or 4B, and/or the Canadian Registered Products List, and were judged to be of no toxicological concern.

Short-term/subchronic toxicity
A 90-day dermal study in rats conducted at the limit dose (1000 mg/kg bw/day) as well as an additional dose above that (3000 mg/kg bw/day) did not reveal any specific toxicity end-points. Skin irritation was seen at both doses in the form of erythema, eschar and desquamation. At the highest dose, kidney lesions likely associated with α-2-u globulin (hyaline droplets and chronic nephropathy) were observed in males.

Long-term toxicity
National Toxicology Program (NTP) studies conducted with menthol in rats and mice were referenced by the applicant. These studies were not reviewed by the PMRA. Both studies were negative for oncogenicity.

Genotoxicity
Although p-menthane-3,8-diol (with S9 metabolic activation) did induce a positive response in an in vitro microsomal aberration assay, it did not produce a positive response when tested under in vivo conditions in the mouse micronucleus assay. The overall weight of evidence did not suggest p-menthane-3,8-diol to be genotoxic.

Menthol was reported to yield negative results in the chromosome aberration and sister chromatid exchange assays using human lymphocytes in vitro. It did not induce mutation in *Salmonella typhimurium* TA 92, 1535, 100, 1537, 94 and 98 tester strains with or without metabolic activation. Menthol did not induce chromosome aberrations in Chinese hamster fibroblast cells.

The combined information for p-menthane-3,8-diol and menthol did not suggest alerts for genotoxicity.

Carcinogenicity
On the basis of the weight of evidence for p-menthane-3,8-diol and menthol combined, p–menthane-3,8-diol is not considered to pose a hazard in terms of carcinogenicity.

Developmental and reproductive toxicity
The rat developmental toxicity study indicated that p-menthane-3,8-diol was not teratogenic at doses up to and including 3000 mg/kg bw/day. Fetotoxicity included increased skeletal variation and reduced ossification, observed at the highest dose. The no observed adverse effect level (NOAEL) for maternal toxicity was established at 1000 mg/kg bw/day, based on reduced body-weight gain (bwg) and food consumption at the early part of gestation period (gestation days 6–9) in 3000 mg/kg bw/day animals.

A reproductive toxicity study with p-menthane-3,8-diol was not submitted. No evidence of toxicity to reproductive organs was observed in the subchronic dermal toxicity study in rats at doses exceeding the limit dose for testing (3000 mg/kg bw/day). Overall, the information provided does not suggest that the reproduction system, per se, is a target for toxicity. However, key studies in assessing potential sensitivity of the young include the reproductive toxicity study and two developmental toxicity studies. The lack of

reproductive toxicity testing, coupled with the lack of a second developmental toxicity study, therefore, does not allow for a full assessment of potential sensitivity to the young associated with p-menthane-3,8-diol for the proposed use as an insect repellent.

Special studies
A 28-day dermal immunotoxicity study in B6C3F1 female mice did not show immune suppression at 3000 mg/kg bw/day, the highest dose tested. This study was considered supplemental because only one immunologic parameter was measured.

3.2 Determination of acceptable daily intake

An acceptable daily intake (ADI) is not required as there are no food uses being petitioned for this active ingredient.

3.3 Acute reference dose

Since the end-use product is not for food use, an acute reference dose (ARfD) is not being determined.

3.4 Toxicological end-point selection: occupational and bystander risk assessment

The submitted toxicology studies were primarily conducted via the dermal route. p-Menthane-3,8-diol was of low acute toxicity by the oral, dermal and inhalation routes of administration.

In both the subchronic dermal toxicity study and the teratogenicity study, at the limit dose of 1000 mg/kg bw/day, p-menthane-3,8-diol-treated animals did not exhibit any treatment-related systemic effects, nor was there any evidence suggestive of neurotoxic effects. Although only one immunologic parameter was measured in the 28-day immunotoxicity study, p-menthane-3,8-diol did not show any evidence of immune suppression. The battery of test assays for both p-menthane-3,8-diol and menthol do not suggest genotoxic potential. The results of the referenced NTP chronic/oncogenicity bioassays with menthol in rats and mice were negative.

Menthol has a long history of use as a food ingredient and in products used orally and dermally, such as pharmaceuticals and personal care products. Menthol is approved as a direct food additive by the U.S. Food and Drug Administration.

Overall, the submitted toxicology data for p-menthane-3,8-diol as well as available information for menthol did not identify any toxicological endpoints of concern; therefore, a quantitative risk assessment was not conducted for the proposed use. Potential sensitivity to the young, however, was not fully addressed.

3.5 Impact on human and animal health arising from exposure to the active substance or to its impurities

3.5.1 Operator exposure assessment

Not applicable

3.5.2 Bystanders

Not applicable

3.5.3 Workers

Not applicable

3.5.4 Consumers

Off! Botanicals Lotion Insect Repellent 1 contains p-menthane-3,8-diol at a guarantee of 10.0%. The product is effective against mosquitoes and black flies for about two and five hours, respectively. The product would be used by both children and adults.

Since insect repellents are applied directly to the skin, exposure is considered to be very high. Typically, insect repellents are used intermittently during the insect season (i.e., May to August). Insect repellents are to be used sparingly and are to be applied only when biting insects are present. Depending on the insect biting-pressure and the concentration of the active ingredients, insect repellents may be applied once to a several times a day.

The product is proposed for use one to six times per day (depending on protection time and assuming 12 hours of protection would be needed). The general population would typically apply the proposed product two to three times per day. However, under heavy insect pressure (e.g., forestry occupations) or where longer protection times are needed, up to six applications could be made in a day.

Potential exposure would occur in three population groups: adults, children and toddlers. For all populations, two exposure scenarios were identified for risk assessment of insect repellents: acute (occasional use) and intermediate (prolonged seasonal use) dermal exposure. For toddlers, one additional exposure scenario was identified: non-dietary oral exposure resulting from transfer of residues from the skin to the mouth from hand-to-mouth activities.

Risk Assessment
Since no toxicological endpoints of concern were identified (see Section 3.4, *Toxicology endpoint selection: occupational and bystander risk assessment*), a quantitative risk assessment was not conducted for the proposed use. The potential exposure to p-menthane-3,8-diol is considered to be very high since it is directly applied to skin, can

be applied several times per day, and can be used frequently throughout the summer months in Canada. p-Menthane-3,8-diol is a metabolite of menthol, which is used as a food additive and is also present in a number of pharmaceutical preparations such as external analgesics (typical concentrations of approximately 10%), dermal rub preparations to control against symptoms of coughs and colds (typical concentrations from 1 to 4%) and cough tablets (typically 10 mg/tablet).

Based on the results of the toxicology studies conducted with p-menthane-3,8-diol and menthol in which no toxicological endpoints of concern were identified, and based on the long history of use of products containing menthol, no adverse effects are expected to occur from the proposed use of OFF! Botanicals Lotion Insect Repellent 1, provided that exposure from insect repellent use would be comparable to exposure from other sources.

The use of this product in very young children, however, will be restricted in the absence of further information to fully address potential sensitivity to the young. Consequently, this product will not be used on children three years of age and younger. In addition, use of the product will be limited to two applications per day for both adults and children, as an assurance that exposure to p-menthane-3,8-diol from insect repellent use will be comparable or lower than exposure to menthol from other sources such as pharmaceuticals.

4.0 Residues

Not applicable

5.0 Fate and behaviour in the environment

Not applicable

6.0 Effects on non-target species

Not applicable

7.0 Efficacy

7.1 Effectiveness

7.1.1 Intended use

OFF! Botanicals Lotion Insect Repellent 1 is proposed for use as a domestic class personal insect repellent containing 10.0% p-menthane-3,8-diol to repel mosquitoes and black flies.

7.1.2 Mode of action

p-Menthane-3,8-diol is a synthetic analogue of a compound derived from the lemon eucalyptus plant (*Eucalyptus maculata citriodon*) that, according to the applicant, is believed to repel biting flies by blocking or interfering with the receptor sites used in host location.

7.1.3 Effectiveness against pest

7.1.3.1 Description of pest problem

Mosquitoes and black flies are considered pests because they are known to bite people and feed on blood. In mosquitoes (Culicidae) and black flies (Simuliidae), only the adult females are blood feeders.

Blood-feeding can cause annoyance, blood loss and allergic reactions, and may be the means by which people can become infected with pathogenic organisms. Arthropod-borne pathogens known to occur in Canada include several types of viral encephalitis (Western Equine, Eastern Equine, St. Louis and West Nile), which are transmitted by several species of mosquitoes.

7.1.3.2 Efficacy Trials

Studies were submitted to test the effectiveness of p-menthane-3,8-diol in repelling mosquitoes, black flies and biting midges. To verify the repellency of the active ingredient itself, a laboratory trial using 50% p-menthane-3,8-diol in ethanol against laboratory-reared mosquitoes (*Aedes aegypti*) and stable flies (*Stomoxys calcitrans*), and field trials using 5% and 10% p-menthane-3,8-diol in ethanol against field populations of mosquitoes (*A. taeniorhynchus*) were submitted. These studies demonstrated that the active ingredient is, indeed, repellent. To demonstrate the repellency of the 10.0% p-menthane-3,8-diol formulation proposed for registration, efficacy trials against field populations of mosquitoes, black flies and biting midges were submitted. The three field trials using the proposed product against mosquitoes were conducted in Florida (against *A. taeniorhynchus*, *Psorophora ferox* and *Mansonia dyari*) and Manitoba (*A. vexans, A. cinereus* and *A. dorsalis*). In all cases, the product was found to be effective for at least 1.5 hours. The two field trials using the proposed product against black flies were conducted in Michigan (against *Simulium venustum* and *Prosimulium mixtum*) and Ontario (against *S. venustum, S. truncatum, S. rostratum* and *S. decorum*). The proposed product was found to be effective for at least four hours in one trial (complete protection time not determined as the trial was terminated after four hours) and 5.75 hours in the other trial. One field trial was submitted using the proposed product against biting midges (*Culicoides* spp., also known as “no-see-ums”) in Florida, but the species of biting midge tested was not identified (unknown whether it would occur in Canada) and the study design was not strong enough to allow the data to be used to support this pest claim

because control counts were not taken throughout the efficacy trial to demonstrate that biting pressure was maintained.

7.2 Economics

Not assessed

7.3 Sustainability

7.3.1 Survey of alternatives (chemical and non-chemical)

Most personal insect repellents registered in Canada contain DEET as the principal active ingredient. Other personal repellents are registered that contain oil of citronella or oil of lavender as the active ingredient. DEET has recently been re-evaluated by the PMRA, and oil of citronella and oil of lavender are currently under re-evaluation. For comparison, a product containing 10% DEET is expected to provide approximately three hours of protection from mosquitoes. Performance comparisons of p-menthane-3,8-diol with either oil of citronella or oil of lavender cannot be made at this time because the re-evaluation of these active ingredients has not yet been completed.

7.3.2 Compatibility with current management practices, including integrated pest management

Not assessed

7.3.3 Contribution to risk reduction

Not assessed in the context of value

7.3.4 Information on the occurrence or possible occurrence of the development of resistance

Not assessed as no information was provided. Based on the use pattern as a personal insect repellent, however, the development of resistance is unlikely. Moreover, a resistance-management statement is not required as Regulatory Directive Dir99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action*, applies only to pesticide products that are intended for general agricultural use, not for domestic class products such as personal repellents.

7.4 Conclusions

Based on the submitted efficacy data, the use of the proposed 10.0% p-menthane-3,8-diol product to repel mosquitoes and black flies can be supported as indicated in table 7.4.1.

7.4.1 Summary

	Label claims (based on efficacy assessment)
Pest claims	Repels mosquitoes for about 2 hours. Also repels black flies for about 5 hours.
Application method	For best results, apply a thin uniform layer over all exposed skin. For continued protection from listed insects, reapply after 2 hours for mosquitoes or after 5 hours for black flies, if necessary. Earlier re-application may be necessary after swimming, perspiration, vigorous activity or towelling.
Resistance management	Not required for domestic class products.

8.0 Toxic Substances Management Policy considerations

During the review of OFF! Botanicals Lotion Insect Repellent 1, the PMRA took into account the federal TSMP[1] and has followed Regulatory Directive Dir99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*[2].

Due to the use pattern (personal insect repellent, Use-Site Category 26) of p-menthane-3,8-diol, environmental exposure will not occur. There are no TSMP concerns with the active or any other formulants in the proposed EP.

9.0 Proposed regulatory decision

The PMRA has carried out an assessment of available information in accordance with Section 9 of the PCPR and has found it sufficient pursuant to Section 18.b to allow a determination of the safety, merit and value of the active ingredient p-menthane-3,8-diol and the end-use product OFF! Botanicals Lotion Insect Repellent 1, manufactured by S. C.

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1 The federal Toxic Substances Management Policy is available through Environment Canada's web site at www.ec.gc.ca/toxics.

2 Regulatory Directive DIR99-03 is available through the Pest Management Information Service by telephone at 1-800-267-6315 within Canada or (613) 736-3799 outside Canada (long distance charges apply); facsimile (613) 736-3798; e-mail: pminfoserv@hc-sc.gc.ca; or through the PMRA's web site at www.hc-sc.gc.ca/pmra-arla.

Johnson & Son, Limited. The PMRA has concluded that the use of the active ingredient p-menthane-3,8-diol and the end-use product OFF! Botanicals Lotion Insect Repellent 1 in accordance with the label has merit and value consistent with section 18.c of the PCPR and does not entail an unacceptable risk of harm pursuant to Section 18.d. Therefore, based on the considerations outlined above, the use of the active ingredient p-menthane-3,8-diol and the end-use product OFF! Botanicals Lotion Insect Repellent 1 as a personal insect repellent against mosquitoes and blackflies, with up to two applications per day for adults and children over three-years old, is proposed for full registration pursuant to Section 13 of the PCPR.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

List of abbreviations

ADI	acceptable daily intake
ArfD	acute reference dose
bw	body weight
bwg	body-weight gain
CAS	Chemical Abstracts Service
EPA	Environmental Protection Agency
FID	flame ionization detector
GC	gas chromatography
LCL	lower certified limit
LOAEL	lowest observable adverse effect level
MAS	maximum average score
MIS	maximum irritation score
n	nominal
NOAEL	no observed adverse effect level
NTP	National Toxicology Program
PCPR	Pest Control Products Regulations
PMRA	Pest Management Regulatory Agency
TSMP	Toxic Substances Management Policy
U.S.	United States
UCL	upper certified limit
UV	ultraviolet

Appendix I: Summary tables

Toxicology

Metabolism
p-Menthane-3,8-diol has been reported to be a major urinary metabolite in the rat after oral exposure to menthol; therefore, menthol was cited as a suitable predictor of the toxicological behaviour of p-menthane-3,8-diol (Madyastha and Srivatsan, 1998). The structure of p-menthane-3,8-diol suggests that it is more polar and more accessible to conjugation; thus, more rapidly eliminated than menthol. After an oral dose of 500 mg/kg bw of menthol to Fischer rats (intact or bile duct cannulated), 71% of the dose was excreted in 48 hours with equal amounts in urine and feces (Yamaguchi, 1994). The majority of the fecal excretion occurred in 24 hours. In bile duct cannulated rats, 74% of dose was excreted, 67% in the bile and 7% in the urine. No unchanged menthol could be detected in the urine, feces or bile. There was a significant difference in the metabolites found in the urine and bile, with menthol glucuronide dominating in the bile but with a variety of oxidation products in the urine. Madyastha and Srivatsan also found a number of products of oxidation of the methyl and isopropyl groups as major urinary metabolites after the daily administration of menthol to rats for up to 20 days. The urinary metabolites from hydroxylation at the C-7 methyl group or C-8 and C-9 in the isopropyl moiety, resulting in a series of mono- and dihydroxylmenthols and carboxylic acids, some of which are excreted in part as glucuronic acid conjugates. Menthol glucuronide is also found in urine. This information has enabled the construction of a metabolic map for menthol in the rat that provides the basis for structure-metabolism relationships describing the fate of numerous menthol congeners.

Study	**Species/Strain and Doses**	**LD_{50}/NOAEL (mg/kg bw/day)**	**Lowest observable adverse effect level (LOAEL) (mg/kg bw/day) target organ/significant effects/ comments**
Acute Studies: Technical p-menthane-3,8-diol (98.3%)			
Oral	Rat, Sprague-Dawley (SD)	LD_{50} > 5000 mg/kg bw	Low toxicity
Dermal	Rabbit, New Zealand White (NZW)	LD_{50} > 5000 mg/kg bw	Low toxicity
Inhalation	N/A	N/A	Waiver granted
Skin Irritation	Rabbit, NZW	Maximum irritation score (MIS) = 1.67 Maximum average score (MAS) = 1.06	Mildly irritating (caution skin irritant)
Eye Irritation	Rabbit, NZW	MIS = 51.00 MAS = 48.56	Severely irritating (danger severe eye irritant)
Skin Sensitization (Buehler method)	Guinea pig, Hartley-derived		Not a skin sensitizer
Acute Studies: Formulation (10.0% p-menthane-3,8-diol)			
Oral	Rat, SD	LD_{50} >5000 mg/kg bw	Low toxicity
Dermal	Rabbit, NZW	LD_{50} > 5000 mg/kg bw	Low toxicity
Inhalation	N/A	N/A	Waiver granted

Study	Species/Strain and Doses	LD_{50}/NOAEL (mg/kg bw/day)	Lowest observable adverse effect level (LOAEL) (mg/kg bw/day) target organ/significant effects/ comments
Skin Irritation	Rabbit, NZW	Primary irritation score = 0.92 MAS = 0.833	Slightly irritating
Eye Irritation	Rabbit, NZW	MIS = 6.67 MAS = 3.06	Mildly irritating (caution eye irritant)
Skin Sensitization (patch test)	Human volunteers	No dermal irritation during induction or sensitization reaction after challenge	Not a sensitizer
Short-term Toxicity: Technical p-menthane-3,8-diol (98.3%)			
28-day immunotoxicity (dermal exposure)	Mouse, B6C3F1females, 10/dose, 0, 1000 or 3000 mg/kg bw	LOAEL and NOAEL could not be determined due to the absence of a dose-related response	At 3000 mg/kg bw/day: immune suppression was not detected Study considered supplemental because only one immunologic parameter was measured
Subchronic Toxicity: Technical p-menthane-3,8-diol (98.3%)			
90-day dermal application	Rat, SD, 15/sex/group, 0, 1000, or 3000 mg/kg/day	Systemic Toxicity: NOAEL = 1000 LOAEL = 3000 Dermal Irritation: LOAEL = 1000	At 1000 mg/kg bw/day: skin irritation (erythema, eschar, desquamation) At 3000 mg/kg bw/day: ↓bw/bwg (males),↑ kidney lesions in males (hyaline droplet formation, chronic nephropathy); skin damage (acanthosis, parakeratosis and chronic inflammation)
Developmental Toxicity: Technical p-menthane-3,8-diol (98.3%)			
Teratogenicity (Dermal application from days 6–19 of gestation)	Rat, SD, 25/group, 0, 1000 and 3000 mg/kg bw/day	Maternal Toxicity: NOAEL = 1000 LOAEL = 3000	At 3000 mg/kg bw/day: ↓bwg during the treatment period (days 6–19)and food consumption during days 6–9
		Developmental Toxicity: NOAEL = 1000 LOAEL = 3000	At 3000 mg/kg bw/day: ↑ skeletal variations and reduced ossification in the fetuses p-menthane-3,8 -diol was not teratogenic
Genotoxicity: Technical p-menthane-3,8-diol (98.3%)			
Salmonella Ames assay, in vitro	*S. typhimurium*, TA 98, TA 100, TA 1535, TA 1537; *E. Coli* - WP2uvrA	6.7–5000 µg/plate (±S9)	Negative
In vitro mammalian cytogenetics (chromosomal aberration) assay	Chinese hamster ovary CHO-K1 cells	Initial study: 50, 150, 500 and 1500 ug/mL (±S9) Repeat study: 125, 250, 500, 1000 ug/mL (-S9; 20/44 hours treatment) 250, 500, 1000 and 1500 ug/mL (6 hours treatment, 14 and 38 hours recovery)	Negative (without S9 metabolic activation) positive (with S9 metabolic activation)

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Mammalian cells in culture gene mutation assay	L5178Y/TK $^{\pm}$ cells	500–2000 ug/mL (±S9)	Negative
In vivo mammalian cytogenetic (micronucleus) assay	Mouse, ICR	0, 104, 208 or 416 mg/kg bw with sacrifice at 24 hr for all doses, and 24 and 48 hours for vehicle control and high-dose groups	Negative
Compound-Induced Mortality: None			
Recommended ARfD: Since no food use is being proposed, an ARfD is not being established			
Recommended ADI: Since no food use is being proposed, an ADI is not being established			