p-Menthane-3,8-diol (011550) Biopesticide Registration Eligibility Document

Issued: 5/00

I. Executive Summary

The Biopesticides and Pollution Prevention Division (BPPD) has reviewed data submitted under Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) EXIT Disclaimer by S.C. Johnson & Son, Inc. This data has been submitted for the purpose of assessing the potential hazards and exposures that might result from the proposed technical grade product, containing the new active ingredient, p-Menthane-3,8-diol. This new pesticide will be used to formulate pesticide products that can be applied to human skin and clothing to repel insects. Based on the review of submitted information, dose levels and toxicity endpoints were evaluated to characterize potential risks.

Based upon the evaluation of the submitted data and information, there is reasonable certainty of no harm to the U.S. population or subpopulations including infants and children as the result of the pesticidal uses of p-Menthane-3,8-diol.

A. Identity

p-Menthane-3,8-diol Technical, formerly submitted as Granola 97, is an insect repellent manufacturing use product that consists of p-methane-3,8-diol as the active ingredient. p-Menthane-3,8-diol is made from extracts of eucalyptus plants. The product is a mixture of +/-cis and +/-trans isomers of p-methane-3,8-diol.

B. Use

The active ingredient, p-Menthane-3,8-diol, is used as an insect repellent on human skin and clothing.

C. Risk Assessment

The technical grade active ingredient, p-Menthane-3,8-diol, is placed into Toxicity Category IV for acute oral toxicity, dermal toxicity and skin irritation, and Toxicity Category I for eye irritation (Toxicity Category II for the end-use product). It is not a skin sensitizer. The no-observed-adverse-effect level (NOAEL) from a 90-day dermal toxicity study in rats was established at a limit dose of 1000 mg/kg/day. The NOAEL for immune suppression, as determined in a 28-day dermal study, via a primary antibody response to sheep red blood cells/plaque forming cell assay was > 3000

mg/kg/day in mice. The NOAEL for maternal and developmental toxicity was established in rabbits at 3000 mg/kg/day by the dermal route. Mutagenicity studies evaluated p-Menthane-3,8-diol for its potential to cause point mutations in bacteria and mammalian cells, chromosomal aberrations in mammalian cells, and induction of micronuclei in polychromatic erythrocytes from mouse bone marrow, and found no genotoxicity at the doses tested, with and without metabolic activation.

Based on the evaluation of the submitted data, there were no endpoints of concern. Thus, there is reasonable certainty of no harm to the U.S. population or subpopulations, including infants and children, from the labeled use of the technical grade active ingredient. Two end use repellent products were submitted for registration. Analysis of potential risks from exposure to the end-use (spray) pesticide product has been conducted. BPPD considered the possible effects of the other ingredients and the dilution factor of the active ingredient in those formulations, and a determination of an appropriate safety factor for risk characterization has been made. The end use product, OFF! Botanicals Insect Repellent, originally submitted as UICK II, (EPA Reg. No. 4822-509) complies with the requirements of FIFRA.

II. Overview

A. Chemical Overview

The technical grade active ingredient, p-Menthane-3,8-diol, is a new biochemical pesticide that is approximately 99% pure. This biochemical is to be formulated into repellent products designed for application to human skin and clothing for the purpose of repelling insects.

B. Regulatory History

On November 28, 1997, the Agency received an application from S.C. Johnson & Son, Inc. to register the Manufacturing Use Product (MUP), p-Menthane-3,8-diol Technical, formerly called Granola 97, containing p-Menthane-3,8-diol, a new biochemical active ingredient used as an insect repellent . A notice of receipt of the application for registration of p-Menthane-3,8-diol as a new active ingredient was published in the *Federal Register* on March 24, 1998 with a 30-day comment period. No comments were received as a result of this publication.

On August 31, 1998, the Agency received an application from S.C. Johnson & Son, Inc. to register an end use product (spray) containing p-Menthane-3,8-diol for use as an insect repellent, UICK II, now registered as OFF! Botanticals Insect Repellent 1

(EPA File Reg. No. 4822-509). And then on May 25, 1999, the Agency received another application from S.C. Johnson & Son, Inc. to register an end use product (lotion) containing p-Menthane-3,8-diol for use as an insect repellent, UICK III, now named OFF! Botanticals Insect Repellent 2 (EPA File Reg. No. 4822-515).

III. Science Assessment

A. Physical and Chemical Properties

Information discussed in this section was reported in MRID 44438712 and -13, and MRID 44489301.

1. **Chemical Identity** (Guideline Reference No. 151-10-16)

   p-Menthane-3,8-diol (Pesticide Chemical Code 011550) is a colorless liquid, that is extracted from the leaves and twigs of eucalyptus plants. Commercially, it is created through a chemical synthesis process that produces a similar and functionally identical biochemical. The chemical name includes the following synonym:

   Cyclohexanemethanol, 2-hydroxy-alpha, alpha, 4-trimethyl

   The CAS Registry number for p-Menthane-3,8-diol is: 42822-86-6

   The molecular formula for p-Menthane-3,8-diol: $C_{10}H_{20}O_2$

2. **Physical and Chemical Properties of p-Menthane-3,8-diol** (Guideline Reference No. 151-17)

Table 1

Property	Result
Color	Opaque white
Physical State	Solid, specific observation temperature not noted
Odor	Faint mint
Melting Point	34.5Â°C
Boiling Point/Range	Not required; solid at room temperature

Density	0.989 g/mL at 24Â°C
Solubility	0.29 g/L at 25Â°C
Vapor Pressure	0.181 Pa, determined by gas saturation method
Dissociation Constant in Water	Not reported; product is not dispersible in water
Octanol/Water Partition Coefficient	Not required, intended use pattern not an environmental fate concern
pH	Not applicable; not dispersible with water (see structure on page 6
Stability	Stable to sunlight, heat (54Â°C), metal (iron, aluminum), and metal ions (iron II acetate, aluminum acetate)
Oxidizing/Reducing Action	Not discussed
Flammability	Flash point 139.8Â°C
Storage stability	Not applicable, product is a technical grade active ingredient
Viscosity	56.1 cP at 60Â°C
Miscibility	Not applicable, product not intended for dilution with petroleum solvents
Corrosion characteristics	Not applicable, product is a technical grade active ingredient

B. Human Risk Assessment

1. Hazard Assessment

There is sufficient data available to support a hazard assessment of p-Menthane-3,8-diol.

a. Acute Toxicity Studies

Seven (five for the MUP) acute toxicity studies were submitted to support the registration of p-Menthane-3,8-diol. All studies were acceptable, and the results are listed in Table 2, (first study is the

MUP; second study is the end-use product) below, and summarized as follows:

Table 1

Guideline Reference No.	Study	MIRD	Results	Toxicity Category
152-10	Acute Oral-rat	44438701	LD_{50}>5000 mg/kg	IV
		44642101	LD_{50}>5000 mg/kg	IV
152-11	Acute Dermal-rabbit	44438702	LD50>5000 mg/kg	IV
		44642102	LD50>5000 mg/kg	IV
152-12	Acute Inhalation	44642103	Waived* LC50 (rat)>2.17mg/L	IV
152-13	Eye Irritation-rabbit	44438703	Corrosive	I (unwashed eyes;
		44642104	Severe	II (washed eyes)
152-14	Skin Irritation-rabbit	44438704	Slight irritant	IV
		44642105	Slight irritant	IV

* p-Menthane-3,8-diol Technical is a solid material at room temperature. The acute inhalation toxicity data requirement is waived due to lack of exposure under conditions of use; inhalable materials are not expected with the manufacturing-use product.

1. **Acute Oral Toxicity** (MRID 44438701)

   In an acute oral toxicity study, 5 groups of 5 female rats were dosed with 500, 875, 1250, 2000 and 5000 mg/kg body weight, and 1 group of 5 male rats was dosed at 5000 mg/kg body weight. The primary clinical signs of toxicity were

decreased activity in 1 female (500 mg/kg group) and in all 5 females in the 1250 mg/kg group, and reduced/no feces were observed in 2 rats in this dose group. Wobbly gait was observed in 5 female rats at 1250 mg/kg. Other clinical effects noted in the 3 other dose groups included breathing abnormalities, prostration, apparent hypothermia, hunched posture, urine stain, ocular discharge, decreased food consumption, and/or dark material around the facial area. All rats had normal body weight gains except 1 female in the 1250 mg/kg group. Two females in the 2000 mg/kg group and 2 females in the 5000 mg/kg group died by day 3 of the study; none of the male rats died during the study. The timing of these observations was not specified, so it cannot be determined if these were immediate or delayed effects. In addition, at necropsy, the only notable effects were observed in the animals that died early in the study, and included: abnormal contents in the digestive tract, reddened mucosa of the stomach, dilated pelvis of the kidney, pale liver, blackish-purple spleen, distended ureters, and dark red thymus.

2. **Acute Dermal Toxicity** (MRID 44438702)

In this study, 5 male and 5 female NZW rabbits were tested at 5000 mg/kg. All rats survived and gained weight. Transient dark material around the mouth was observed in one animal. Significant dermal irritation was noted at the site of test material application, which included erythema, edema, dermal lesions, eschar, necrosis, desquamation and blanching, to varying degrees in all animals tested. (See the Primary Skin Irritation (MRID 44438704) study below, which is the appropriate study for determining skin irritation.) No significant changes were observed at necropsy. Three incidences of cysts on the oviducts were observed; however, these findings were not considered to be related to the test material application, as they are "commonly found in rabbits of this strain," according to the study author.

3. **Acute Inhalation Toxicity** (MRID 44642103)

In the acute inhalation study Sprague-Dawley strain rats (5/sex) were exposed by nose-only inhalation to UICK-2 for 4 hours at a concentration of 2.17 mg/L. No mortality

occurred, and clinical signs exhibited by the animals included breathing abnormalities, salivation, rough hair coat, and dark material on the facial area; these occurred prior to day 7. The males and one female gained weight throughout the study; four females lost body weight for the day 0-7 test interval but gained weight thereafter. Gross pathology at necropsy consisted of lung foci and enlarged mediastinal lymph nodes, which were found in most (7/10) of the animals.

4. **Primary Eye Irritation** (MRID 44438703)

Nine male NZW rabbits (5 males, 4 females) were treated with 0.1 mL of p-Menthane-3,8-diol. The treated eyes of 3 (1 male, 2 females) of the animals were rinsed with physiological saline approximately 30 seconds after instillation of the test material. All rabbits exhibited corneal opacity, iritis, and conjunctival irritation 1 hour after test material instillation, which persisted through 72 hours. In the group with unwashed eyes, corneal opacity persisted in 4 rabbits through day 7, and in 1 rabbit until the study was terminated at 28 days post instillation. In the rabbits with the washed eyes, corneal opacity and iritis were cleared by day 7. Conjunctival redness above normal level was observed in 2 animals until day 10. The persistence of significant corneal damage in the unwashed group for 28 days places the test substance in toxicity category I (corrosive) for eye irritation. (The guidelines no longer require unwashed eyes.) For washed eyes, the test substance is in toxicity category II. The product labels should clearly emphasize the hazard and first aid treatment for accidental eye exposure.

5. **Primary Skin Irritation** (MRID 44438704)

Six NZW rabbits (3 per sex) were treated dermally with 0.5 mL of the undiluted test substance, and the test site was covered with a semi-occlusive dressing for 4 hours. After the exposure period, the patches were removed and residual test material was wiped from the exposed skin with gauze moistened with distilled water. One hour after patch removal, very slight erythema and well-defined erythema were noted on 4/6 and 2/6 rabbits, respectively. The erythema cleared

by 72 hours on 4/6 rabbits; the remaining 2 animals exhibited barely perceptible erythema at this time point. By day 7, no traces of irritation were observed in these animals.

6. **Dermal Sensitization** (MRID 44438705)

p-Menthane-3,8-diol was evaluated for dermal sensitization potential using a modified Buehler method. For the induction phase, 0.3 mL of the undiluted test material was applied to the shaved backs of 10 male and 10 female Hartley-derived albino guinea pigs under occlusion for 6 hours once each week for 3 weeks. The animals were left untreated for 2 weeks before challenge. The animals were challenged with 0.3 mL of the undiluted test material under occlusion at naive sites for 6 hours. A naive control group consisting of 5 male and 5 female guinea pigs was treated with 0.3 mL of the undiluted test material at challenge only. Reactions were scored at 24 and 48 hours post exposure.

The test animals demonstrated little (slight, patchy) or no erythema after each induction and challenge dose. The naive control animals also exhibited little or no erythema after the challenge dose. The results of this test were compared to historical positive controls, in which 10 animals/sex were treated with DNCB as a contact sensitizer (all animals exhibited slight-to-moderate, confluent erythema following challenge) within 6 months of the present study. The test substance did not cause contact sensitization under the conditions of this study.

7. **Dermal Sensitization (MRID 44642106)**

In a dermal sensitization study with the end-use product, UICK-2 (10.0% a.i.), male and female Hartley albino guinea pigs (20 test, 10 controls) were tested using the Buehler method. A dermal response consisting of erythema (grade 1) and desquamation was seen on 5/20 animals after the second induction, and on 9 or 10/20 animals after the third induction with the end-use product after 24 and 48 hours. Very slight edema (grade 1) occurred on one animal after the second induction and on 2 animals after the third induction. Challenge resulted in slight or moderate confluent erythema

(grade 1 or 2) on 13/20 animals after 24 hours and on 4/20 animals after 48 hours. Very slight edema (grade 1) was also seen on 8 animals after 24 hours and on 2 animals after 48 hours. The mean dermal scores after 24 and 48 hours were 0.9 and 0.6, respectively, compared to 0.0 (no response) for the challenge control animals. The positive control experiment utilized DNCB and was conducted appropriately. In this study, the end-use product was a dermal sensitizer to male and female Hartley albino guinea pigs

8. **Dermal Sensitization in Humans (MRID 44642107)**

In a non-guideline dermal patch testing study, the potential of the end-use product (9.82-10.1% a.i.) to cause dermal sensitization in humans was tested in 110 volunteers, ages 18-71. The test was conducted using 0.2 mL of the end-use product per application. Nine applications per volunteer were given over a 3-week induction period. After an 11-13 day rest period, a challenge dose (0.2 mL) was applied and the skin examined at 24 and 48 hours post-application for signs of sensitization.

Of the 106 subjects who completed the test regimen, none developed a definitive dermal response. One individual had a "questionable" response (minimal irritation; slightly different from the surrounding skin) during the induction phase of the study, although this person had no response during the challenge reading. Another individual had a questionable response at the two challenge readings. Based on these tests, it is concluded that UICK-2 was not a human skin sensitizer under the conditions of this Repeated Insult Patch Test.

b. **Immunotoxicity: 28-day Dermal Study** (MRID 44438709)

In a dermal immunotoxicity study, female $B_6C_3F_1$ mice (10/dose) were exposed to undiluted p-Menthane-3,8-diol (a.i. 98.3%) at doses of 0.0, 1000, and 3000 mg/kg once per day for 28 days. Parameters tested were total body weight gains, weekly food consumption,

absolute and relative spleen and thymus weights, and antibody plaque forming cell assay

No mortality or clinically related signs of toxicity were observed. Mice exposed to p-Menthane-3,8-diol showed no statistically significant changes in body weight, or relative and absolute spleen and thymus weight compared with controls. Mice from both 1000 and 3000 mg/kg/day dosage groups did show statistically increased food consumption (17% and 16%, respectively) on day 21 but not on days 7, 14, or 28.

There are some problems interpreting the results of the plaque forming cell assay performed in this study. Exposure to 1000 mg/kg p-Menthane-3,8-diol resulted in a statistically significant 43% increase in antibody plaque forming cells/106 viable spleen cells. Total antibody plaque forming cells/spleen was increased 44% in the low dose group, but the enhancement was not statistically significant. Mice exposed to 3000 mg/kg showed no enhancement of either plaque forming cells/106 viable spleen cells or total plaque forming cells. Neither treatment group showed statistically significant changes in total number of viable cells per spleen and there were no differences in absolute and relative spleen and thymus weights in either test group.

The enhancement of the primary antibody response to sheep red blood cells in the low dose but not the high dose group, coupled with only two doses being tested, makes the lowest-observed-adverse-effect levels (LOAEL) appear to be lower than the NOAEL.

However, for the purposes of hazard identification, the NOAEL should be considered to be greater than 3000 mg/kg/day. The reason for this is that since the plaque forming cell assay is currently only considered to be sufficiently validated as a test for immune suppression, and no *suppression* of immune response occurred at a limit dose of 1000 mg/kg/day, the stimulatory effect noted at 1000 mg/kg/day (a limit dose) is not considered to be an endpoint of concern. Thus, repeating the plaque forming cell assay at lower doses is not suggested for the purposes of risk assessment and registration of this technical pesticide product. It is advisable, however, to assess any formulations which include p-Menthane-3,8-diol for effects on the immune system.

This immunotoxicity dermal exposure study is classified as supplementary. The study only partially fulfills the requirements outlined in the guideline, since only one immunologic parameter, humoral immune function measured by an antibody plaque forming cell assay, was tested. The study cannot be upgraded without the completion of the other assays included in that guideline. However, for the purposes of this risk assessment and the registration of p-Menthane-3,8-diol, further immunotoxicity testing is not required. The reasons for this are as follows: 1) the substance is a technical grade active ingredient, which will ultimately be incorporated into repellents for use on the skin and clothing; 2) no dermal sensitization was observed in a modified Buehler assay in guinea pigs (MRID 44438705); 3) no effects on absolute and relative spleen and thymus weights, which are valid endpoints for immune suppression, occurred in the 28-day study nor in a 90-day dermal toxicity study (MRID 44438710); and 4) the results of the 28-day immunotoxicity test indicated that no suppression of the primary antibody response to sheep red blood cells at a limit dose and higher. Thus, there is reasonable certainty that further immunotoxicity testing would not likely change the low level of concern for this endpoint.

c. **Subchronic (90-Day) Dermal Toxicity Study** (MRID 44438710)

In a 90-day subchronic dermal toxicity study, groups of 15 male and female Sprague-Dawley rats were treated with p-Menthane-3,8-diol (98.3%) at doses of 0, 1000 or 3000 mg/kg/day for 6 hours per day

Decreased body weight (-8% day 36; -9% day 43, p # 0.05) and body weight gain (-30% days 29-36, p # 0.05) were observed in the high dose males. Low dose males displayed decreased (-71% days 64-71, p # 0.05) and increased (+260% days 71-78, p # 0.01) body weight gain. No other effects on body weight were observed.

Barely perceptible erythema and desquamation was reported in all low dose male and female animals. In addition, a number of high dose male and female animals displayed well-defined erythema (23% male, 33% female), slight edema (8% male, 0% female) and pinpoint to moderate eschar (77% male, 40% female). Dermal findings in the control group were limited to one female with desquamation.

Treatment-related microscopic lesions were observed in the kidneys from high dose males and in treated skin from high dose males and females. Hyaline droplets, likely due to alpha-2u-globulin inclusions, were seen in kidneys of control males (20%, minimal to mild) and high dose males (100%, 73% moderate). Minimal acanthosis was observed in 53% of control males' treated skin, while minimal to mild acanthosis was seen in 93% of high dose males. Chronic inflammation was observed in male control (20%, minimal to mild), female control (13%, minimal), and high dose male (100%, 67% mild) and female (100%, 60% mild) animals. In addition, parakeratosis was seen in 7% of high dose males and 27% of high dose females.

Statistically significant increased absolute liver weight (+18%, p#0.001) and relative liver weight (+15%, p#0.001) were observed in high dose females. Relative liver weight (+9%, p#0.05), relative kidney weight (+12%, p#0.001), and relative adrenal weight (+15%, p#0.05) were increased in high dose males. There were no statistical differences noted for low dose male or female animals. No treatment-related effects were observed with regard to hematology, clinical chemistry, neurotoxicity, or ophthalmology.

Based on the data presented in this study, the NOAEL is 1000 mg/kg/day; the LOAEL is 3000 mg/kg/day. The LOAEL is based on dermal observations in treated skin (increased erythema, edema and eschar) and histological observations in treated skin (increased acanthosis and inflammation). **This subchronic dermal toxicity study in rats is classified as acceptable.**

d. **Developmental Toxicity Study** (MRID 44438711)

Twenty five pregnant Sprague-Dawley Crl:CD7BR rats per group were administered p-Menthane-3,8-diol (SCJ NB# 14735R108) (98.5% a.i., batch number 703002) by dermal application at doses of 0, 1, and 3 g/kg/day on gestation days (GD) 6-19, inclusive. All animals survived to scheduled sacrifice, and no treatment-related clinical signs of toxicity were observed during the study. The skin at the application site of treated animals also did not show signs of irritation. No statistically significant differences in absolute body weights occurred between the treated and control groups during the

study, but slightly decreased body weight gains (91% of controls; p # 0.05 during gestation days 6-20) and similar decreases in food consumption (90% of controls; p # 0.01 during gestation days 6-9) were observed at the highest dose tested. At all other times during the study, food consumption and body weight gains by the treated groups were comparable to the controls. No abnormalities were noted at maternal necropsy. **Therefore, the maternal toxicity NOAEL is >3 g/kg/day and the maternal toxicity LOAEL was not identified.** The study is acceptable and does not demonstrate toxic effects at or above a limit dose.

No dose-or treatment-related statistically significant effects on pregnancy rate, number of corpora lutea, pre- or postimplantation losses, resorptions/dam, fetuses/litter, fetal body weights, or fetal sex ratios were observed in the treated groups as compared to the controls. Two low-dose dams had complete litter resorption. No treatment-related external, visceral, or skeletal malformations/variations were observed in any litter. The number of litters in the 0, 1, and 3 g/kg/day groups containing fetuses with major malformations was 1/23, 2/21, and 1/22, respectively. All treated and control litters contained fetuses with minor variations in skeletal ossification. Therefore, the developmental toxicity NOAEL is >3 g/kg/day and the developmental toxicity LOAEL was not identified. The study is acceptable.

e. **Reproduction Toxicity**

Reproduction studies are not required (as a Tier 1 study) to support registration of biochemical pesticides. However, this information would be useful in the risk characterization of end use products, for determining an appropriate FQPA safety factor for infants and children. Without this study, and with only one developmental study in one species, it is possible that a ten-fold uncertainty factor will be applied to formulations containing p-Menthane-3,8-diol as the active ingredient.

f. **Mutagenicity Studies**

Four acceptable studies were conducted to evaluate the genotoxic potential of p-Menthane-3,8-diol (98.3% a.i.) including a bacterial

gene mutation assay (Harmonized Test Guideline 870.5100), an *in vitro* mammalian cell gene mutation assay (Harmonized Test Guideline 870.5300), an *in vitro* chromosomal aberration test (Harmonized Test Guideline 870.5), and a mammalian erythrocyte micronucleus test (Harmonized Test Guideline 870.5395). These studies satisfy the Tier I requirements for genotoxicity data (40 CFR, '158.690(c)).

1. **Reverse gene mutation assay (Ames Test;** MRID 44487801

   Strains TA98, TA100, TA1535 and TA1537 of *Salmonella typhimurium* and strain WP2(uvrA) of *Escherichia coli* were exposed to p-Menthane-3,8-diol (Batch No. 703001, 98.3% a.i.) in DMSO at concentrations of 25 (WP2(uvrA) only), 75, 200, 600, 1800, and 5000 µg/plate (limit concentration) in the presence and absence of mammalian metabolic activation (S9-mix). **There was no evidence of induced mutant colonies over background.**

2. **Mammalian cell gene mutation assay at the thymidine kinase locus** (MRID 44438706).

   L5178Y/TK" cells cultured in vitro were exposed to p-Menthane-3,8-diol (98.3% a.i., batch No. 703001) in DMSO at concentrations of 600, 800, 1000, 1250, 1500 and 2000 µg/mL in the absence of mammalian metabolic activation (S9-mix) and to concentrations of 500, 600, 800, 1000, 1250 and 1500 µg/mL in the presence of S9-mix. The 2000 µg/mL and 1500 µg/mL doses were too toxic to clone in the absence and presence of S9-mix, respectively, but no visible precipitate was seen in the treatment medium at any dose level. There was no evidence of induced mutant colonies over background.

3. **Mammalian cell chromosomal aberration cytogenetics assay** (MRID 44438708).

   Chinese hamster ovary CHO-K1 cell cultures were exposed to p-Menthane-3,8-diol (98.3% a.i., batch No. 703001) in DMSO in two independent assays. In the initial assay, concentrations of 50, 150, 500 and 1500 µg/mL, with and without metabolic activation (S9-mix), were evaluated

following a 6 hour treatment and a 14 hour recovery period. In the repeat assay without S9-mix, concentrations of 250, 500, 1000 and 1500 µg/mL were evaluated after 20 hours continuous treatment and concentrations of 125, 250, 500 and 1000 µg/mL were evaluated after 44 hours of continuous treatment. In the repeat assay with S9-mix, concentrations of 250, 500, 1000 and 1500 µg/mL were evaluated after 6 hours treatment and either a 14 hour or 38 hour recovery period. **There was no evidence in the results of the two assays that chromosomal aberrations were increased by the test material.**

4. **Mouse Micronucleus Assay** (MRID 44438707).

In an ICR mouse bone marrow micronucleus assay, five mice/sex/dose were treated once i.p. with p-Menthane-3,8-diol in corn oil (98.3% a.i., batch No. 703001) at doses of 104, 208, 416 mg/kg or dermally over four days with 3 mL/kg total of neat agent. Bone marrow cells were harvested at 24 hours (all doses) and at 48 hours (416 mg/kg only) post-treatment. All mice in the 208 and 416 mg/kg groups were lethargic following treatment. Convulsions and prostration were also seen in all mice in the 416 mg/kg group. Seven of 15 males and 7/15 females in the 416 mg/kg group displayed piloerection. All mice in the dermal application group showed both hyperactivity and lethargy after treatment. **There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow at any dose, harvest time or route of exposure.**

g. **Metabolism Studies**

Not required (as a Tier I study) for the registration of biochemical pesticides.

2. Not required (as a Tier I study) for the registration of biochemical pesticides.

a. **Endpoint Selection:** The endpoints, NOAEL and LOAEL are summarized from the submitted toxicological data as follows:

Table 3 Toxicity Profile of p-Menthane-3,8-diol (98.3%)

Guideline Reference No.	Study Type	MRID No.	Results
152-18	Immunotoxicity - mouse	44438709	NOAEL>3000 mg/kg/day (HDT) LOAEL not established
152-21	Subchronic Toxicity, Dermal - Rat	44438710	NOAEL=1000 mg/kg/day; LOAEL=3000 mg/kg/day (incre skin erythema, edema and esch
52-23	Developmental Toxicity - Rat	44438711	Maternal NOAEL>3 g/kg/day (HDT); LOAEL not established. Developmental: NOAEL > 3 g/kg/day (HDT), LOAEL not established
152-17	Gene Mutation - S. typhimurium / E. Coli (WP2(uvrA))	44487801	Non-mutagenic " activation;
152-17	Mouse Lymphoma	44438706	Non-mutagenic " activation
152-17	Micronucleus Assay	44438707	Non-mutagenic
152-17	Chromosomal Aberration-CHO-K1 cells	44438708	Non-mutagenic " activation

Not required (as a Tier I study) for biochemical pesticide registration. However, this information would be very useful for risk assessment purposes and determination of the Margin of Exposure (MOE) for end use products that use p-Menthane-3,8-diol as the active ingredient, since these types of products would be repeatedly applied directly to the skin. Without this data, dermal absorption would be assumed to be 100%; of course, the effects of the other ingredients in a formulation, as well as the dilution factor of the active ingredient, would be considered in characterizing risk.

3. **Exposure Assessment**

   a. **Dietary Exposure**

There are no food uses proposed for p-Menthane-3,8-diol, so acute and chronic dietary risk assessments are not required.

b. **Occupational and Residential Exposure**

No occupational estimates are made in this assessment since p-Menthane-3,8-diol is a technical grade active ingredient, and is to be used to formulate insect repellents.

c. **Aggregate Exposure**

The technical grade active ingredient, p-Menthane-3,8-diol, will be used to formulate pesticide products that can be applied to human skin and clothing to repel insects. This active ingredient is considered GRAS and is used to flavor foods and medicines, and is found in many consumer products. Based on this, the use pattern, and the hazard assessment described above, an assessment of aggregate exposure was not necessary for p-Menthane-3,8-diol.

4. **Risk Characterization**

a. **Sensitivity of Infants and Children**

There is only one developmental toxicity study (in one species) required as a Tier I study for the registration of biochemical pesticides. The study submitted for the registration of p-Menthane-3,8-diol was performed in the rabbit. This study indicated that there was no difference in sensitivity to p-Menthane-3,8-diol between rabbit fetuses and their mothers with respect to the dermal route of exposure. However, with only one developmental study, and no reproduction study, it is likely that a ten-fold safety factor may be applied when characterizing risk of any formulations using p-Menthane-3,8-diol as the active ingredient. See discussion under 5. c., Determination of Safety (U.S. Population, Infants and Children), below.

b. **Non-occupational Risk Characterization**

Margins of exposure (MOE) were not calculated. There was no level of concern (endpoints) identified from the submitted data, and since p-Menthane-3,8-diol is a technical grade product, non-occupational exposure is not expected. End-use skin applied insect repellent products containing this active ingredient have been submitted to the

Agency for registration. Risk has been characterized based upon the other ingredients as well as the dilution of the active ingredient within the formulation. See discussion under 5. c. Determination of Safety (U.S. Population, Infants and Children), below.

5.

6. **Other Food Quality Protection Act Considerations**

a. **Cumulative Risk from Exposure to Substances with a Common Mechanism of Toxicity**

Section 408(b)(2)(D)(v) of the Food Quality Protection Act requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The Agency believes that "available information" in this context might include not only toxicity, chemistry, and exposure data, but also scientific policies and methodologies for understanding common mechanisms of toxicity and conducting cumulative risk assessments.

Although the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, for most pesticides, EPA does not at this time have methodologies to resolve the complex scientific issues concerning common mechanisms of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will increase the Agency's scientific understanding of this question such that EPA will be able to develop and apply scientific principles for better determining which chemicals have a common mechanism of toxicity and evaluating the cumulative effects of such chemicals. The Agency anticipates, however, that even as its understanding of the science of common mechanisms increases, decisions on specific classes of chemicals will be heavily dependent on chemical specific data, much of which may not be presently available.

Although at present the Agency does not know how to apply the information in its files concerning common mechanism issues to most

risk assessments, there are pesticides as to which the common mechanism issues can be resolved. These substances include pesticides that are toxicologically dissimilar to existing chemicals. In this case, the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of toxicity with other substances. However, with other pesticides that produce a common toxic metabolite, the Agency will assume a common mechanism of toxicity.

In this registration, the active ingredient, p-Menthane-3,8-diol, is a technical product which will be used to formulate insect repellents to be applied to human skin and clothing. Its activity as an insect repellent is considered to be nonspecific and as a repellent the biochemical is considered to have a non-toxic mechanism of action. The non-toxic mechanism of activity, when used as an insect repellent, precludes attempting a cumulative risk assessment for this biochemical pesticide.

b. **Endocrine Disrupter Effects**

Even though EPA is still developing a screening program to determine whether certain substances [including all pesticide active ingredients, in addition to all other (inert) ingredients] "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...", the Agency has no reason to believe p-Menthane-3,8-diol has any effect on the endocrine system. When the screening and testing program has been established, EPA may require further testing of p-Menthane-3,8-diol for endocrine effects.

c. **Determination of Safety (U.S. Population, Infants and Children)**

Based on the evaluation of the submitted information, no endpoints of concern were identified from the studies required for registration of the technical grade active ingredient, p-Menthane-3,8-diol, which could be used in a risk assessment. Thus, there is reasonable certainty of no harm to the U.S. population or subpopulations, including infants and children, as the result of the uses of p-Menthane-3,8-diol to formulate repellents.

Even though there are no food uses at this time for this pesticide, it is intended for direct application to the skin, including that of infants

and children, and therefore, FQPA considerations apply. In this analysis, the appropriate safety factor is determined, which by Office of Pesticide Programs (OPP) policy (in addition to the FQPA requirements) includes a ten-fold uncertainty factor to be applied for infants and children unless appropriate data are available to justify its removal. For example, the conventional chemical pesticides that OPP regulates require a database which includes two developmental studies (in different species) and a two-generation reproduction study; based on the results of those studies, a decision is made to remove or retain the ten-fold safety factor. However, the requirements for a biochemical pesticide registration include only one developmental study (in one species), and there are usually no data available which demonstrate whether young animals are differentially affected upon exposure to that pesticide. Therefore, the ten-fold FQPA safety factor could be retained for biochemical pesticides, although the MOE (e.g., if exposure is equivalent to 1/1000th of the appropriate NOAEL) would be considered in this decision.

C.

D. Environmental Risk Assessment

1. Avian, Freshwater Fish, and Freshwater Invertebrate Toxicity (Guideline Reference No. 155-6-11)

Data is generally required on a case-by-case basis depending on the use pattern, production volumes and other pertinent factors. The use pattern of an personal insect repellent for humans does not indicate any significant exposure to birds, fish, invertebrates, or any other non-target organisms. Therefore, this data has not been required.

2. Ecological Exposure and Risk Characterization

For this registration action, the need for environmental fate and groundwater data or non-target organisms data are not triggered under current data requirements (See: 40 CFR 158.690(d)(2)(vii through xv).

E. Efficacy Data

Efficacy data (MRID 44642110) were submitted to support the registration of the end-use products. p-Menthane-3,8-diol was found to be efficacious against mosquitoes, however, only one field trial was submitted to support efficacy on biting flies, gnats, and no-see-ums. (This one study did support efficacy for biting flies,

gnats, and no-see-ums.) Therefore, the **registration of p-Menthane-3,8-diol is conditional on the submission of these data**. At the time the additional field study is submitted and found to support the use on biting flies, gnats, and no-see-ums, the registrations will have met the full requirements of FIFRA.

IV. Risk Management Decision

A. Determination of Registration Eligibility

FIFRA Section 3(c)(5) provides for the registration of new active ingredients if it is determined that:

A. its composition is such as to warrant the proposed claims for it;

B. its labeling and other materials required to be submitted comply with the requirements of FIFRA

C. it will perform its intended function without unreasonable adverse effects on the environment; and

D. when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment.

Accordingly, p-Menthane-3,8-diol is not expected to cause unreasonable adverse effects when used according to label instructions. Criteria "B" (above) is satisfied by the current labeling and by the data presented in this document. It is believed that this new pesticidal active ingredient will not cause any unreasonable adverse effects, will provide useful insect repellence for humans, as claimed, satisfying Criteria "C". Criteria "D" is satisfied in that the toxicological properties of this pesticide are not generally expected to cause unreasonable adverse effects on the environmen

However, efficacy data were not complete for a satisfactory finding for Criteria A. Therefore, p-Menthane-3,8-diol is only eligible for Conditional registration. The registered uses are listed below

p-Menthane-3,8-diol

- **Uses:** Insect repellent designed for application to human skin and clothing for the purpose of repelling insects.
- **Official date registered:** March 2000

B. Regulatory Position

0. **Conditional Registration**

All data requirements, except for one efficacy field test for biting flies and gnats are fulfilled for the Manufacturing Use Product, p-Menthane-3,8-diol Technical and the end-use product, OFF! Botanicals Insect Repellent 1. BPPD

has issued a Conditional registration for both of these new product registrations for repelling insects.

1. **Tolerance**

   There are no food uses for p-Menthane-3,8-diol, therefore, no tolerances have been established.

2. **CODEX Harmonization**

   Since there are no food uses associated with this registration, therefore, there are no CODEX harmonization considerations.

3. **Risk Mitigation**

   Since there are no outstanding issues of risk, additional risk mitigation measures are not required at this time, except for those required on the label to mitigate risks associated with exposure to eyes (see below).

4. **Endangered Species Statement**

   No Endangered Species Statement is required.

C. Labeling

It is the Agency's position that the labeling for the MUP, p-Menthane-3,8-diol Technical, (EPA Reg. No. 4822-499) containing 99.0% p-Menthane-3,8-diol complies with the current pesticide labeling requirements. It has also been determined that the labeling for the end-use product, OFF! Botanticals Insect Repellent 1 (EPA Reg. No. 4822-509) also complies with current labeling requirements.

0. **Human Health Hazard**

   a. **Worker Protection Standard**

      This product does not come under the provisions of the Worker Protection Standard (WPS).

   b. **Non-Worker Protection Standard**

      There are no non-WPS human health hazard issues.

   c. **Precautionary Labeling**

The Agency has examined the toxicological data base for the p-Menthane-3,8-diol products and concluded that the proposed precautionary labeling (i.e. Signal Word, First Aid statement, and other label precautionary statements) adequately mitigates the risks associated with the proposed uses.

Manufacturing-Use Product Precautionary Labeling: For p-Menthane-3,8-diol Technical (EPA Reg. No. 4822-499), the correct Signal Word is "DANGER". The proper precautionary labeling is:

Corrosive. Causes irreversible eye damage. Do not get in eyes or on clothing. Wear protective eyewear (goggles or face shield). Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash clothing before reuse.

End-Use Product Precautionary Labeling: For OFF! Botanticals Insect Repellent 1 (EPA Reg. No. 4822-509), the correct Signal Word is "WARNING". The proper precautionary labeling is:

Causes substantial but temporary eye injury. Do not get in eyes. Do not apply on the face or hands of small children. Do not allow children to apply this product to themselves. Do not apply to excessively sunburned or damaged skin. For external use only. Wash hands thoroughly with soap and water after applying.

d. **Spray Drift Advisory**

No spray drift advisory statement is necessary for this use.

1. **Environmental Hazards Labeling**

Manufacturing-Use Product Environmental Hazards Labeling:

"Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or other waters unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA."

End-Use Product Environmental Hazards Labeling:

Since OFF! Botanticals Insect Repellent 1 (EPA Reg. No. 4822-509) is considered indoor use, the environmental hazard statement is not required on this label.

2. **Application Rate**

It is the Agency's position that the labeling for the pesticide products containing p-Menthane-3,8-diol complies with the current pesticide labeling requirements. Based upon submitted efficacy data, for continued protection from biting insects, the end-use product should be reapplied "every two hours or after swimming, perspiration, vigorous activity or toweling".

V. Actions Required by Registrants

A. Report all incidences of adverse effects to humans or domestic animals under FIFRA, Section 6(a)2, and incidents of hypersensitivity under 40 CFR Part 158.690(c), guideline reference number 152-16.

B. Since these products are being registered after November 1984, they are not subject to Reregistration. No existing stocks provisions are applicable at this time, because this p-Menthane 3,8-diol is a new active ingredient and there are no existing stocks.

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