UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

APR 30 2003

MEMORANDUM

SUBJECT: Registration of UICK-T (EPA File Symbol 4822-LEA), Containing 8 % p-Methane-3,8-diol (PC Code 011550) as Active Ingredient. Review of Product Chemistry Data and Eye Irritation Study. D282656. Case No. 071468. Submission No. S613609. MRID Nos. 45615201 - 45615205.

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NOTE: This document contains Confidential Business Information (CBI).

ACTION REQUESTED

S.C. Johnson and Son, Inc. requests registration of UICK-T (EPA File Symbol No. 4822-LEA) containing 8 % p-methane -3,8-diol (PC Code 011550) as its active ingredient. UICK-T is intended for non-food use only. The product is a new formulation of the EPA-registered product, OFF! Botanicals 1 (EPA Reg. No. 4822-509).

The UICK-T product consists of a non-woven towel material that functions as a means of delivering the liquid insect repellant which is intended for application to the skin.

CONCLUSIONS

The Biopesticides Branch (BPB) has reviewed data submitted by S.C. Johnson & Son, Inc. to assess potential hazards and exposures that might result from the proposed use of UICK-T (EPA File Symbol No. 4822-LEA), a new insect repellant product containing the active ingredient, p-methane-3,8-diol (PC Code 011550).

Inert ingredient information not included.

1. All submitted product chemistry data are considered acceptable with the exception of two minor issues regarding *Product Identity and Composition* and *Certified Limits* (MRID 45615201).

1a. Regarding *Product Identity and Composition*, a discrepancy exists between the fragrance material listed in the CSF [redacted] CSF, which are identical to those used in OFF! Botanicals 1 (EPA Reg. No. 4822-509). The registrant must resolve these discrepancies, and CAS numbers for fragrance(s) must be listed on the CSF.

Note to RAL: The registrant must submit a list of the components that comprise [redacted] and [redacted] and demonstrate that they are identical to fragrances used in EPA Reg. No. 4822-509. Furthermore, the registrant must describe the components of the [redacted] towel and provide a CAS No. on the CSF.

1b. Regarding *Certified Limits*, upper and lower certified limits for the active ingredient, p-menthane-3,8-diol, and the inert towel are ±13% of the nominal concentration and are out of the recommended range proposed in OPPTS 830.1750. The registrant requested an increased variance of certified limits of the active ingredient and the inert towelettes based on the towel manufacturer's difficulty in cutting the towels to final finished dimensions. BPPD concurs with the registrant's request; no additional data are required.

2. The physical/chemical characteristics of UICK-T, Formula No. 15125P71 are adequately addressed with the exception of storage stability and corrosion characteristics. Flammability and density were not addressed but values are provided on the CSF for the UICK-T (MRID 45615201). This guideline is satisfied pending receipt of report of completed one year storage stability and corrosion characteristics studies.

3. Two acceptable acute eye irritation studies conducted in rabbits were submitted with this action. Based on the study results, the end-use product UICK-T is practically non-irritating and falls into category IV for primary eye irritation. The proposed labeling for UICK-T is acceptable.

4. An exposure and risk assessments was submitted based on the proposed use pattern for UICK-T. The results of the assessment indicate that risk estimates for adults and children do not exceed BPPD's level of concern (i.e., MOEs are greater than 100). BPB has reviewed the toxicological database and determined that there are no appropriate endpoints available from subchronic toxicity studies (including developmental toxicity studies in rats). Therefore, risk assessments are not required.

5. The proposed label states that the product contains 8 % p-menthane-3,8-diol, but in several places, the submission reports that UICK-T will contain 10 % active ingredient. In the administrative materials, the registrant explains that the inclusion of the towel in the formula

implies a level of 8.08 % p-menthane-3,8-diol, but the actual percentage of active ingredient delivered to the skin is 10.1 % (since the towel is a solid). The explanation provided by the registrant is acceptable.

6. The registrant requests that toxicity data from OFF! Botanicals 1 (EPA reg. No. 4822-509) be bridged to UICK-T. The rationale is based on the fact that both products contain essentially the same formulations and the inert nature of the towelette material which is not expected to alter the toxicological profile of the formulation. BPPD concurs with the registrant's request.

7. The registrant requests that bioefficacy data from OFF! Botanicals 1 (EPA reg. No. 4822-509) be bridged to UICK-T. The rationale is based on the amount of formulation delivered to the skin surface. The registrant claims to have performed a test in which UICK-T was used to deliver an average dose of 1.92 mg/cm^2 of the formulation to the skin surface. However, the study upon which the rationale is based was not submitted. This study/data must be submitted.

8. Based on the evaluation of submitted and previously reviewed data, there were no endpoints of concern identified 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, from the labeled use of the end-use product UICK-T (EPA File Symbol No. 4822-LEA).

I. EXECUTIVE SUMMARY

The Biopesticides and Pollution Prevention Division (BPPD) has reviewed product chemistry and acute toxicity data submitted by S.C. Johnson & Son, Inc. and used it to assess potential hazards and exposures that might result from the proposed use of UICK-T, containing the active ingredient, p-methane-3,8-diol (PC Code 011550). UICK-T is comprised of individually wrapped towelettes which are saturated with 8 % p-menthane-3,8-diol as the active ingredient. The registrant claims that UICK-T repels mosquitos, black flies, and biting flies for up to two hours. Based on the review of submitted information, dose levels and toxicity endpoints were evaluated to characterize potential risks.

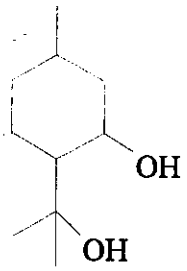
The technical grade active ingredient, p-methane-3,8-diol, falls into Toxicity Category IV for acute oral toxicity, dermal toxicity and skin irritation, and Toxicity Category I for eye irritation. It was not a skin sensitizer. The no-observed-effect level (NOEL) from a 90-day dermal toxicity study in rats was established at a limit dose of 1000 mg/kg/day. The NOEL 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 NOEL for maternal and developmental toxicity was established in rabbits at 3000 mg/kg/day by the dermal route. Mutagenicity studies evaluated p-methane-3,8-diol for its potential to cause point mutations in bacteria and mammalian cells, chromosomal aberrations in mammalian cells, and induction of micro nuclei in polychromatic erythrocytes from mouse bone marrow, and found no genotoxicity at the doses tested, with and without metabolic activation.

In this submission, product chemistry data, acute toxicity data and an exposure assessment were included. Based on the evaluation of the submitted and previously reviewed data, there were no appropriate endpoints of concern identified which could be used for risk assessment. Thus, there is reasonable certainty of no harm to the U.S. population or subpopulations, including infants and children, from the labeled use of UICK-T (EPA File Symbol No. 4822-LEA) containing 8 % p-methane-3,8-diol (PC Code 011550) as its active ingredient.

II. SCIENCE ASSESSMENT

A. Chemical Properties and Identity

The structural formula of p-methane-3,8-diol is shown below:



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

Product Chemistry MRID 45615201

Inert ingredient information not included.

[redacted]

No impurities are produced during the manufacturing process. No chemical reaction is expected to occur. Upper and lower certified limits of the inerts are within the acceptable range, but the upper and lower limits for the active ingredient, p-menthane-3,8-diol, and the inert towel are ±13% of the nominal concentration and are out of the recommended range proposed in OPPTS 830.1750. The registrant requested an increased variance of certified limits of the active ingredient and the inert towelettes based on the towel manufacturer's difficulty in cutting the towels to final finished dimensions. BPPD concurs with the registrant's request.

The enforcement analytical method was adequately described. The registrant indicated that they intend to register one basic and three alternate formulations but no data were provided for the latter.

This study is upgradable if the registrant clarifies which fragrance is used for the basic product and in any alternate formulations. If both fragrances are used as stated in the transmittal letter, then IFF 4060-AX needs to be listed on the CSF also. Data (CSFs) need to be provided for any alternate formulations to be registered.

Physical and Chemical Characteristics MRID 45615202

The physical/chemical characteristics of UICK-T, Formula No. 15125P71 are adequately addressed with the exception of storage stability and corrosion characteristics. Flammability and density were not addressed but values are provided on the CSF for the EP (MRID 45615201). According to the study summary, storage stability and corrosion characteristics will be evaluated in a separate study.

This study can be considered acceptable pending receipt of report of completed one year storage stability and corrosion characteristics studies. The physical and chemical characteristics of UICK-T are listed in the table below.

Table 1. Physical and Chemical Characteristics of UICK-T

Parameters	Results
Color	White
Physical State	Liquid saturated towelette
Odor	Light floral with characteristic alcohol
Oxidation/reduction	Product does not contain any oxidizing or reducing agents.
Flammability	56.8°F, TOC
Explodability	Product does not contain explosive components.
Storage Stability	Not reported[a]
Miscibility	Product is a solid substrate.
Corrosion Characteristics	Not reported[a]
Dielectric Breakdown Voltage	Product is not for use in and around electrical outlets.
pH	7.5 for 5% w/v in deionized water at 23°C
UV/visible absorption	Not required for end-use product.
Viscosity	Product is a solid substrate.
Melting Point	Not required for end-use product.
Boiling Point	Not required for end-use product.
Density	6.93 lb/gal
Dissociation Constant	Not required for end-use product.
Partition Coefficient	Not required for end-use product.
Water Solubility	Not required for end-use product.
Vapor Pressure	Not required for end-use product.

[a] The report indicated that storage stability and corrosion characteristics are evaluated in a separate study.

Classification: Unacceptable but upgradable to acceptable upon resolution of deficiencies described in conclusions 1a, 2 and 7.

B. Hazard Assessment

The toxicity database for p-methane 3,8-diol supports the registration of UICK-T (EPA File Symbol 4822-LEA).

1) Hazard Identification

a. Acute Toxicity

Primary Eye Irritation Study with Technical MRID 45615203

In this study, the irritant/corrosive effects of p-methane 3,8-diol were evaluated on the eyes of New Zealand White rabbits. Four dose levels were tested: 50 μL, 25 μL, 10 μL or 5 μL. Based on the presented/submitted data, corneal opacity was noted on 5/6, 6/6, 5/6, 5/6, 1/6, and 1/6 rabbits treated with 50 μL of UICK-2 one hour, 24 hours, 48 hours, 72 hours, 7 days, and 10 days after test material instillation, respectively, with resolution by day 14 or earlier.

Iritis and positive conjunctival irritation were noted on all rabbits one hour after test material instillation with resolution by day 7 or earlier. The maximum average score was 50.33 at one hour after test material instillation. In addition, neovascularization, sloughing of the corneal epithelium, corneal mineralization, and/or stippling on the cornea were noted on the eyes. When the eyes of the rabbits were treated with 25 μL, 10 μL, or 5 μL UICK-2, corneal opacity, iritis, and positive conjunctival irritation were noted on most the rabbits but with earlier recovery. When eyes of the rabbits were treated with 50 μL UICK-2, the test material was corrosive.

The results of the study show that the technical material falls into Toxicity Category I for acute eye irritation. However, a primary eye irritation study using the end-use product as the test substance was submitted (see below: MRID 45615204). Eye irritation label statements need not be based on the toxicity of the technical.

Primary Eye Irritation Study Using the End Use Product MRID 45615204

In this study, eye effects from UICK-T were tested on rabbits. Neither corneal opacity nor iritis was noted on any rabbit. Slight erythema (score 1) was noted on three rabbits treated with the towelette with UICK-2 one hour after the eyes were touched by the towelette with resolution on two rabbits by 24 hours and on another rabbit by 48 hours. The maximum average score was 1.00 at one hour after treatment. The rabbits treated with the placebo had no conjunctival irritation. SCJ NB# 15125P42 is practically non-irritating.

The study meets Agency criteria for a primary eye irritation study. The results of the study confirm that UICK-T falls into Toxicity Category IV. No statements are required, although the proposed labeling (based on Category III labeling) is acceptable.

b. Subchronic Toxicity

A 90-day subchronic dermal toxicity study was previously reviewed by BPB and found to be acceptable (RED: January, 2000; MRID 44438710). A summary of the review follows.

Groups of 15 male and female Sprague-Dawley rats were treated with p-methane-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, $p \leq 0.05$) and body weight gain (-30% days 29-36, $p \leq 0.05$) were observed in the high dose males. Low dose males displayed decreased (-71% days 64-71, $p \leq 0.05$) and increased (+260% days 71-78, $p \leq 0.01$) 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%, $p \leq 0.001$) and relative liver weight (+15%, $p \leq 0.001$) were observed in high dose females. Relative liver weight (+9%, $p \leq 0.05$), relative kidney weight (+12%, $p \leq 0.001$), and relative adrenal weight (+15%, $p \leq 0.05$) 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.

c. Developmental Toxicity

A developmental toxicity study in rats was previously reviewed by BPB and found to be acceptable (RED: January, 2000; MRID 44438711). A summary of the review follows.

Twenty-five pregnant Sprague-Dawley Crl:CD®BR 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; $p \leq 0.05$ during gestation days 6-20) and similar decreases in food consumption (90%of controls; $p \leq 0.01$ 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.

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.

d. Reproductive 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 any 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.

e. Mutagenicity

Four acceptable mutagenicity studies were previously submitted and reviewed by BPB (RED: January, 2000). The studies were conducted to evaluate the genotoxic potential of p-menthane-3,8-diol (98.3% a.i.), and include a bacterial gene mutation assay (OPPTS 870.5100), an *in vitro* mammalian cell gene mutation assay (OPPTS 870.5300), an *in vitro* chromosomal aberration test (OPPTS 870.5), and a mammalian erythrocyte micronucleus test (OPPTS 870.5395). These studies satisfy the Tier I requirements for genotoxicity data (40 CFR, §158.690(c)). The study summaries are presented below.

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). Some reduction in the number of revertants per plate was seen both with and without S9-mix at 1000 µg/plate and higher concentrations in WP2(uvrA). The mean number of revertants per plate at 1000, 3333 and 5000 µg/plate in this strain was reduced, compared to the solvent control value of 21 both with and without S9-mix, to 8, 5, and 3, respectively, with S9-mix and to 7, 8 and 4, respectively, without S9-mix. **There was no evidence of induced mutant colonies over background.**

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

L5178Y/TK$^{\pm}$ 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.**

Mammalian cell chromosomal aberration cytogenetics assay (MRID 444387-08)

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.**

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.**

f. Dermal Absorption

Dermal absorption data are 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 MOEs for any 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.

g. Metabolism

Data on the metabolism of p-menthane-3,8-diol are not required (as a Tier I study) for the registration of biochemical pesticides.

2) Dose Response Assessment

Endpoint Selection

No appropriate endpoints of concern were identified for p-menthane-3,8-diol in subchronic toxicity studies (including developmental toxicity studies in rats). Further, mutagenicity studies did not indicate any toxic effects. Therefore, human health risk assessments (oral, dermal and inhalation) for UICK-T are unnecessary. The toxicological profile for technical p-menthane-3,8-diol is presented in Table 2 below.

Table 2. Toxicity Profile of p-menthane-3,8-diol (98.3%)

Study Type	MRID No.	Results	Coregrade
Immunotoxicity - mouse	444387-09	NOAEL>3000 mg/kg/day (HDT); LOAEL not established	Supplementary
Subchronic Toxicity, Dermal - Rat	444387-10	NOAEL=1000 mg/kg/day; LOAEL=3000 mg/kg/day (increased skin erythema, edema and eschar)	Acceptable
Developmental Toxicity - Rat	444387-11	Maternal NOAEL>3 g/kg/day (HDT); LOAEL not established. Developmental: NOAEL > 3 g/kg/day (HDT), LOAEL not established	Acceptable
Gene Mutation - *S. typhimurium/E. Coli* (WP2(uvrA))	444878-01	Non-mutagenic ± activation	Acceptable
Mouse Lymphoma	444387-06	Non-mutagenic ± activation	Acceptable
Micronucleus Assay	444387-07	Non-mutagenic ± activation	Acceptable
Chromosomal Aberration-CHO-K1 cells	444387-08	Non-mutagenic ± activation	Acceptable

C. Exposure Assessment

1) Use Pattern

UICK-T is comprised of individually wrapped towelettes (8" by 10" when unfolded) which contain approximately 0.7 grams of active ingredient p-menthane-3,8-diol (at the rate of 0.109375 grams formulation per inch^2). The label states that the product contains 8 % p-menthane-3,8-diol, but in several places, the submission reports that UICK-T will contain10 % active ingredient. The proposed UICK-T label instructs users to "open package, remove and unfold towelette, using it to moisten all exposed skin evenly and completely." It warns users not to apply to eyes, lips, or mouth and not to apply to the hands of young children. Users are directed to wash hands thoroughly with soap and water after applying. For continued protection from listed insects, users are told to reapply every two hours or after swimming, perspiration, vigorous activity or toweling. After returning indoors, users should wash treated skin with soap and water.

2) Exposure Estimates

Included in this submission is an exposure assessment and a risk characterization for UICK-T (MRID 45615205). The registrant makes several reasonable health-protective assumptions in the exposure assessment. The registrant's analysis from a single use event

(involving the use of 2 towelettes for an adult and less than one for a child) results in margins of exposure that range from 220 to 430 for adults and 170 to 350 for children. Subchronic margins of exposure ranged from >880 to 1800 for adults and >1100 to 2100 for children. The registrant needs to resolve the discrepancy regarding the concentrations of the active ingredient of the EP given in the text and on the product label.

Upon review of the toxicological database for p-menthane-3,8-diol, BPB has determined that there are no appropriate endpoints available from subchronic studies (including developmental studies in rats) for use in risk assessment. Therefore, a risk assessment for this product is not required.

D. Risk Characterization

a. Dietary Exposure

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

b. Occupational and Residential Exposure

The intended use of UICK-T is for direct skin application as an insect repellant, but since no endpoints were identified for use in risk assessment, neither a residential nor an occupational risk assessment is required.

c. Aggregate Exposure

Based on the proposed use pattern, dermal exposure would be expected for adults and dermal and oral exposure would be expected for children. However, since no endpoints were identified for use in risk assessment, an aggregate risk assessment is not required.

4. Risk Characterization

a. Sensitivity of Infants and Children

There is only one developmental toxicity study (in rats) required as a Tier I study. The submitted study (MRID 44438711) indicated that there was no difference in sensitivity to p-menthane-3,8-diol between rat fetuses and their mothers with respect to the dermal route of exposure. For details, see Section B. 1) c. above.

b. Non-Occupational Risk Characterization

The intended use of UICK-T is for direct skin application as an insect repellant, but since no endpoints were identified for use in risk assessment, neither a residential nor an occupational

risk assessment is required.

5. Other Food Quality Protection Act Considerations

a. Cumulative Risk

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.

For most pesticides, although the Agency has some information in its files that may turn out to be helpful eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, 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 which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

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.

Before undertaking a cumulative risk assessment, BPPD will follow procedures for

identifying chemicals that have a common mechanism of toxicity as set forth in the "*Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity*" (64 FR 5795-5796, February 5, 1999).

b. Endocrine Disruptor Effects

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, p-menthane-3,8-diol may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

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-Methane-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-methane-3,8-diol to formulate repellents.

However, at such time as an end-use product is submitted to the Agency for registration, the potential effects of other ingredients and the dilution factor for the active ingredient within the formulation would have to be considered in the risk characterization. The reason for this is that even though there are no food uses for this pesticide, it is intended for direct application to the skin, including infants and children, and therefore, FQPA considerations apply. In this analysis, the appropriate safety factor will be determined, which by OPP policy includes a ten-fold uncertainty factor to be applied for infants and children unless appropriate data are available to its justify removal. For example, the 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 demonstrates whether young animals are differentially affected upon exposure to that pesticide. Therefore, the ten-fold FQPA safety factor would be probably be retained for biochemical pesticides, although the magnitude of exposure (e.g., if exposure is equivalent to 1/1000th of the appropriate NOAEL) would be considered in this decision.

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