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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 24 2000

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Registration of UICK 3 (EPA Symbol No. 4822-LRL), Containing 10% p-Menthane-3,8-Diol (Chemical No. 011550) as its Active Ingredient. Review of Product Chemistry and Acute Toxicity Studies (MRIDs 448376-01 to -07); Case No. 065963, Submission No. S566861; DP Barcode D258722.

FROM: Russell S. Jones, Ph.D., Biologist
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511C)

THROUGH: Freshteh Toghrol, Ph.D., Senior Scientist
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511C)

TO: James Downing, Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511C)

ACTION REQUESTED

S. C. Johnson & Son, Inc. requests registration of UICK 3 (EPA Symbol No. 4822-LRL), containing 10% p-menthane-3, 8-diol as its active ingredient. The end-use product is intended for use on human skin as a repellent against mosquitoes, black flies, gnats, no-see-ums, and chiggers. In support of the registration, the registrant has submitted product chemistry and acute toxicity studies, two Confidential Statements of Formula (CSF, dated 5/14/99) for two alternate formulations, and a proposed label.

BPB's CONCLUSIONS AND RECOMMENDATIONS

1. PBP does not support the registration of UICK 3 (EPA Symbol No. 4822-LRL) due to deficiencies in the CSFs, the proposed label, and the product performance (efficacy) data.

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2. The CSFs are unacceptable, but upgradable. To upgrade the CSFs to acceptable, the revised CSFs must show the percentage of active ingredient in the TGAI (Section 10 of the CSF) and list the name and address of the suppliers of all inert ingredients in place of the word "commodity" (Section 11 of the CSF).

3. The product chemistry studies submitted in fulfillment of Subdivision M Guidelines 151-10 to -17 are acceptable; no additional data are required.

4. The acute toxicity studies submitted in fulfillment of Subdivision M Guidelines 152-10 to 152-15 are acceptable; no additional data are required.

5a. The proposed product label is unacceptable. A revised label must be submitted. Label claims regarding the length of time the product repels biting flies and biting gnats cannot be assessed for accuracy until the requirement for additional field testing is satisfied (see Memorandum from R. S. Jones to J. Downing, dated 6/29/99). Data contained in previously reviewed and submitted studies indicate repellency of up to 5 hours for black flies and up to 2 hours for sand gnats, but the proposed label claims are supported by only one study each. Under new, proposed guidelines (OPPTS 810.3700 *Insect Repellents for Human Skin and Outdoor Premises*, EPA-712-C-99-389, DRAFT), at least two field tests will be required for each public health species.

5b. A label claim for two hours repellency against mosquitoes is acceptable. Label statements indicating that the product repels insects and/or bugs are to broad. The registrant must only list those insect species for which complete and acceptable product performance studies have been submitted (see Conclusion 5a above).

5c. There are numerous product claims on the front panel that are redundant and/or overlapping; these statements must be edited for accuracy and clarity. Statements indicating that the product repels "naturally" should be removed. Statements indicating that the product repels any insect species (other than mosquitoes) must be removed (see Conclusion 5a above). The statement indicating that the product contains no fragrances is misleading; one of the two formulations contains a fragrance as an inert ingredient.

6. Ecotoxicity/nontarget organism studies (154-6 to -15 and 155-4 to -13) are not required because the end-use product is an insect repellent applied to human skin.

7. No product performance (efficacy) studies were submitted to support this registration. However, efficacy data submitted to support the registration of a similar product (UICK 2, containing 10% *p*-menthane-3, 8-diol as its active ingredient) are bridged to support this registration. The previously submitted and reviewed data (MRID 44642110) may only be used to support proposed label claims for mosquitoes.

STUDY SUMMARIES

Product Chemistry

Product chemistry studies for UICK 3 were presented in MRIDs 448367-06 and -07. The end-use product consists of one basic and one alternate formulation. The active ingredient is p-menthane-3, 8-diol which comprises 10% of the product. The TGAI is not currently registered by EPA but is under review for registration (EPA File No. 4822-UOO). The end-use product is manufactured via a simple mixing process with no chemical reactions. Therefore, no discussion of manufacturing impurities, preliminary analysis, or analytical methods data are required. The submitted certified ingredient limits for the active and inert ingredients were acceptable. An analytical method was not submitted but none is required because the end-use product is produced via a simple mixing process. The product is an opaque, off-white liquid with a faint floral odor. It has a density of 0.98 g/mL at 21°C and a pH 7.3 (for a 5% solution). It does not contain any oxidizing/reducing agents, is not explosive, and is flammable at 98°C, but has no observed flash point.

Classification: Acceptable; no additional product chemistry studies are required, but the CSFs are unacceptable and must be revised (see Conclusion 2 above). Additionally, if the TGAI (EPA File No. 4822-UOO) is successfully, the registrant must list the percentage of a.i. in the TGAI on the CSFs.

Acute Toxicity

The registrant submitted five acute toxicity studies in MRIDs (448367-01 to -05). Based on a lack of mortality observed in ten rats orally-dosed with 5000 mg/kg UICK 3 (containing 10% *p*-menthane-3, 8-diol as its active ingredient), the LD_{50} is estimated to be >5000 mg/kg; tox category IV. Based on the lack of mortality in rabbits following dermal doses of 5000 mg/kg, the dermal LD_{50} for UICK 3 is >5000 mg/kg. However, because of observed mild toxicity symptoms in rabbits, the registrant should consider using toxicity category III precautionary statements on its label; tox category IV based on mortality data. No acute inhalation toxicity study was submitted. Since the new end-use product is dermally applied and not expected to produce significant amounts of its components in the air, it is not likely that significant human exposure would occur via inhalation. Ocular instillation of 0.1 mL of UICK 3 caused mild eye irritation symptoms in rabbits which cleared by 7 days posttreatment in unrinsed eyes; tox category III. Application of 0.5 mL of UICK 3 to the skin of rabbits causes mild skin irritation effects lasting up to 7 days. If these data alone were submitted, the product would have been classified in tox category III for skin irritation. However, BPB classifies UICK 3 in tox category IV for skin irritation based on results of human testing. No toxicity symptoms of irritation or hypersensitivity were observed in 102 humans treated with 0.2 g of test substance in a repeated insult patch study over a period of six weeks; UICK 3 is not an dermal irritant or sensitizer of human skin.

Classification: Acceptable; no additional data are required.

The registrant also submitted a "Hazard Identification and Evaluation of Potential Exposures and Health Risks Associated with Consumer Use of *p*-Menthane-3, 8-diol in UICK-3 Insect Repellent - Lotion Formulation" (MRID 448367-08). This information is summarized below:

Use Directions: The product is intended for use as an insect repellent and is to be applied as a lotion. It contains 10% *p*-menthane-3, 8-diol as its active ingredient. The proposed label claims that the product will repel mosquitoes, biting flies, gnats, and no-see-ums) for up to two hours. The product is to be applied by spreading evenly and completely over all exposed skin. There are precautionary statements against application to eyes and mouth or to the hands of young children. The product may be reapplied every two hours, or after swimming, perspiration, of vigorous activity. The product user is further instructed to wash treated areas of skin with soap and water after returning indoors.

Toxicological Profile: Based on data obtained from acute toxicity studies (see above) and other published studies in the open technical literature (see attachments), the active ingredient, *p*-menthane-3, 8-diol, has low oral toxicity and no subchronic, neurologic, and/or developmental toxicity via dermal exposure. Bacterial and mammalian test systems did not exhibit evidence for immunotoxicity or genotoxicty. Inhalation toxicity is not expected because inhalation is considered an unlikely route of exposure. Incidental ingestion via "hand-to-mouth" exposure by young children is considered low. Furthermore, the proposed product label contains a statement "Do not apply to the hands of young children." Since little or no toxicity was observed in a battery of acute, subchronic, and developmental toxicity studies, the highest doses tested in these studies may be used as No Observed Adverse Effect Levels (NOAELs). Thus, based on the data, the acute dermal NOAEL is 5000 mg/kg and the subchronic, developmental, and neurotoxicity NOAEL is >3000 mg/kg.

Exposure Assessment: A survey conducted by Boomsa and Parthasarathy (1990; see attachments) evaluated representative distribution information regarding the frequency and amount applied per use of several insect repellent products. These data were used to estimate potential exposure distributions for adults and children under 12 years of age. The survey determined that the mean amount of all lotion products used on skin and clothing was 1.0 g/application. Since UICK 3 contains 10% active ingredient, only 0.1 g of *p*-menthane-3, 8-diol is applied to skin per application of product. The use frequency for all insect repellent products during the peak use season (July and August) ranged from a mean of 8.0-8.5 for adults to 5.5-5.6 for children up to age 17. Based on these data, adults were estimated to use lotion products an average of 9 times during the peak use season, and children under 12, an average of 6 times (rounded to the nearest whole number). If an estimated 1 g of UICK 3 is used per application, the resulting average dermal exposure per application was calculated to be 1.4 mg a.i./kg boy weight (for 70 kg adults) and 6.7 mg a.i./kg body weight (for 15 kg children, 2-4 years of age). The

average subchronic, daily subchronic dermal exposure was calculated to be 0.21 mg a.i./kg/day for adults and 0.65 mg a.i./kg /day for children.

Risk Characterization: In order to characterize potential health risks associated with the use of UICK 3, the highest doses tested in the acute oral toxicity study (5000 mg/kg) and dermal subchronic toxicity studies (3000 mg/kg) were compared with the estimated average and 95th percentile values for dermal exposures for both acute (single application) and subchronic (multiple application) scenarios (see MRID 448367-08, pp. 14-18 for details). The relative safety of a given exposure was expressed as a Margin of Exposure (MOE) that is defined as the NOAEL divided by the exposure. A MOE of ≥100 is considered to be an acceptable level of safety. The MOEs for UICK 3 are shown in the table below.

Estimated Dermal Exposures (Applied Doses) and Margins of Exposure (MOEs) for Children and Adults Exposed to *p*-Menthane-3, 8-Diol in UICK-based Insect Repellent Lotions (from MRID 446783-08, p. 20)

Exposure	Mean Dermal Exposure (mg/kg/day)	95th Percentile Dermal Exposure	MOEs* for Mean Dermal Exposures	MOEs* for 95th Percentile Dermal Exposure
Child Acute (per application) Exposure	6.7	19.3	>750	>260
Child Subchronic (repeated application) Exposure	0.65	1.9	>4600	>1600
Adult Acute Exposure	1.4	4.0	>3600	>1250
Adult Subchronic Exposure	0.21	0.59	>14000	>5100

* Based on dividing either the acute dermal NOAEL (>5000 mg/kg/day) or the subchronic dermal NOAEL (>3000 mg/kg/day) by dermal exposure (applied dose); rounded to two significant figures.

Conclusions: Based on the submitted toxicity and calculated MOEs (greatly exceeding 100), dermal exposure to *p*-menthane-3, 8-diol in UICK 3 is unlikely to cause any significant adverse health effects.

Classification: Acceptable; no additional data are required for UICK 3.

Product Performance (Efficacy)

No product performance (efficacy) studies were submitted. However, previously submitted and reviewed efficacy data (see Memorandum from R. S. Jones to J. Downing, dated 6/29/99), using a product similar to UICK 3 (UICK 2, containing 10% *p*-menthane-3, 8-diol as its active

ingredient; EPA Symbol No. 4822-LNO), are bridged to support the registration of UICK 3. In the previously submitted studies (MRID 44642110), one field study each was submitted for black flies (*Simulium* spp.) and biting gnats (*Culicoides* spp.), and two field studies were submitted for mosquitoes (*Aedes* spp. and *Mansonia* spp.). Data contained in the submitted studies indicate repellency of up to 5 hours for black flies, up to 2 hours for sand gnats, and for up to 2 hours repellency against mosquitoes. The black fly test was conducted in MI, the sand gnat test was conducted in FL, and the two mosquito tests were respectively conducted in FL and WI. Current guidelines {OPPTS 810.3400 [*Mosquito, Black Fly, and Biting Midge (Sand Fly) Treatments, EPA 712-C-98-419, March 1998*]} require five field tests for each species at geographically separate locations. New, proposed guidelines will specify that only two field trials are required. Based on the above information, the black fly and sand gnat tests are considered supplemental; to upgrade these studies to acceptable, one additional field test must be submitted for each species at a location that is geographically separated from the first tests. Therefore, label claims regarding the length of time the product repels biting flies and biting gnats cannot be assessed for accuracy until the requirement for additional field testing is satisfied. A label claim for up to two hours repellency against mosquitoes is acceptable.

Classification: Acceptable for mosquitoes. Supplemental for sand gnats and black flies; to upgrade the studies to acceptable, the deficiencies described above and in Conclusion ~~4~~5a above must be resolved.

LABEL REVIEW

A proposed product label was submitted and reviewed. The product label is unacceptable. To upgrade the label to acceptable the deficiencies identified in Conclusions 5a, 5b, and 5c above must be resolved.

Based on the submitted toxicity data, UICK 3 is classified in toxicity category IV for acute oral toxicity, acute dermal toxicity, and primary dermal irritation. It is not a sensitizer. Although no acute inhalation toxicity study was submitted, none was required because inhalation is not a likely pathway of exposure. The product is classified in toxicity category III for primary eye irritation. The signal word, precautionary statements, and first aid statements are appropriate for a toxicity category III eye irritation classification.

cc: R. S. Jones, J. Downing, BPPD Subject File
R. S. Jones: F.T. CM2, 703/308-5071: 2/24/2000

DATA EVALUATION REPORT

Reviewed by: Russell S. Jones, Ph.D. BPPD
Secondary Reviewer: Freshteh Toghrol, Ph.D. BPPD

STUDY TYPE:	Toxicology Studies; Guideline Nos. 152-10 through 152-15 (MRID 44332105).
TOX. CHEM. No.:	None
CASE No.:	065963
PC CODE:	011550
DP BARCODE:	D258722
SUBMISSION No.:	S566861
MRID Nos:	448367-01 and -05
TEST MATERIALS:	UICK-3 (containing 10% p-menthane-3, 8-diol as its active ingredient)
STUDY Nos:	SLI Study Nos. 3068.187 to 3068.191; SCJ Study No. 390
SPONSOR:	S. C. Johnson & Son, Inc., 1525 Howe St., Racine, WI 53403
TESTING FACILITY:	Springborn Laboratories, Inc. (SLI), Ohio Research Center, 640 North Elazabeth Street, Spencerville, OH 45887 (MRIDs 48367-01 to -04); and TKL Research, Inc., 4 Forest Avenue, Paramus, NJ 07652 (MRID 448367-05)
TITLES OF REPORTS:	An Acute Oral Toxicity Study in Rats with UICK-3 (MRID 448367-01); An Acute Dermal Toxicity Study in Rats with UICK-3 (MRID 448367-02); A Primary Eye Irritation Study in Rabbits with UICK-3 (MRID 448367-03); Primary Skin Irritation Study in Rabbits with UICK-3 (MRID 448367-04); Repeated Insult Patch Study with UICK-3 (MRID 448367-05)
AUTHORS:	Kimberly L. Bonnette, M. S. LATG (MRIDs 48367-01 to -04); Nancy Vendetti (MRID 48367-05).

REPORTS COMPLETED: March 1999 (MRIDs 48367-01 to -04); and April 1999 (MRID 448367-05)

QUALITY ASSURANCE: The studies were conducted under Good Laboratory Practices; compliance statements were signed by the sponsor/submitter and study author(s).

SUMMARY: The registrant submitted five acute toxicity studies in MRIDs (448367-01 to -05). Based on a lack of mortality observed in ten rats orally-dosed with 5000 mg/kg UICK 3 (containing 10% *p*-menthane-3, 8-diol as its active ingredient), the LD_{50} is estimated to be >5000 mg/kg; tox category IV. Based on the lack of mortality in rabbits following dermal doses of 5000 mg/kg, the dermal LD_{50} for UICK 3 is >5000 mg/kg. However, because of observed non-fatal toxicity symptoms in rabbits, the registrant should consider using toxicity category III precautionary statements on its label; tox category IV based on mortality data. No acute inhalation toxicity study was submitted. Since the new end-use product is dermally applied and not expected to produce significant amounts of its components in the air, it is not likely that significant human exposure would occur via inhalation. Ocular instillation of 0.1 mL of UICK 3 caused mild eye irritation symptoms in rabbits which cleared by 10 days posttreatment in unrinsed eyes; tox category III. Application of 0.5 mL of UICK 3 to the skin of rabbits causes mild skin irritation effects lasting up to 7 days. if these data alone were submitted, the product would have been classified in tox category III for skin irritation. However, BPB classifies UICK 3 in tox category IV for skin irritation based on results of human testing. No toxicity symptoms of irritation or hypersensitivity were observed in 102 humans treated with 0.2 g of test substance in a repeated insult patch study over a period of six weeks; UICK 3 is not an irritant or sensitizer of human skin.

I. ACUTE ORAL TOXICITY IN RATS, Limit Test (152-10); MRID 448367-01)

A. MATERIALS

Test Substance:	UICK-3 (containing 10% *p*-menthane-3, 8-diol as its active ingredient)
Lot No.:	390D1
pH:	Not specified; pH 7.3 according to CSF dated 5/14/99
Physical description:	Milky, off-white, viscous liquid
Storage Conditions:	Room temperature
Dose level:	5000 mg test substance/kg body weight
Controls:	None
Test Animals:	Young adult approx. 9 weeks; Harlan Sprague-Dawley® SD® rats
Weight:	Males 257-289 g; females (nulliparous and nonpregnant), 186-201g
No. of animals:	10 (5 male, 5 female)
Acclimitation:	At least 5 days

Housing:	Individually housed in suspended steel cages
Identification:	Cage cards and ear tags
Food:	PMI Certified Rodent Chow #5002 *ad libitum*
Water:	Available *ad libitum*
Temperature:	22-24°C
Relative humidity:	31-43%
Photoperiod:	12 hour light/12 hour dark cycle

B. TEST PERFORMANCE

Dosing: Prior to dosing, rats were weighed and fasted overnight. A single oral dose (5000 mg/kg) was administered to each rat by oral gavage.

Observation: Test animals were observed for mortality and toxic symptoms at least twice/day on day 0 and once daily for the next 14 days.

Necropsy: All rats were euthanized by carbon dioxide inhalation on day 14 and necropsied..

C. RESULTS

Clinical Observations: No mortalities occurred during the study. Except for one female rat, all animals gained weight during the study period. The following toxic symptoms were observed: slight fecal staining in two males at day 1, rales and congested breathing in on male at day 1, and small fecal size in one female at day 12. All symptoms in males cleared by day 2, and in the female by day 13. All rats were otherwise healthy. All necropsies were negative.

D. STUDY DEFICIENCIES

None

E. CONCLUSIONS

No additional data are required for acute oral toxicity (§152-10). Based on a lack of mortality observed in ten experimental rats orally-dosed with 5000 UICK 3 (containing 10% *p*-menthane-3, 8-diol as its active ingredient, the LD_{50} is estimated to be >5000 mg/kg. Classification: Acceptable; Tox category IV.

II. ACUTE DERMAL TOXICITY IN RABBITS; Limit Test; (152-11) MRID 448367-02

A. MATERIALS

Test Substance:	UICK-3 (containing 10% *p*-menthane-3, 8-diol as its active ingredient)
Lot No.:	390D1
pH:	Not specified; pH 7.3 according to CSF dated 5/14/99

Physical description:	Milky, off-white, viscous liquid
Storage Conditions:	Room temperature
Dose level:	5000 mg test substance/kg body weight
Controls:	None
Test Animals:	Adult New Zealand, white rabbits. Approx. 12 weeks old
Weight:	Males 2.5-2.8 kg; females (nulliparous and nonpregnant), 2.5-2.7 kg
No. of animals:	10 (5 male, 5 female)
Acclimitation:	At least 5 days
Housing:	Individually housed in suspended steel cages
Identification:	Cage cards and ear tags
Food:	PMI Certified Rabbit Chow #5322 *ad libitum*
Water:	Available *ad libitum*
Temperature:	16-23°C
Relative humidity:	20-55%
Photoperiod:	12 hour light/12 hour dark cycle

B. TEST PERFORMANCE

Dosing: Experimental animals were prepared by clipping fur from their backs and sides (approximately 10% of body surface area. The test substance (5000/mg/kg) was spread evenly over the treatment area and covered with a 4-ply gauze dressing backed with plastic wrap. An elastic wrap was placed over the occlusive binding and secured with tape. The exposure period was 24 hours, after which the wraps were removed and the test substance was cleaned from the rabbits with gauze moistened with deionized water.

Observation: The skin condition and health of the animal were monitored immediately after the removal of the test substance and daily for the next 14 days.

Necropsy: All rabbits were euthanized via intravenous injection of sodium pentobarbitol at the end of the study and necropsied.

C. RESULTS

No mortalities occurred during the study. Except for two female rabbits, all test animals gained weight throughout the study. All animals exhibited short-term incidents of soft stools, fecal stain, and/or dark material around the facial area. Dermal irritation was also noted at the site of application of the test substance. Necropsies were generally negative, except for two observations of ovarian cysts; the authors state that these cysts are common for this strain of rabbit.

D. STUDY DEFICIENCIES

None

D. CONCLUSIONS

No additional data are required for acute dermal toxicity (152-11). Based on the lack of mortality following dermal doses of 5000 mg/kg, the dermal LD_{50} for UICK 3 (containing 10% *p*-menthane-3, 8-diol as its active ingredient) is >5000 mg/kg. However, because of observed non-fatal toxicity symptoms in rabbits, the registrant should consider using toxicity category III precautionary statements on its label. Classification: Acceptable; tox category IV based on mortality data.

III. ACUTE INHALATION TOXICITY; 152-12

No acute inhalation toxicity study was submitted. Since the new end-use product is dermally applied and not expected to produce significant amounts of its components in the air, it is not likely that significant human exposure would occur via inhalation. Therefore, no data are required to satisfy this guideline.

IV. PRIMARY EYE IRRITATION; (152-13) MRID 448367-03

A. MATERIALS

Test Substance:	UICK-3 (containing 10% *p*-menthane-3, 8-diol as its active ingredient)
Lot No.:	390D1
pH:	Not specified; pH 7.3 according to CSF dated 5/14/99
Physical description:	Milky, off-white, viscous liquid
Storage Conditions:	Room temperature
Dose level:	0.1 mL (8 rabbits, non rinse group; 1, rinse group)
Controls:	None
Test Animals:	Adult New Zealand, white rabbits. Approx. 12-14 weeks old
Weight:	Males 2.6-3.2 kg; females (nulliparous and nonpregnant), 2.2-2.9 kg
No. of animals:	9 (4 male, 5 female)
Acclimitation:	At least 5 days
Housing:	Individually housed in suspended steel cages
Identification:	Cage cards and ear tags
Food:	PMI Certified Rabbit Chow #5322 *ad libitum*
Water:	Available *ad libitum*
Temperature:	16-22°C
Relative humidity:	17-30%
Photoperiod:	12 hour light/12 hour dark cycle

B. TEST PERFORMANCE

Dosing: Prior to dosing, one drop of fluorescien dye was placed into the eyes for 15 seconds (then rinsed) and test rabbits ere examined for ocular irritation or pre-existing injury. One hour after a preliminary examination, the test substance (0.1 mL) was applied by instillation

into the conjunctival sac of the right eye of each of 9 (4 male, 5 female) experimental animals; the left eye served as an untreated control and the treated eyes remained unrinsed in 3 males and 3 females. For the remaining rabbits, the treated eyes were rinsed with deionized water 2-3 minutes after instillation.

Observation: The condition of the cornea, iris, and conjunctiva were evaluated and scored at 1, 24, 48, and 72 hours posttreatment and daily up to 10 days posttreatment.

Necropsy: None

C. RESULTS

No-rinse Group: Mild iritis was observed in two rabbits at 1 hour postdosing which cleared by day 7. Mild to moderate conjunctivitis (redness, swelling, and/or discharge) was exhibited in eyes of all rabbits at 1 hour postdosing and cleared in 5 rabbits by day 10. The author stated that the conjunctival irritation in the eye of the remaining rabbit at day 10 postdosing was not sufficient to be a positive effect. BPB does not agree with this conclusion. Rinsed Group: Conjunctivitis was observed in the eyes of all three treated rabbits at - hour postdosing, but cleared by day 7.

D. STUDY DEFICIENCIES

None

E. CONCLUSIONS

No additional data are required for primary eye irritation (152-13). Ocular instillation of 0.1 mL of the new end-use product caused mild eye irritation symptoms which cleared by 10 days posttreatment in unrinsed eyes. Classification: Acceptable; tox category III.

V. PRIMARY DERMAL IRRITATION; (152-14); MRID 448367-04

A. MATERIALS

Test Substance:	UICK-3 (containing 10% *p*-menthane-3, 8-diol as its active ingredient)
Lot No.:	390D1
pH:	Not specified; pH 7.3 according to CSF dated 5/14/99
Physical description:	Milky, off-white, viscous liquid
Storage Conditions:	Room temperature

Dose level:	0.5 mL
Controls:	None
Test Animals:	Adult New Zealand, white rabbits. Approx. 11 weeks old
Weight:	2.3-2.5 kg
No. of animals:	6 male
Acclimitation:	At least 5 days
Housing:	Individually housed in suspended steel cages
Identification:	Cage cards and ear tags
Food:	PMI Certified Rabbit Chow #5322 *ad libitum*
Water:	Available *ad libitum*
Temperature:	16-22°C
Relative humidity:	20-35%
Photoperiod:	12 hour light/12 hour dark cycle

B. TEST PERFORMANCE

Dosing: Experimental animals were prepared by clipping fur from their backs and sides (approximately 10% of body surface area. The test substance (5000/mg/kg) was spread evenly over the treatment area and covered with a 4-ply gauze dressing backed with plastic wrap. An elastic wrap was placed over the occlusive binding and secured with tape. The exposure period was 4 hours, after which the wraps were removed and the test substance was cleaned from the rabbits with gauze moistened with deionized water.

Observation: The skin condition and health of the animal were monitored 1, 24, 48, and 72 hours posttreatment and daily up to 10 days posttreatment.

Necropsy: All rabbits were euthanized via intravenous injection of sodium pentobarbitol at the end of the study and necropsied.

C. RESULTS

Slight to well-defined erythema was exhibited at the treatment sites on all six rabbits at 1 hour postdosing; symptoms cleared by day 10. Desquamation was observed on two rabbits on day 7 and 10.

D. STUDY DEFICIENCIES

None

E. CONCLUSIONS

No additional data are required for primary dermal irritation (152-14). Based on the submitted data, application of 0.5 mL of UICK 3 to the skin of rabbits causes mild skin

irritation effects lasting up to 7 days. Classification: Acceptable; tox category III, based on these data, but tox category IV based on results of human testing (see below).

VII. REPEATED INSULT PATCH STUDY; (No Guideline No.) MRID 448367-05)

UICK 3 (containing 10% *p*-menthane-3, 8-diol as its active ingredient) was evaluated for its potential to cause skin sensitization in human volunteers.

A. MATERIALS

Test Substance:	UICK-3 (containing 10% *p*-menthane-3, 8-diol as its active ingredient)
Lot No.:	390D1
pH:	Not specified; pH 7.3 according to CSF dated 5/14/99
Physical description:	Lotion base/white cream
Storage Conditions:	Room temperature
Dose level:	0.2 g
Controls:	None
Test Animals:	111 Humans over 18 years of age (20-75); only 102 completed the study.
Weight:	Not applicable
No. of animals:	

B. TEST PERFORMANCE

Dosing: Experimental animals were prepared by clipping fur from their backs and sides (approximately 10% of body surface area. The test substance (5000/mg/kg) was spread evenly over the treatment area and covered with a 4-ply gauze dressing backed with plastic wrap. An elastic wrap was placed over the occlusive binding and secured with tape. The exposure period was 4 hours, after which the wraps were removed and the test substance was cleaned from the rabbits with gauze moistened with deionized water.

Observation: The skin condition and health of the animal were monitored 1, 24, 48, and 72 hours posttreatment and daily up to 10 days posttreatment.

Necropsy: All rabbits were euthanized via intravenous injection of sodium pentobarbitol at the end of the study and necropsied.

C. TEST PERFORMANCE

Dosing: Dosing was accomplished by applying 0.2g of test substance to the infrascapular area of the back, either to the right or left of the midline. Occlusive patches were placed over the application sites and secured with hypo-allergenic tape. Each subject was given a schedule of study activities and told to avoid wetting the patches or engage in activities that caused excessive perspiration The six-week study had three phases: (i) Induction; (ii) Rest; and (3) Challenge. Induction: Nine consecutive applications of the test substance which were removed 24 hours after application. Subjects returned to the test facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Rest Phase: Following the ninth evaluation, subjects were rested for 10

to 14 days (for subjects that missed and evaluation and required a make-up induction). Induction Phase: During the sixth week of the study, identical patches were placed over test substance applied to previously untreated sites, and removed after 24 hours. Induction sites were then evaluated at 24, 48, and 72 hours posttreatment.

D. RESULTS

The study author reported that no symptoms of irritation of hypersensitivity were observed on the treatment or control sites during the experimental period.

E. STUDY DEFICIENCIES

None

F. CONCLUSIONS

No additional data are required. No toxicity symptoms of irritation or hypersensitivity were observed in 102 humans treated with 0.2 g of test substance in a repeated insult patch study over a period of six weeks. Classification: Acceptable; UICK 3 is not an irritant or sensitizer of human skin.

ATTACHMENTS (3) TO NON-CONFIDENTIAL PORTION OF THIS REVIEW

MRID 446783-08, pp. 9, 22, and 23

Table 1. Summary of 3,8-diol Toxicology Studies.

Acute oral toxicity:	LD_{50} rats: males > 5,000 mg/kg; females 5,308 mg/kg (Bonnette 1997)
Acute dermal toxicity:	LD_{50} rats: males and females > 5,000 mg/kg (Bonnette 1997)
Acute inhalation toxicity:	(exposure by inhalation is not considered to be a significant or relevant route of exposure during typical or accidental use conditions)
Skin irritation:	Rabbits - slightly irritating (Bonnette 1997)
Eye irritation:	Rabbits - severe eye irritant (Bonnette 1997)
Sensitization:	Rats - no evidence of sensitizing properties (Bonnette 1997)
Immunotoxicity:	Mice (28-day dermal study) - no detrimental effect on immunogenic response (House, R.V., W.D. Johnson and J.F. Krueger 1997)
Subchronic dermal toxicity:	Rats (90-day dermal study) - no evidence of toxicity at highest dose tested, i.e., 3,000 mg/kg/day (included evaluation of clinical observations, neurotoxicity, systemic toxicity and histopathology) (Rush 1997)
Prenatal developmental tox:	Rats - no evidence of maternal or fetal toxicity at highest dose tested, i.e., 3,000 mg/kg/day (Wakefield 1997)
In vitro mammalian cell gene mutation assay	Negative (San, R.H. and J.J. Clarke 1997)
Bacterial reverse mutation assay	Negative (Wagner, III, V.O. and E.W. Walton 1997)
Mammalian erythrocyte micronucleus assay	Negative (Gudi, R. and P. Ritter 1997)
In vitro mammalian cytogenetic test using chinese hamster ovary (CHO) cells	Negative (Gudi, R. and E.H. Schadly 1997)

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CONFIDENTIAL APPENDIX

THE FOLLOWING PAGES CONTAIN
CONFIDENTIAL BUSINESS INFORMATION
(CBI)
for
UICK 3 (Containing 10% p-Menthane-3, 8-diol)
Chemical No. 011550
EPA Symbol No. 004822-LRL

PRODUCT CHEMISTRY CONCLUSIONS AND RECOMMENDATIONS

1. The submitted product chemistry data are acceptable for registration pending submission of revised CSFs for the basic and alternate formulations. The revised CSFs must show the percentage of active ingredient in the TGAI (Section 10 of the CSF) and list the name and address of the suppliers of all inert ingredients in place of the word "commodity" (Section 11 of the CSF). Furthermore, the registrant must select one of the two submitted formulations as the basic formulation; both of the current CSFs (dated 5/14/99) are listed as alternate formulations.

2. The product chemistry studies submitted in fulfillment of Subdivision M Guidelines 151-10 to -17 are acceptable; no additional data are required.

DATA EVALUATION REPORT

Reviewed by: Russell S. Jones, Ph.D. BPPD
Secondary Reviewer: Freshteh Toghrol, Ph.D. BPPD

STUDY TYPE:	Product Chemistry (Subdivision M Guidelines 151-10 to 151-17)
TOX. CHEM. No.:	None
CASE No.:	065963
PC CODE:	011550
DP BARCODE:	D258722
SUBMISSION No.:	S566861
MRID No:	448367-06 and -07
TEST MATERIALS:	UICK-3 (containing 10% p-menthane-3, 8-diol as its active ingredient)
STUDY Nos:	Project #00A167 Study Nos.: MRID 448367-06 (None); MRID 448367-07 (390A2)
SPONSOR:	S. C. Johnson & Son, Inc., 1525 Howe St., Racine, WI 53403
TESTING FACILITY:	S. C. Johnson & Son, Inc., 1525 Howe St., Racine, WI 53403
TITLES OF REPORTS:	Product Chemistry Data for UICK-3 Formula Number 15028R21 (MRID 448367-06); Physical and Chemical Characteristics of UICK-3 Formula Number 15028R21 (MRID 448367-07).
AUTHORS:	Andrea A. Tran-Lu (MRID 448367-06); Gary A. Smith (MRID 448367-07).
REPORTS COMPLETED:	5/10/99 (MRID 448367-06); 4/12/99 (MRID 448367-07)
QUALITY ASSURANCE:	The studies were not laboratory studies and were not conducted under Good Laboratory Practices; non-compliance statements were signed by the sponsor/submitter.

SUMMARY: Product chemistry studies for UICK 3 were presented in MRIDs 448367-06 and -07. The end-use product consists of one basic and one alternate formulation. The active ingredient is p-menthane-3, 8-diol which comprises 10% of the product. The TGAI is not currently registered by EPA but is under review for registration (EPA File No. 4822-UOO). The end-use product is manufactured via a simple mixing process with no chemical reactions. Therefore, no discussion of manufacturing impurities, preliminary analysis, or analytical methods data are required. The submitted certified ingredient limits for the active and inert ingredients were acceptable. An analytical method was not submitted but none is required because the end-use product is produced via a simple mixing process. The product is an opaque, off-white liquid with a faint floral odor. It has a density of 0.98 g/mL at 21 °C and a pH 7.3 (for a 5% solution). It does not contain any oxidizing/reducing agents, is not explosive, and is flammable at 98 °C, but has no observed flash point.

CLASSIFICATION: Unacceptable, but upgradable. To upgrade the study, the registrant must resolve the discrepancies and deficiencies described above and in the Product Chemistry Recommendations and Conclusions.

I. PRODUCT IDENTITY AND DISCLOSURE OF INGREDIENTS (151-10)

A. *p*-Menthane-3, 8-Diol

Ingredient:	Active
CAS Number:	4822-86-6
Chemical Characterization:	Insect repellent
Supplier:	S. C. Johnson & Sons, Inc., 1525 Howe Street, Racine, WI 53403-2236

[redacted]

Inert ingredient information not included.

PC 011550 P-MENTHANE-3,8-DIOL

Page _____ is not included in this copy.

Pages 24 through 25 are not included in this copy.

The material not included contains the following type of information:

X Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

_____ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Inert ingredient information not included.
Manufacturing process information not included.

[redacted]

II. MANUFACTURING PROCESS (Subdivision M Guideline 151-11; OPPTS 880.1200); MRID 448367-06

[redacted]

III. DISCUSSION OF THE FORMATION OF IMPURITIES (Subdivision M Guideline 151-12; OPPTS 880.1400)

No impurities are likely to form because no chemical reactions occur are required in the manufacturing process.

IV. PRELIMINARY ANALYSIS (Subdivision M Guideline 151-13)

A five-batch preliminary analysis was not submitted, but are not required because the product is not produced via an integrated process but by simple mixing of pre-made ingredients.

V. CERTIFICATION OF LIMITS (151-15); MRID 444961-03

The nominal concentrations and certified ingredient limits (by % weight) were as follows:

EP Basic Formulation (CSF, dated 5/14/99; MRID 448367-06)			
Ingredient	% by weight	Certified Limits (% by weight)	
		Upper	Lower
p-Menthane-3, 8-diol, Technical *p*-Menthane-3, 8-diol	10.1 10.0	10.50	9.50

[redacted]

Inert ingredient information not included.

EP Alternate Formulation (CSF, dated 5/14/99; MRID 448367-06)			
Ingredient	% by weight	Certified Limits (% by weight)	
		Upper	Lower
p-Menthane-3, 8-diol, Technical *p*-Menthane-3, 8-diol	10.1 10.0	10.50	9.50

[redacted]

Inert ingredient information not included.

VI. ANALYTICAL METHODS (Subdivision M Guideline 151-16; OPPTS 830.1750); MRID 448376-06

The registrant submitted a gas chromatography method (GC) for the determination of *p*-menthane-3, 8-diol. In this method, 0.4 to 0.6 g of *p*-menthane-3, 8-diol is dissolved 10 mL of acetone in a 100 mL volumetric flask. To this container is added 0.3% dipropyl phthalate (10 mL) as an internal standard, and the remainder is filled to volume with acetone. The sample is then filtered through a 0.45 micron syringe filter and analyzed by GC on a 30 M, DB-1 fused silica column equipped with a flame ionization detector (FID). The amount of test substance is determined via an internal standard method compares the area ratio of the peaks for sample and internal standard. Analysis of six samples demonstrated that the method was precise and accurate with a mean concentration of 9.88 ±0.32% (relative standard deviation, or RSD); analytical recoveries ranged 97.8 to 102% with and RSD of ± 1.67%. Determination from an analysis of 5

samples in the concentration ranges of 5.0 to 15% demonstrated that the analysis was linear in the concentration range tested. No interfering substances were detected in an analysis of a sample matrix (without the active ingredient). A sample chromatogram was also submitted, but the limits of detection data were not reported. However, since an analytical method is not required for a product that is not produced via an integrated process, limits of detection data are not required, but should be submitted as soon as they are available.

VI. PHYSICAL AND CHEMICAL CHARACTERISTICS (151-17); MRID 444158-02 as amended by MRID 446101-02

Property	EP
Color	Opaque, white lotion
Physical state	Liquid
Odor	Faint floral
Melting point	Not required (NR)
Boiling point	NR
Density	0.98 g/mL at 21 °C
Solubility	NR
Vapor Pressure	NR
Octanol/Water Partition Coefficient	NR
pH	7.3 for a 5% solution in deionized water
Stability to Metals and Temperature	NR
UV/Visible absorption	NR
Flammability (flash point)	98 °C flame extinguished, no flash observed
Oxidation/Reduction	Does not contain oxidizing or reducing agents
Storage stability	To be evaluated in a separate study
Viscosity	25 °C: 6.46E+01 to 2.91E-01 (shear rate 0.1 to 100); 50 °C: 9.48 to 1.01E-01 (shear rate 0.1 to 100)
Miscibility	Not applicable (NA)
Corrosion characteristics	To be evaluated in a separate study
Dielectric breakdown voltage	NA