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

OFFICE OF PREVENTION,
PESTICIDES AND TOXIC
SUBSTANCES

August 27, 1999

Memorandum

Subject: Secondary Review of Data Evaluation Records on Acute Toxicity Studies with UICK II (ID# 4822-LNO) Containing p-Menthane-3,8-diol (PC 011550). DP Barcode D252712; Submission S555602.

From: Roger Gardner, Toxicologist Roger Gardner 8/27/99
Biochemical Pesticides Branch
Biopesticides and Pollution Prevention Division (7511C)

Thru: Sheryl Reilly, Ph.D., Acting Chief Sheryl K Reilly 9/3/99
Biochemical Pesticides Branch
Biopesticides and Pollution Prevention Division (7511C)

To: Jim Downing, Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides and Pollution Prevention Division (7511C)

Action Requested

Secondary review of Data Evaluation Reports (DER, Attached) on seven acute toxicity studies submitted by S. C. Johnson & Son, Inc., (MRIDs 446421-01 through -07) for UICK II (Reg. No. 4822-LNO).

I. EXECUTIVE SUMMARY

There were seven acceptable acute toxicity study reports submitted for consideration. Based on the study reviews prepared by the Chemical Hazard Evaluation Group at Oakridge National Laboratory, Moeller Plus (containing 10.0% p-menthane-3,8-diol) is placed into Toxicity Category IV for acute oral and dermal toxicity as well as primary dermal irritation. UICK 2 (containing 9.8% p-menthane-3,8-diol) was also placed into Toxicity Category IV for acute inhalation toxicity and Toxicity Category II for eye irritation. The Moeller Plus product was found to be a skin sensitizer in a Buehler test in guinea pigs, but a non-guideline study in 106 human volunteers

found no similar activity.

II. Acute Toxicity Studies

Six acute toxicity studies were submitted to support the registration of Moeller Plus (p-menthane 3,8 diol, 10.0% a.i.) and UICK 2 (9.8% a.i.). All studies were acceptable, and the results are listed as follows:

Study	MRID No.	Results	Toxicity Category
Acute Oral-rat	44642101	LD_{50}>5000 mg/kg	IV
Acute Dermal-rabbit	44642102	LD_{50}>5000 mg/kg	IV
Acute Inhalation-rat	44642103	LC_{50}>2.17 mg/L	IV
Eye Irritation-rabbit	44642104	Severe	II
Skin Irritation-rabbit	44642105	Slight irritant	IV
Skin Sensitization-guinea pig (Modified Buehler)	444642106	Sensitizer	N/A

A. **Acute Oral Toxicity (MRID 44642101)** In a limit dose acute oral toxicity study in Sprague-Dawley strain rats (5/sex) given a single oral gavage dose of 5000 mg of the test substance per kg body weight, all 5 males and 4/5 females survived. The one mortality occurred on the 8th day of the study. Clinical signs were observed from both sexes on day 0-2 (day 0-8 for premature decedent), and included decreased activity, wobbly gait, salivation, breathing abnormalities, urine stain, decreased defecation, and dark material on the face. All surviving rats gained weight during the course of the study; the early death female lost a considerable amount of weight. No gross lesions were found in the animals surviving to terminal sacrifice. The premature decedent female had reddened adrenal glands, abnormal contents in the stomach and small intestine, a distended large intestine, mottled lungs, stomach striations, and body fat depletion.

B. **Acute Dermal Toxicity (MRID 44642102)** In a limit dose acute dermal toxicity study with New Zealand White rabbits (5/sex) given a single dermal dose of 5000 mg/kg, none of the animals died prior to the scheduled sacrifice. Clinical observations included occasional soft stools, fecal stains, and/or dark material around the mouth in a few animals. Dermal irritation at the test site (grade 1 or 2 erythema and grade 1 edema) was seen on all rabbits; some also had desquamation and/or skin lightening (grade 1 or 2). No treatment-related effects on body weight or necropsy were found.

C. **Acute Inhalation Toxicity (MRID 44642103)** In the acute inhalation toxicity 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.

D. **Primary Eye Irritation (MRID 44642104)** In a primary eye irritation study 0.1 mL (~81 mg) UICK-2 (9.82% a.i.) was instilled into the conjunctival sac of the right eye of 2 male and 7 female New Zealand White rabbits. Both eyes of 3 of the females were rinsed with physiological saline at 2-3 minutes post-instillation. Corneal opacity, iritis, and conjunctivitis (redness, swelling, and discharge) were evident in all eyes, i.e., the 6/6 non-rinsed and the 3/3 eye-rinsed eyes, at the 1-hour examination time. At 72 hours, corneal opacity, conjunctival swelling, and conjunctival redness were present in all non-rinsed and rinsed eyes, whereas conjunctival discharge was present in 4/6 non-rinsed and 1/3 rinsed eyes, and iritis was seen in 5/6 non-rinsed and 2/3 rinsed eyes. In both groups, iritis resolved by day 7, and corneal opacity and conjunctivitis resolved by day 21. UICK-2 was classified as a severe irritant by the method of Kay and Calandra and as an irritant for corneal opacity and conjunctival edema by EEC ocular evaluation criteria. These results indicate UICK-2 is a severe eye irritant, and is placed in Toxicity Category II for primary eye irritation.

E. **Primary Dermal Irritation (MRID 44642105)** In a primary dermal irritation study six male New Zealand White rabbits were dermally exposed for 4 hours to 0.5 mL Moeller Plus (10.0% a.i.). All six rabbits had slight erythema (score = 1) and one rabbit had slight edema (score = 1) at the test site one hour after patch removal. The erythema resolved by 24 hours on 2 rabbits and by 48 hours on one rabbit, but persisted through 72 hours (resolved by 7 days) on the other 3 animals. The Primary Irritation Index for erythema and edema combined was calculated as 0.71.

F. **Dermal Sensitization (MRID 44642106)** In a dermal sensitization study with Moeller Plus (10.0% a.i.), male and female Hartley albino guinea pigs (20 test, 10 controls) were tested using the method of Buehler. 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 Moeller Plus 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. These results indicate that Moeller Plus was a dermal sensitizer. The positive control experiment utilized DNCB and was conducted appropriately. In this study, Moeller Plus was a dermal sensitizer to male and female Hartley albino guinea pigs.

G. **Dermal Sensitization in Humans (44642107)** In a non-guideline dermal patch testing study, the potential of Moeller Plus (9.82-10.1% a.i.) to cause dermal sensitization was tested in 110 volunteers age 18-71. The 6-week treatment regimen consisted of a 3-week induction period (9 applications of 0.2 mL) followed by a 11-13 day rest period and a challenge treatment (0.2 mL).

Application was on the back with occlusive dermal patches for a 24-hour period; the test sites were evaluated 48-96 hours after each application. Sensitization was based on the test results of only "completed cases", i.e., subjects who had received 9 induction applications, at least 8 subsequent readings during induction, and 2 readings during challenge.

Of the 106 subjects who completed the test regimen, none developed a definitive dermal response at the test site during the induction or challenge phases. One individual had a "questionable" response (minimal or doubtful response, slightly different from the surrounding skin) for the second through the 9th induction reading, although this person had no response during the challenge reading. Another individual had a questionable response only at the two challenge readings. Based on these results, it is concluded that UICK-2 was not a human skin sensitizer under the conditions of this Repeated Insult Patch Test.

References

44642101. Bonnette, K.L. (1998) An acute oral toxicity study in rats with Moeller Plus, Notebook #14735R126-3. Springborn Laboratories, Inc. (SLI), 640 North Elizabeth Street, Spencerville, OH 45887. SLI study no. 3068.105, June 16, 1988 and July 14, 1988 are the original and amended study completion dates, respectively. Unpublished.

44642102. Bonnette, K.L. (1998) An acute dermal toxicity study in rabbits with Moeller Plus, Notebook #14735R126-3. Springborn Laboratories, Inc. (SLI), 640 North Elizabeth Street, Spencerville, OH 45887. SLI study no. 3068.106, June 16, 1988 (original study completion date) and July 14, 1988 (amended study completion date). Unpublished.

44642103 Bonnette, K.L. (1998) An acute nose-only inhalation toxicity study in rats with UICK-2 (SCJ Notebook #15045R59-2). Springborn Laboratories, Inc. (SLI), Ohio Research Center, 640 North Elizabeth Street, Spencerville, OH 45887. SLI study no. 3068.154, July 14, 1988. Unpublished.

44642104. Bonnette, K.L. (1998) A primary eye irritation study in rabbits with UICK-2 (SCJ Notebook #15045R59-2). Amended final report. Springborn Laboratories, Inc. (SLI), Ohio Research Center, 640 North Elizabeth Street, Spencerville, OH 45887. SLI study no. 3068.153, July 14, 1988. Unpublished.

44642105 Bonnette, K.L. (1998) A primary skin irritation study in rabbits with Moeller Plus Notebook #14735R126-3). Springborn Laboratories, Inc. (SLI), Ohio Research Center, 640 North Elizabeth Street, Spencerville, OH 45887. SLI study no. 3068.109, June 16, 1988 (original study completion date) and July 14, 1988 (amended study completion date). Unpublished.

44642106 Bonnette, K.L. (1998) A dermal sensitization study in guinea pigs with Moeller Plus, Notebook #14735R126-3). Modified Buehler design. Springborn Laboratories, Inc. (SLI), Ohio Research Center, 640 North Elizabeth Street, Spencerville, OH 45887. SLI study no.

3068.110, June 16, 1988 (original study completion date) and July 14, 1988 (amended study completion date). Unpublished.

44642107 Vendetti, N. (1998) Repeated insult patch study with UICK-2 (SCJ Notebook No. 15045R59-2, SCJ GLP #377). TKL Research, Inc., 4 Forest Avenue, Paramus, NJ 07652. TKL Study no. 981020, August 26, 1998. Unpublished.

DATA EVALUATION REPORT

UICK-2 (p-menthane 3,8 diol)
(Moeller Plus)

STUDY TYPE: ACUTE ORAL TOXICITY - RAT (81-1)

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2800 Crystal Drive
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830
Task Order No. 26

Primary Reviewer:
Sylvia Milanez, Ph.D., D.A.B.T.

Signature: [signature]
Date: APR 2 6 1999

Secondary Reviewers:
H. Tim Borges, Ph.D., D.A.B.T., MT(ASCP)

Signature: [signature]
Date: APR 2 6 1999

Robert H. Ross, M.S., Group Leader

Signature: [signature]
Date: APR 2 6 1999

Quality Assurance:
Eric B. Lewis, M.S.

Signature: [signature]
Date: APR 2 6 1999

Disclaimer

This Data Evaluation Report may have been altered by the BPPD subsequent to signing by Oak Ridge National Laboratory personnel.

Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

EPA Reviewer: Roger Gardner Date, 6/30/99
EPA Work Assignment Manager: Sheryl K. Reilly Date, 9/3/99
Sheryl K. Reilly, Ph.D.
Biopesticides & Pollution Prevention Division (7511W)

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity - Rat (81-1)
DP BARCODE: D252712
P.C. BARCODE: 011550
SUBMISSION CODE: S555602
CASE: 062676

TEST MATERIAL (PURITY):UICK-2 (10% p-menthane 3,8 diol, a.i.)

SYNONYMS: Moeller Plus; p-menthane 3,8 diol

CITATION: Bonnette, K.L. (1998) An acute oral toxicity study in rats with Moeller Plus, Notebook #14735R126-3. Springborn Laboratories, Inc. (SLI), 640 North Elizabeth Street, Spencerville, OH 45887. SLI study no. 3068.105, June 16, 1988 and July 14, 1988 are the original and amended study completion dates, respectively. MRID 44642101. Unpublished.

SPONSOR: S.C. Johnson & Son, Inc., Product Safety, Toxicology and Environmental Assessment, Mail Station 122, 1525 Howe Street, Racine, Wisconsin 53403-2236.

EXECUTIVE SUMMARY: In a limit dose acute oral toxicity study (MRID 44642101), groups of fasted, young adult Sprague-Dawley Crl:CD®BR VAF/Plus® rats (5/sex) were given a single oral gavage dose of 5000 mg/kg Moeller Plus (p-menthane 3,8 diol, 10.0% a.i., lot no. 359D1). Surviving rats were observed for 14 days.

Mortality for males was 0/5 and for females was 1/5 (died on day 8). Clinical signs were observed from both sexes on day 0-2 (day 0-8 for premature decedent), and included decreased activity, wobbly gait, salivation, breathing abnormalities, urine stain, decreased defecation, and dark material on the face. All surviving rats gained weight during the course of the study; the early death female lost a considerable amount of weight. No gross lesions were found in the animals surviving to terminal sacrifice. The premature decedent female had reddened adrenal glands, abnormal contents in the stomach and small intestine, a distended large intestine, mottled lungs, stomach striations, and body fat depletion.

The oral LD_{50} for male and females rats is > 5000 mg/kg, which places the test material in TOXICITY CATEGORY IV.

This acute oral study is classified **Acceptable (guideline)** and satisfies the guideline requirement for an acute oral study (81-1) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: UICK-2 (Moeller Plus)

   Description: Clear colorless liquid
   Lot #: 359D1
   Purity: 10.0% a.i.
   Stability: Stable at room temperature for duration of study
   CAS Number: 42822-86-6

2. Vehicle: None: test article was given (by gavage) as supplied by the sponsor.

3. Test animals: Species: rat
   Strain: Sprague-Dawley Crl:CD®BR VAF/Plus®
   Age and/or weight at dosing: young adult; weight of males was 239-257 g on day -1 (pre-fasted) and of females was 202-208 g on day -1
   Source: Charles River Laboratories, Inc., Portage, MI
   Acclimation period: ≥ 5 days
   Diet: PMI Certified Rodent Chow #5002 (Purina Mills, Inc.), *ad libitum*
   Water: municipal tap water treated by reverse osmosis, *ad libitum*
   Housing: individually in suspended stainless steel cages
   Environmental conditions:
   Temperature: 70-73°F
   Humidity: not controlled; anticipated to be 41-89%
   Air changes: 10-15/hour
   Photoperiod: 12 hour light/dark cycle

B. STUDY DESIGN and METHODS

1. In life dates

   Start: August 7, 1997 end: August 21, 1997 (terminal sacrifice)

2. Animal assignment and treatment

   Animals were assigned arbitrarily to the test groups noted in Table 1. Following an overnight fast, the rats were gavaged with a single dose of ~5000 mg/kg Moeller Plus as supplied by the manufacturer. Individual animal doses were calculated based on

the animal's fasted day 0 body weight and the dosing volume of 6.17 mL/kg. The animals were observed for clinical signs of toxicity twice on the day of dosing (day 0) and daily thereafter for 14 days. The animals were weighed prior to fasting (day -1), following fasting but prior to treatment (day 0), and on days 7 and 14. Rats that died during the study were also weighed. Necropsies were performed on all rats that survived (after CO_2 euthanasia) and that died on study, but no tissues were retained.

TABLE 1. Doses and mortality of rats gavaged with Moeller Plus

Dose (mg/kg)	Males	Females	Combined
5000	0/5	1/5	1/10

3. Statistics - Calculation of an oral LD_{50} was not required.

II. RESULTS AND DISCUSSION

A. MORTALITY

Mortality is given in Table 1. Only one animal died during the study, a female on day 8. The oral LD_{50} is estimated to be > 5000 mg/kg, which places the test material in TOXICITY CATEGORY IV.

B. CLINICAL OBSERVATIONS

Commonly observed signs included decreased activity, wobbly gait, salivation, breathing abnormalities, urine stain, decreased defecation, and dark material on the face. These signs were seen from both sexes only on day 0-2, but were seen on days 0-8 from the female that was found dead on day 8.

C. BODY WEIGHT

All surviving rats gained weight during the course of the study. The female rat that died early weighed considerably less than at the beginning of the study (127 g vs. 184 g on study day 0 after fasting).

D. NECROPSY

There were no gross pathological findings in the animals that survived to terminal sacrifice. The female that died on day 8 had reddened adrenal glands, abnormal consents in the stomach and small intestine, a distended large intestine, mottled lungs, striations

in the stomach, and body fat depletion.

E. DEFICIENCIES

The relative humidity of the animal room was greater than the range recommended by GLP. This deficiency was not considered to have adversely impacted the study results.

DATA EVALUATION REPORT

UICK-2 (p-menthane 3,8 diol)
(Moeller Plus)

STUDY TYPE: ACUTE DERMAL TOXICITY - RABBIT (81-2)

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2800 Crystal Drive
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830
Task Order No. 26

Primary Reviewer:
Sylvia Milanez, Ph.D., D.A.B.T.
Signature: [signature]
Date: APR 26 1999

H. Tim Borges, Ph.D., D.A.B.T., MT(ASCP)
Signature: [signature]
Date: APR 26 1999

Robert H. Ross, M.S., Group Leader
Signature: [signature]
Date: APR 26 1999

Quality Assurance:
Eric B. Lewis, M.S.
Signature: [signature]
Date: APR 26 1999

Disclaimer

This Data Evaluation Report may have been altered by the BPPD subsequent to signing by Oak Ridge National Laboratory personnel.

Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

EPA Reviewer: Roger Gardner Date, 6/30/99
EPA Work Assignment Manager: Sheryl K. Reilly Date, 9/3/99
Sheryl K. Reilly, Ph.D.
Biopesticides & Pollution Prevention Division (7511W)

DATA EVALUATION RECORD

STUDY TYPE: Acute Dermal Toxicity - Rabbit (81-2)
DP BARCODE: D252712
P.C. BARCODE: 011550
SUBMISSION CODE: S555602
CASE: 062676

TEST MATERIAL (PURITY): UICK II (p-menthane 3,8 diol, 10% a.i.)

SYNONYMS: Moeller Plus; p-menthane 3,8 diol

CITATION: Bonnette, K.L. (1998) An acute dermal toxicity study in rabbits with Moeller Plus, Notebook #14735R126-3. Springborn Laboratories, Inc. (SLI), 640 North Elizabeth Street, Spencerville, OH 45887. SLI study no. 3068.106, June 16, 1988 (original study completion date) and July 14, 1988 (amended study completion date). MRID 44642102. Unpublished.

SPONSOR: S.C. Johnson & Son, Inc., Product Safety, Toxicology and Environmental Assessment, Mail Station 122, 1525 Howe Street, Racine, Wisconsin 53403-2236.

EXECUTIVE SUMMARY: In a limit dose acute dermal toxicity study (MRID 44642102), adult New Zealand White rabbits (5/sex) were given a single dermal dose of 5000 mg/kg Moeller Plus (p-menthane 3,8 diol, 10.0% a.i., lot no. 359D1). Dosing volume was 6.17 mL/kg. The rabbits were observed for 14 days following the treatment day.

No animal died prior to the scheduled sacrifice. Clinical observations included occasional soft stools, fecal stains, and/or dark material around the mouth in a few animals. Dermal irritation at the test site (grade 1 or 2 erythema and grade 1 edema) was seen on all rabbits; some also had desquamation and/or skin lightening (grade 1 or 2). No treatment-related effects on body weight or necropsy were found.

The dermal LD_{50} for male and females rabbits is > 5000 mg/kg, which places the test material in TOXICITY CATEGORY IV.

This acute dermal study is classified **Acceptable (guideline)** and satisfies the guideline requirement for an acute dermal study (81-2) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. An exception to the GLP provisions was noted in that the sponsor was responsible for tracking the identity, strength, purity, composition, and synthesis of the test compound.

12

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: UICK-2 (Moeller Plus)

   Description: Clear colorless liquid
   Lot #: 359D1
   Purity: 10.0% a.i.
   Stability: Stable at room temperature for duration of study
   CAS Number: 42822-86-6
   Density: 0.81 g/mL

2. Vehicle: None: test article was given as received from the sponsor.

3. Test animals: Species: rabbit
   Strain: New Zealand White (NZW)
   Age and/or weight at dosing: approximately 12 weeks; males weighed 2.4-2.9 kg and females weighed 2.5-2.7 kg
   Source: Myrtle's Rabbitry, Thompson Station, TN
   Acclimation period: ≥ 5 days
   Diet: PMI Certified Rabbit Chow #5322 (Purina Mills, Inc.), *ad libitum*
   Water: municipal tap water treated by reverse osmosis, *ad libitum*
   Housing: individually in suspended stainless steel cages
   Environmental conditions:
   Temperature: 68-71°F
   Humidity: not controlled; anticipated to be 41-66%
   Air changes: 10-15/hour
   Photoperiod: 12 hour light/dark cycle

B. STUDY DESIGN and METHODS

1. In life dates - Start: August 20, 1997 end: September 3, 1997 (terminal sacrifice)

2. Animal assignment and treatment - Animals (5/sex) were assigned arbitrarily from the healthy stock animals to the test groups noted in Table 1. Each animal received a single 5000 mg/kg dermal dose of Moeller Plus in a dosing volume of 6.17 mL/kg, applied evenly to a shaved area on the dorsal trunk equivalent to approximately 10% of the animal's body surface area. Collars were placed on the rabbits after dosing and were removed on study day 3. The dosing site was covered with a 4-ply porous gauze backed with a plastic wrap (occlusive binding). An elastic wrap was placed over the trunk and test area and secured with adhesive tape at the cranial and caudal areas to prevent removal and ingestion of the test article. After approximately 24 hours, the dressings were removed and residual test article was removed using gauze moistened with deionized water followed by dry gauze.

The animals were observed for clinical signs of toxicity twice after dosing (day 0) and daily for days 1-14. A general health/mortality check was performed twice daily and the application site was examined for erythema and edema (and graded by the Draize method) following patch removal on day 1 and daily on days 2-14; hair was reclipped as necessary. The rabbits were weighed before treatment (day 0) and on days 7 and 14. Survivors were sacrificed by i.v. injection of sodium pentobarbital on day 14 and a necropsy was performed on each animal.

TABLE 1. Dose and mortality of rabbits treated dermally with Moeller Plus

Dose (mg/kg)	Males	Females	Combined
5000	0/5	0/5	0/10

3. Statistics - Calculation of a dermal LD_{50} was not required.

II. RESULTS AND DISCUSSION

A. MORTALITY

Mortality is given in Table 1: no animals died during the study. The dermal LD_{50} is estimated to be > 5000 mg/kg, which places the test material in TOXICITY CATEGORY IV.

B. CLINICAL OBSERVATIONS

Soft stools, fecal stains, and/or dark material around the mouth were seen on 3 animals on one or two occasions. All rabbits had dermal erythema (grade 1 or 2) and edema (grade 1) at the test site, most had desquamation and/or superficial lightening of the skin (grade 1 or 2), and one rabbit had eschar (grade 1). Three rabbits had dermal irritation outside the test site.

C. BODY WEIGHT

All rabbits gained weight during the course of the study except one female that had slight weight loss for the day 0-7 interval. This female's incisors were broken on day 1, which likely caused the initial weight loss.

D. NECROPSY

Three females had oviduct cysts. The study author stated that this is a common finding in NZW rabbits and was not treatment-related.

E. DEFICIENCIES

Minor exceptions to the GLP were noted with respect to providing information about the test material; this does not adversely impact the study results.

DATA EVALUATION REPORT

UICK-2 (p-menthane 3,8 diol)
(Moeller Plus)

STUDY TYPE: ACUTE INHALATION TOXICITY - RAT (81-3)

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2800 Crystal Drive
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830
Task Order No. 26

Primary Reviewer:
Sylvia Milanez, Ph.D., D.A.B.T.
Signature: _____
Date: APR 2 6 1999

H. Tim Borges, Ph.D., D.A.B.T.,MT(ASCP)
Signature: _____
Date: APR 2 6 1999

Robert H. Ross, M.S., Group Leader
Signature: _____
Date: APR 2 6 1999

Quality Assurance:
Eric B. Lewis, M.S.
Signature: _____
Date: APR 2 6 1999

Disclaimer

This Data Evaluation Report may have been altered by the BPPD subsequent to signing by Oak Ridge National Laboratory personnel.

Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

EPA Reviewer: Roger Gardner Date, 6/30/99
EPA Work Assignment Manager: Date, 9/3/99
Sheryl K. Reilly, Ph.D.
Biopesticides & Pollution Prevention Division (7511W)

DATA EVALUATION RECORD

STUDY TYPE: Acute Inhalation Toxicity - Rat (81-3)
DP BARCODE: D252712
P.C. BARCODE: 011550

SUBMISSION CODE: S555602
CASE: 062676

TEST MATERIAL (PURITY): UICK-2 (p-menthane 3,8 diol, 9.82% a.i.)

SYNONYMS: Moeller Plus (MRID 44642101)

CITATION: Bonnette, K.L. (1998) An acute nose-only inhalation toxicity study in rats with UICK-2 (SCJ Notebook #15045R59-2). Springborn Laboratories, Inc. (SLI), Ohio Research Center, 640 North Elizabeth Street, Spencerville, OH 45887. SLI study no. 3068.154, July 14, 1988. MRID 44642103. Unpublished.

SPONSOR: S.C. Johnson & Son, Inc., Product Safety, Toxicology and Environmental Assessment, Mail Station 122, 1525 Howe Street, Racine, Wisconsin 53403-2236.

EXECUTIVE SUMMARY: In an acute inhalation limit toxicity study (MRID 44642103), groups of young adult Sprague-Dawley albino rats (5/sex) were exposed by nose-only inhalation to UICK-2 (lot no. 377D1; p-menthane 3,8 diol, 9.82% a.i.) for 4 hours at a concentration of 2.17 mg/L and observed for 14 days.

No mortality occurred. 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.

The LC_{50} (4 hour) for male, female, and male and female combined Sprague Dawley rats is >2.17 mg/L. This places UICK-2 in TOXICITY CATEGORY IV.

This study is classified as **Acceptable (guideline)** and satisfies the guideline requirement for an acute inhalation study (81-3) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: UICK-2 (p-menthane 3,8 diol)

   Description: Clear colorless liquid; density determined as 0.81 g/mL.
   Lot #: 377D1
   Purity: 9.82% a.i.
   Stability: Stable at room temperature for duration of study
   CAS Number: 42822-86-6

2. Vehicle and/or positive control: None: test article given as received from sponsor

3. Test animals: Species: rat
   Strain: Hsd: Sprague-Dawley® SD®
   Age and/or weight at dosing: young adult; weight of males was 258-275 g and of females was 223-237 g
   Source: Harlan Sprague Dawley, Inc., Indianapolis, IN
   Acclimation period: ≥ 5 days
   Diet: PMI Certified Rodent Chow #5002 (Purina Mills, Inc.), *ad libitum* except during exposure and pre-exposure acclimation (~1 hour)
   Water: municipal tap water treated by reverse osmosis, *ad libitum* except during exposure and pre-exposure acclimation (~1 hour)
   Housing: individually in suspended stainless steel cages
   Environmental conditions:
   Temperature: 70-75°F
   Humidity: 37-63%
   Air changes: 10-15/hour
   Photoperiod: 12 hour light/dark cycle

B. STUDY DESIGN and METHODS

1. In life dates

   Start: May 13, 1998 end: May 27, 1998

2. Exposure conditions

   Chamber airflow was measured at the beginning of the (9 minute) equilibration period, at approximately 30 minute intervals throughout the 4-hour exposure period, and at the end of the (9 minute) de-equilibration period. Temperature, humidity, and the chamber oxygen content were recorded at approximately 30 minute intervals throughout the exposure period (recorded at 0, 30, 60, 91, 120, 150, 180, 210, and 240 minutes).

Exposure concentration and UICK-2 particle size in the animal exposure chamber were determined gravimetrically during the 4-hour exposure.

3. Animal assignment and treatment

Rats (5/sex; see Table 1) were exposed to UICK-2 nose-only for 4 hours (day 0) plus a 9-minute equilibration period and a 9 minute de-equilibration period. Only animals that were able to acclimate to the nose-only exposure tube earlier that day (with minimal struggling and no inversion after ~1 hour) were used for the study. Following the aerosol exposure, the rats were removed from the exposure tubes and residual test material was wiped off their haircoat with a towel.

The rats were observed for clinical abnormalities during exposure, twice after the exposure (day 0), and daily during the 14-day observation period. Rats were checked every morning and afternoon for general health and mortality. The animals were weighed prior to dosing and on days 7 and 14. All animals were sacrificed on day 14 and necropsied.

TABLE 1. Concentrations, exposure conditions, and mortality of rats treated with UICK-2

Exposure conc. (mg/L)	Chamber air parameters	MMAD (μm)	GSD (μm)	Mortality / animals treated		
				Males	Females	Combined
Nominal: 5.37 Gravimetric: 0.44 Analytical: 2.17	Temp.: 73.7-77.7°F Humidity: 22.7-27.9% O_2 conc.: 20.3-20.9%	2.2[1]	1.8	0/5	0/5	0/10

MMAD = mass median aerodynamic diameter
GSD = geometric standard deviation
[1]84% of particles were ≤ 4 μm

4. Generation of the test atmosphere and description of the chamber

The animals were exposed in a Unifab 100L nose-only inhalation chamber. The test aerosol was generated with a PDH 2000 Infusion Pump and a Spraying Systems ¼J SS atomizer using conditioned high pressure external air. The chamber air flow rate was 53.81 L/minute, and the equilibration time was 9 minutes.

Test atmosphere concentration was measured gravimetrically at the beginning and end of the 4-hour exposure period (after equilibration; before de-equilibration) and at approximately 30-minute intervals during exposure (recorded at 0, 30, 60, 91, 120, 150, 180, 210, and 240 minutes). Each air sample was withdrawn through a weighed glass fiber filter (L/minute not given; possibly 7 L/minute since chamber air for the particle size determination was collected at 7 L/minute). Analytic concentrations were obtained by analysis of the gravimetrically obtained samples by gas chromatography for p-menthane-3,8-diol, which is a non-volatile component of the test material. Results for the gravimetric and analytic concentration analyses are given in Table 1 as a time-

weighed average over the 4-hour exposure period. The analytic concentration was the actual concentration to which the animals were exposed; preliminary trials showed that UICK-2 did not have sufficiently low volatility for an accurate gravimetric determination of the aerosol concentration. The nominal concentration was reported to be 5.37 mg/L. The percentage of particles ≤ 4 μm was 84%.

Particle size determination was performed gravimetrically twice during the exposure (at least 1 hour passed between the two analyses; actual time not given) using the ITP 7 L/minute 7-stage cascade impactor. The test material collected by each stage was weighed and used to determine the particle size distribution, which was plotted on three cycle logarithmic probability paper.

5. Statistics

An LC_{50} was not calculated.

II. RESULTS AND DISCUSSION

A. MORTALITY

None of the animals died during the study. The LC_{50} (4 hour) for male and female Sprague Dawley rats is >2.17 mg/L. This places UICK-2 in TOXICITY CATEGORY IV.

B. CLINICAL OBSERVATIONS

All rats salivated on only the first treatment day and had breathing abnormalities (rales and/or congested breathing) that resolved by day 7. Other clinical signs included rough hair coat, few or small feces, and dark material on the facial area; these also occurred prior to day 7.

C. BODY WEIGHT

All males and one female showed weight gain at the day 7 and day 14 time points. Four females lost a small amount of weight (4.0-8.4%) for days 0-7. These four females, however, gained weight from day 7-14, and only one of them weighed less (2.2%) on day 14 than on day 0.

D. NECROPSY

Gross pathology findings at necropsy consisted of multiple lung foci and/or enlarged mediastinal lymph nodes, which were seen in 3/5 males and 4/5 females.

E. DEFICIENCIES

The rate of chamber air collection (L/minute) for the exposure concentration measurements was not given; it was possibly 7 L/minute since chamber air for the particle size determination was collected at 7 L/minute. This deficiency does not invalidate the study results and the information can probably be easily obtained from the registrant.

DATA EVALUATION REPORT

UICK-2 (p-menthane 3,8 diol)
(Moeller Plus)

STUDY TYPE: PRIMARY EYE IRRITATION - RABBIT (81-4)

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2800 Crystal Drive
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830
Task Order No. 26

Primary Reviewer:
Sylvia Milanez, Ph.D., D.A.B.T.
Signature: [signature]
Date: APR 2 6 1999

H. Tim Borges, Ph.D., D.A.B.T., MT(ASCP)
Signature: [signature]
Date: APR 2 6 1999

Robert H. Ross, M.S., Group Leader
Signature: [signature]
Date: APR 2 6 1999

Quality Assurance:
Eric B. Lewis, M.S.
Signature: [signature]
Date: APR 2 6 1999

Disclaimer

This Data Evaluation Report may have been altered by the BPPD subsequent to signing by Oak Ridge National Laboratory personnel.

22

Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

EPA Reviewer: Date, 6/30/99
EPA Work Assignment Manager: Date, 9/3/99
Sheryl K. Reilly, Ph.D.
Biopesticides & Pollution Prevention Division (7511W)

DATA EVALUATION RECORD

STUDY TYPE: Primary Eye Irritation - Rabbit (81-4)
DP BARCODE: D252712
P.C. BARCODE: 011550
SUBMISSION CODE: S555602
CASE: 062676

TEST MATERIAL (PURITY):UICK-2 (p-menthane 3,8 diol, 9.82% a.i.)

SYNONYMS: Moeller Plus (MRID 44642101)

CITATION: Bonnette, K.L. (1998) A primary eye irritation study in rabbits with UICK-2 (SCJ Notebook #15045R59-2). Amended final report. Springborn Laboratories, Inc. (SLI), Ohio Research Center, 640 North Elizabeth Street, Spencerville, OH 45887. SLI study no. 3068.153, July 14, 1988. MRID 44642104. Unpublished.

SPONSOR: S.C. Johnson & Son, Inc., Product Safety, Toxicology and Environmental Assessment, Mail Station 122, 1525 Howe Street, Racine, Wisconsin 54303-2236.

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 44642104), 0.1 mL (~81 mg) UICK-2 (lot no. 377D1; p-menthane 3,8 diol, 9.82% a.i.) was instilled into the conjunctival sac of the right eye of 2 male and 7 female young adult New Zealand White rabbits. Both eyes of 3 of the females were rinsed with physiological saline at 2-3 minutes post-instillation. The animals were then observed for up to 21 days. Irritation was scored by the Draize method and classified according to Kay and Calandra.

Corneal opacity, iritis, and conjunctivitis (redness, swelling, and discharge) were evident in all eyes, i.e., the 6/6 non-rinsed and the 3/3 eye-rinsed eyes, at the 1-hour examination time. At 72 hours, corneal opacity, conjunctival swelling, and conjunctival redness were present in all non-rinsed and rinsed eyes, whereas conjunctival discharge was present in 4/6 non-rinsed and 1/3 rinsed eyes, and iritis was seen in 5/6 non-rinsed and 2/3 rinsed eyes. In both groups, iritis resolved by day 7, and corneal opacity and conjunctivitis resolved by day 21. UICK-2 was classified as a severe irritant by the method of Kay and Calandra and as an irritant for corneal opacity and conjunctival edema by EEC ocular evaluation criteria. **These results indicate UICK-2 is a severe eye irritant, and is placed in Toxicity Category II for primary eye irritation.**

This study is classified as **Acceptable (guideline)** and satisfies the guideline requirement for a primary eye irritation study (81-4) in the rabbit.

23

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. An exception to the GLP provisions was noted in that the sponsor was responsible for tracking the identity, strength, purity, composition, and synthesis of the test compound.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: UICK-2 (p-menthane 3,8 diol)

   Description: Clear colorless liquid; density given as 0.81 g/mL in MRID 44642101.
   Lot #: 377D1
   Purity: 9.82% a.i.
   Stability: Stable at room temperature for duration of study
   CAS Number: 42822-86-6

2. Vehicle and/or positive control: None: test article given as received from sponsor

3. Test animals: Species: rabbit
   Strain: New Zealand White (NZW)
   Age and/or weight at dosing: ~11 weeks old; males: 2.4-2.5 kg, females: 2.2-2.6 kg
   Source: Myrtle's Rabbitry, Thompson Station, TN
   Acclimation period: ≥ 5 days
   Diet: PMI Certified Rabbit Chow #5322 (Purina Mills, Inc.), *ad libitum*
   Water: municipal tap water treated by reverse osmosis, *ad libitum*
   Housing: individually in suspended stainless steel cages
   Environmental conditions:
   Temperature: 60-73°F
   Humidity: not controlled; anticipated to be 27-68%
   Air changes: 10-15/hour
   Photoperiod: 12 hour light/dark cycle

B. STUDY DESIGN and METHODS

1. In life dates

   Start: March 19, 1998 end: April 9, 1998 (final scoring)

2. Animal assignment and treatment

   Prior to treatment (day 0; ≥1 hour before dosing), eyes of rabbits were examined for ocular irritation or previous corneal injury macroscopically and using fluorescein sodium dye. Two males and seven females without ocular effects were identified for dosing. At treatment,

0.1 mL (~81 mg) of the undiluted test material was instilled into the conjunctival sac of the right eye of all rabbits and the lids held together for one second. The contralateral eye served as a control. Approximately 2-3 minutes after instillation, the test and control eyes of 3 females were rinsed with physiological saline to remove the test article. The treated eyes of all rabbits were examined for ocular irritation and scored 1, 24, 48, and 72 hours and on study days 7, 10, 14, and 21 after treatment. Following the 24-hour observation, all test and control eyes were examined with sodium fluorescein, and any eyes with residual test material were rinsed with physiological saline. Corneas exhibiting a positive response were reexamined with fluorescein at each subsequent observation until corneal staining no longer occurred, or as instructed by the study director. Ocular irritation was scored according to the Draize method and classified according to the method of Kay and Calandra.

II. RESULTS AND DISCUSSION

A. RESULTS AND DISCUSSION

No ocular effects were seen in the control eyes of either group. In the UICK-2 treated animals, corneal opacity, iritis, and conjunctivitis (redness, swelling, and discharge) were evident in all eyes, i.e., the 6/6 non-rinsed and the 3/3 eye-rinsed eyes, at the 1-hour examination time. Corneal opacity was confirmed by fluorescein staining at 24 hours. At 72 hours, corneal opacity, conjunctival swelling, and conjunctival redness were present in all non-rinsed and rinsed eyes. Also at 72 hours, conjunctival discharge was present in 4/6 non-rinsed and 1/3 rinsed eyes, and iritis was seen in 5/6 non-rinsed and 2/3 rinsed eyes. In both groups, iritis resolved by day 7, and corneal opacity and conjunctivitis resolved by day 21. Other ocular findings in treated eyes included corneal epithelial sloughing (1/6; 1/3), lower lid blanching (4/6; 1/3), nictitating membrane blanching (6/6; 2/3), raised corneal area (1/6), slight dulling of the corneal luster (1/3), and corneal neovascularization (6/6; 3/3). Stippling was observed during fluorescein examination (3/6; 1/3), but was transient and therefore not considered significant. The mean ocular irritation scores for corneal opacity, iritis, and conjunctival redness and edema, as calculated by the study author, are shown in Table 1. The study author's calculated maximum average ocular irritation scores are shown in Table 1. Based on these results, UICK-2 is classified as a severe irritant.

25

TABLE 1. Maximum average ocular irritation scores following treatment with UICK-2								
Study group	Hour				Day			
	1	24	48	72	7	10	14	21
Non-rinsed eyes (n=6)	36.17	53.17	51.67	52.83	12.00	7.33	3.00	0
Rinsed eyes (n=3)	40.33	42.33	39.33	38.67	25.00	16.00	6.33	0

Data from pp. 20 and 22, MRID 44642104.

Analysis of the ocular irritation scores individually for corneal opacity, iris lesion, conjunctival redness, and conjunctival edema by the EEC ocular evaluation criteria showed that UICK-2 was classified as an irritant for corneal opacity and conjunctival edema.

B. DEFICIENCIES

No major study deficiencies were identified. The amount of test material applied to the eyes on a weight basis was not given, although the reviewer was able to determine this using the density of the test substance as given in another document (MRID 44642101).

26

DATA EVALUATION REPORT

UICK-2 (p-menthane 3,8 diol)
(Moeller Plus)

STUDY TYPE: PRIMARY DERMAL IRRITATION - RABBIT (81-5)

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2800 Crystal Drive
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830
Task Order No. 26

Primary Reviewer:
Sylvia Milanez, Ph.D., D.A.B.T.
Signature: [signature]
Date: APR 2 6 1999

H. Tim Borges, Ph.D., D.A.B.T., MT(ASCP)
Signature: [signature]
Date: APR 2 6 1999

Robert H. Ross, M.S., Group Leader
Signature: [signature]
Date: APR 2 6 1999

Quality Assurance:
Eric B. Lewis, M.S.
Signature: [signature]
Date: APR 2 6 1999

Disclaimer

This Data Evaluation Report may have been altered by the BPPD subsequent to signing by Oak Ridge National Laboratory personnel.

27

Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

EPA Reviewer: Date, 6/30/99
EPA Work Assignment Manager: Date, 9/3/99
Sheryl K. Reilly, Ph.D.
Biopesticides & Pollution Prevention Division (7511W)

DATA EVALUATION RECORD

STUDY TYPE: Primary Dermal Irritation - Rabbit (81-5)
DP BARCODE: D252712
P.C. BARCODE: 011550
SUBMISSION CODE: S555602
CASE: 062676

TEST MATERIAL (PURITY): UICK-2 (p-menthane 3,8 diol, 10.0% a.i.)

SYNONYMS: Moeller Plus

CITATION: Bonnette, K.L. (1998) A primary skin irritation study in rabbits with Moeller Plus Notebook #14735R126-3). Springborn Laboratories, Inc. (SLI), Ohio Research Center, 640 North Elizabeth Street, Spencerville, OH 45887. SLI study no. 3068.109, June 16, 1988 (original study completion date) and July 14, 1988 (amended study completion date). MRID 44642105. Unpublished.

SPONSOR: S.C. Johnson & Son, Inc., Product Safety, Toxicology and Environmental Assessment, Mail Station 122, 1525 Howe Street, Racine, Wisconsin 53403-2236.

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 44642105), six young adult male New Zealand White rabbits were dermally exposed for 4 hours to 0.5 mL Moeller Plus (p-menthane 3,8 diol, 10.0% a.i., lot no. 359D1). The test material was applied to a clipped dorsal area of the trunk under a 1 x 1 inch gauze patch covered with a semi-occlusive binder. The treatment site was scored for erythema and edema 1, 24, 48, and 72 hours after patch removal; scoring was based on the method of Draize.

All six rabbits had slight erythema (score = 1) and one rabbit had slight edema (score = 1) at the test site one hour after patch removal. The erythema resolved by 24 hours on 2 rabbits and by 48 hours on one rabbit, but persisted through 72 hours (resolved by 7 days) on the other 3 animals. The Primary Irritation Index for erythema and edema combined was calculated as 0.71, classifying Moeller Plus as a slight skin irritant to male New Zealand White rabbits under the conditions of this study and placing it in **Toxicity Category IV** for primary dermal irritation.

This study is classified as **Acceptable (guideline)** and satisfies the guideline requirement for a primary dermal irritation study (81-5) in the rabbit.

28

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. An exception to the GLP provisions was noted in that the sponsor was responsible for tracking the identity, strength, purity, composition, and synthesis of the test compound.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: UICK-2 (p-menthane 3,8 diol, a.i.)

   Description: Clear colorless liquid; density given as 0.81 g/mL in MRID 44642101.
   Lot #: 359D1
   Purity: 10.0% a.i. (p-menthane 3,8 diol)
   Stability: Stable at room temperature for duration of study
   CAS Number: 42822-86-6

2. Vehicle and/or positive control: None: test article given as received from sponsor

3. Test animals: Species: rabbit
   Strain: New Zealand White (NZW)
   Age and/or weight at dosing: ~11 week old males; 2.4-2.7 kg
   Source: Myrtle's Rabbitry, Thompson Station, TN
   Acclimation period: ≥ 5 days
   Diet: PMI Certified Rabbit Chow #5322 (Purina Mills, Inc.), *ad libitum*
   Water: municipal tap water treated by reverse osmosis, *ad libitum*
   Housing: individually in suspended stainless steel cages
   Environmental conditions:
   Temperature: 69-72°F
   Humidity: not controlled; anticipated to be 40-70%
   Air changes: 10-15/hour
   Photoperiod: 12 hour light/dark cycle

B. STUDY DESIGN and METHODS

1. In life dates

   Start: August 6, 1997 end: August 13, 1997 (final scoring)

2. Animal assignment and treatment - On the day before treatment, fur was clipped from the dorsal area of the trunk (clipped area not given) of 6 male rabbits. The next day, 0.5 mL Moeller Plus was applied underneath a 1 x 1 inch 4-ply gauze patch that was held in contact with the skin with nonirritating tape. The trunk and test area of the animal were then wrapped with elastic wrap secured with tape around the trunk at the cranial 29

and caudal ends. Collars were placed on each animal after dosing and removed on day 3. Four hours after application of the test dose, the wrappings and gauze were removed and the corners of the test site were delineated with a marker. Residual test material was wiped off with moistened and then dry gauze.

The application site was evaluated and scored for erythema and edema 1, 24, 48, and 72 hours and up to 7 days after removal of the gauze. The dermal responses were scored based on the method of Draize.

II. RESULTS AND DISCUSSION

A. RESULTS AND DISCUSSION

One hour after removal of the gauze patch, all six rabbits had slight erythema (score = 1) at the test site. The erythema resolved by 24 hours on 2 rabbits and by 48 hours on one rabbit, but persisted through 72 hours (resolved by 7 days) on the other 3 animals. One rabbit had slight edema (score = 1) at the application site, but only at the 1-hour test point. Desquamation was noted on 2/6 test sites. The Primary Irritation Index for erythema and edema combined was calculated as 0.71, classifying Moeller Plus as a slight irritant by the study's dermal evaluation criteria.

B. DEFICIENCIES

No major study deficiencies were identified. It was not stated whether a control site was shaved on each animal.

30

DATA EVALUATION REPORT

UICK-2 (p-menthane 3,8 diol)
(Moeller Plus)

STUDY TYPE: DERMAL SENSITIZATION - GUINEA PIG (81-6)

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2800 Crystal Drive
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830
Task Order No. 26

Primary Reviewer:
Sylvia Milanez, Ph.D., D.A.B.T.
Signature: [signature]
Date: APR 26 1999

H. Tim Borges, Ph.D., D.A.B.T., MT(ASCP)
Signature: [signature]
Date: APR 26 1999

Robert H. Ross, M.S., Group Leader
Signature: [signature]
Date: APR 26 1999

Quality Assurance:
Eric B. Lewis, M.S.
Signature: [signature]
Date: APR 26 1999

Disclaimer

This Data Evaluation Report may have been altered by the BPPD subsequent to signing by Oak Ridge National Laboratory personnel.

31

Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

EPA Reviewer: Roger Gardner Date, 6/30/99
EPA Work Assignment Manager: Date, 9/3/99
Sheryl K. Reilly, Ph.D.
Biopesticides & Pollution Prevention Division (7511W)

DATA EVALUATION RECORD

STUDY Type: Dermal Sensitization - Guinea Pig (81-6)
DP BARCODE: D252712
P.C. BARCODE: 011550
SUBMISSION CODE: S555602
CASE: 062676

TEST MATERIAL (PURITY):UICK-2 (p-menthane 3,8 diol, 10.0% a.i.)

SYNONYMS: Moeller Plus

CITATION: Bonnette, K.L. (1998) A dermal sensitization study in guinea pigs with Moeller Plus, Notebook #14735R126-3). Modified Buehler design. Springborn Laboratories, Inc. (SLI), Ohio Research Center, 640 North Elizabeth Street, Spencerville, OH 45887. SLI study no. 3068.110, June 16, 1988 (original study completion date) and July 14, 1988 (amended study completion date). MRID 44642106. Unpublished.

SPONSOR: S.C. Johnson & Son, Inc., Product Safety, Toxicology and Environmental Assessment, Mail Station 122, 1525 Howe Street, Racine, Wisconsin 53403-2236.

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 44642106) with Moeller Plus (p-menthane 3,8 diol, 10.0% a.i., lot no. 359D1), young male and female Hartley albino guinea pigs (20 test, 10 controls) were tested using the method of Buehler.

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 Moeller Plus 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. These results indicate that Moeller Plus was a dermal sensitizer. The positive control experiment utilized DNCB and was conducted appropriately.

In this study, Moeller Plus was a dermal sensitizer to male and female Hartley albino guinea pigs.

32

This study is classified as **Acceptable (guideline)** and satisfies the guideline requirement for a dermal sensitization study (81-6) in the guinea pig.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. An exception to the GLP provisions was noted in that the sponsor was responsible for tracking the identity, strength, purity, composition, and synthesis of the test compound.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: UICK-2 (p-menthane 3,8 diol, a.i.)

   Description: Clear colorless liquid; density given as 0.81 g/mL in MRID 44642101.
   Lot #: 359D1
   Purity: 10.0% a.i. (p-menthane 3,8 diol)
   Stability: Stable at room temperature for duration of study
   CAS Number: 42822-86-6

2. Vehicle and/or positive control: No vehicle control; positive control was 1-chloro-2,4-dinitrobenzene (DNCB; >99% pure, lot no. 12423MZ)

3. Test animals: Species: guinea pig
   Strain: Hartley Albino
   Age and weight at start of treatment: males: 5-7 weeks old, 326-454 g; females: 5-6 weeks old, 303-410 g
   Source: Charles River Laboratories, Kingston, NY
   Acclimation period: ≥ 5 days
   Diet: PMI Certified Guinea Pig Chow #5026 (Purina Mills, Inc.), *ad libitum*
   Water: municipal tap water treated by reverse osmosis, *ad libitum*
   Housing: individually in suspended stainless steel cages
   Environmental conditions:
   Temperature: 64-72°F
   Humidity: not controlled; anticipated to be 39-85%
   Air changes: 10-15/hour
   Photoperiod: 12 hour light/dark cycle

B. STUDY DESIGN and METHODS

1. In life dates

   Test Material - start: 08/07/97, end: 09/25/97
   Positive control - start: 04/29/97, end: 05/29/97

33

2. Animal assignment and treatment

Before the start of the definitive study, two range-finding studies were performed each with two male and two female guinea pigs. Based on the results of these studies, the inductions and challenge were done with 0.3 mL undiluted (approximately 243 mg, assuming density of 0.81 g/mL) Moeller Plus.

The definitive study was conducted according to the Buehler method. Induction and challenge with Moeller Plus were performed using 10 males and 10 females. The 5 additional males and 5 females used as challenge controls were untreated during the induction portion of the study. The day before each of three inductions (study days 0, 7, and 14), hair was removed from the left side of the animals (shaved area not specified). On the day of induction, 0.3 mL Moeller Plus (undiluted) was placed on a Hilltop chamber backed by adhesive tape (occlusive patch) and the chamber was applied to the shaved skin. The trunk of the animals was wrapped with elastic which was secured with adhesive tape to prevent removal of the chamber. The animal was then placed in its cage for 6 hours, after which time the wrappings and chamber were removed and the test site was wiped with gauze to remove test material residue. Dermal observations were made at the test site approximately 24 and 48 hours after induction.

Two weeks after the third induction (day 28), the test and challenge control animals were challenged on their right side (they were shaved the previous day) with 0.3 mL Moeller Plus. The challenge was performed using Hilltop chambers, similarly to the induction treatments, and dermal reactions were recorded 24 and 48 hours after the challenge treatment.

3. Positive control

Conducted approximately 3 months prior to the sensitization test with Moeller Plus, using the same procedure except that the test material was 1-chloro-2,4-dinitrobenzene (DNCB; >99% pure, lot no. 12423MZ). The induction phase used 0.1% w/v DNCB in acetone/ethanol and the challenge phase used 0.05 and 0.1% w/v DNCB in acetone/ethanol.

II. RESULTS AND DISCUSSION

A. INDUCTION REACTIONS AND DURATION

None of the test animals developed a dermal irritation response (other than 0 or ±) at the test site after the first induction. After the second induction, erythema (grade 1), often with desquamation, was seen on 5/20 animals after 24 and 48 hours. One female also had grade 2 erythema, very slight edema (grade 1), and desquamation at 24 hours. After the third induction, 10/20 and 9/20 animals had slight confluent

3 4

erythema (grade 1) after 24 and 48 hours, respectively, with 1 or 2 animals also having very slight edema (grade 1).

B. CHALLENGE REACTIONS AND DURATION

At 24 hours after challenge, 13/20 animals induced with Moeller Plus had slight or moderate confluent erythema (grade 1 or 2); 8 of these animals also had very slight edema (grade 1). At 48 hours after challenge, 4/20 animals had slight erythema (grade 1 or 2); two of these animals also had very slight (grade 1) edema. The mean dermal scores after 24 and 48 hours were 0.9 and 0.6, respectively.

None of the challenge control animals had dermal reactions at the challenge site 24 or 48 hours after test material application (mean dermal score of 0.0). A comparison of the results of the challenge control and induced animals indicates that in this study, Moeller Plus was a dermal sensitizing agent.

C. POSITIVE CONTROL

Results showed that DNCB was a dermal sensitizing agent.

D. DEFICIENCIES

The relative humidity of the animal room exceeded the preferred range (30-70%); this is not considered to have affected the study results.

DATA EVALUATION REPORT

UICK-2 (p-menthane 3,8 diol)
(Moeller Plus)

STUDY TYPE: REPEATED DERMAL INSULT - HUMAN (non-guideline)

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2800 Crystal Drive
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830
Task Order No. 26

Primary Reviewer:
Sylvia Milanez, Ph.D., D.A.B.T.
Signature:
Date: APR 2 6 1999

H. Tim Borges, Ph.D., D.A.B.T., MT(ASCP)
Signature:
Date: APR 2 6 1999

Robert H. Ross, M.S., Group Leader
Signature:
Date: APR 2 6 1999

Quality Assurance:
Eric B. Lewis, M.S.
Signature:
Date: APR 2 6 1999

Disclaimer

This Data Evaluation Report may have been altered by the BPPD subsequent to signing by Oak Ridge National Laboratory personnel.

Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

EPA Reviewer: Roger Gardner Date, 6/30/99
EPA Work Assignment Manager: Date, 9/3/99
Sheryl K. Reilly, Ph.D.
Biopesticides & Pollution Prevention Division (7511W)

DATA EVALUATION RECORD

STUDY Type: Repeated Dermal Insult – Human (non-guideline)
DP BARCODE: D252712 SUBMISSION CODE: S555602
P.C. BARCODE: 011550 CASE: 062676

TEST MATERIAL (PURITY):UICK-2 (p-menthane 3,8 diol, 9.82-10.1% a.i.)

SYNONYMS: Moeller Plus

CITATION: Vendetti, N. (1998) Repeated insult patch study with UICK-2 (SCJ Notebook No. 15045R59-2, SCJ GLP #377). TKL Research, Inc., 4 Forest Avenue, Paramus, NJ 07652. TKL Study no. 981020, August 26, 1998. MRID 44642107. Unpublished.

SPONSOR: S.C. Johnson & Son, Inc., Product Safety, Toxicology and Environmental Assessment, Mail Station 122, 1525 Howe Street, Racine, Wisconsin 53403-2236.

EXECUTIVE SUMMARY: In a non-guideline dermal patch testing study (MRID 44642107),the potential of Moeller Plus (p-menthane 3,8 diol, 9.82-10.1% a.i., lot no. 377D1) to cause dermal sensitization was tested in 110 volunteers age 18-71. The 6-week treatment regimen consisted of a 3-week induction period (9 applications of 0.2 mL) followed by a 11-13 day rest period and a challenge treatment (0.2 mL). Application was on the back with occlusive dermal patches for a 24-hour period; the test sites were evaluated 48-96 hours after each application. Sensitization was based on the test results of only "completed cases", i.e., subjects who had received 9 induction applications, at least 8 subsequent readings during induction, and 2 readings during challenge.

Of the 106 subjects who completed the test regimen, none developed a definitive dermal response at the test site during the induction or challenge phases. One individual had a "questionable" response (minimal or doubtful response, slightly different from the surrounding skin) for the second through the 9th induction reading, although this person had no response during the challenge reading. Another individual had a questionable response only at the two challenge readings. **Based on these results, it is concluded that UICK-2 was not a human skin sensitizer under the conditions of this Repeated Insult Patch Test.**

This study is classified as **Acceptable/non-guideline**. It satisfies the intended goal of assessing the sensitization potential of repeated dermal exposures of Moeller Plus under controlled patch study conditions.

37

COMPLIANCE: Quality Assurance and Data Confidentiality statements were provided. GLP provisions were not followed, but all aspects of the clinical study were performed in accordance with federal regulations and proposed guidelines for good clinical practice (see p. 3 of MRID 44642107).

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: UICK-2 (p-menthane 3,8 diol, a.i.)

   Description: Clear colorless liquid; density given as 0.81 g/mL in MRID 44642101.
   Lot #: 377D1
   Purity: 9.82-10.1% a.i. (p-menthane 3,8 diol)
   Stability: Stable at room temperature for duration of study
   CAS Number: 42822-86-6

2. Vehicle and/or positive control: No vehicle (test article given as received from sponsor) or positive control.

B. STUDY DESIGN and METHODS

1. In life dates

   Start: 05/04/98, end: 06/12/98

2. Human test subjects

   A study group of 110 volunteers (ages of 18-71) was used; this group was "non-exclusive", i.e. other companies' products were (or could have been) evaluated on them simultaneously. A number of inclusion and exclusion criteria were used to select the test subjects, including the presence of uniformly-colored skin on the infrascapular area of the back, and the absence of relevant systemic or dermatological disorders, medical conditions and treatments, and sensitivity to related chemicals. All individuals signed Informed Consent agreements.

3. Test procedure

   The test procedure used by the performing laboratory was Protocol No. TKL-1000M. The test material (0.2 mL; product was volatilized for 15-20 minutes) was applied to pre-marked sites on the back with an occlusive patch, consisting of non-porous plastic film adhesive bandage with a 2 cm x 2 cm Webril pad, affixed with hypo-allergenic tape (Micropore) as needed. Subjects were told to avoid wetting the patches and not to

engage in activities that cause excessive perspiration.

The study was scheduled over a 6-week period. The first phase, i.e. induction, consisted of 9 consecutive applications of the test material at 48 to 96-hour intervals. The subjects were required to remove the patches approximately 24 hours after each application. The test sites were evaluated 48 hours after each application except patches applied Friday were assessed the following Monday, or Tuesday, if Monday was a holiday. At the time of skin evaluation, the next patch was applied. The subjects had an 11-13 day rest period after the 9th evaluation, followed by the challenge phase, which was initiated during the 6th study week. The challenge consisted of application of identical patches to previously unexposed study sites, which were graded 48 and 72 hours after application. One person evaluated all the skin test sites in the study.

Sensitization was assessed using only "completed cases", i.e., subjects who had received 9 induction applications, at least 8 subsequent readings during induction, and 2 readings during challenge.

II. RESULTS AND DISCUSSION

A. RESULTS AND DISCUSSION

Of the 110 subjects who were enrolled in the study, 106 completed the test regimen. None of the 106 subjects developed a definitive dermal response at the test site during the induction or challenge phases. One individual had a response graded as "questionable" (meaning minimal or doubtful response, slightly different from the surrounding skin) for the second through the 9th induction reading, although this person had no response during the challenge reading. Another individual had a questionable response at both challenge readings; this person had no response during the induction phase. Based on these results, it was concluded that there was no evidence of sensitization to UICK-2 in humans under the conditions of this Repeated Insult Patch Test.

B. DEFICIENCIES

It is stated on p. 10 of MRID 44642107 "Special Instructions: Product was volatilized 15-20 minutes." It is unclear what this means or how it might have affected the sensitization response of the test subjects. The volunteers used for this study were "non-exclusive", i.e. other companies' products could have been evaluated on them simultaneously. The study author did not address the possible effects on the study results of simultaneous exposure of the subjects to other products, including whether it played a role in the questionable responses obtained for two individuals (one during induction only and the other during challenge only). It would have been informative if the sex and age of each test subject were provided in the study report. The reviewer does not consider these deficiencies to invalidate the study results.