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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Octhilinone-Evaluation of Several Toxicity Studies Submitted in Support of Reregistration

Tox Chem No.:	613C
PC No.:	099901
DP No.:	D227387
Submission No.:	S506628

FROM: William B. Greear, M.P.H. William B. Greear 1/23/98
Toxicology Branch II
Health Effects Division (7509C)

TO: Karen Whitby
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

THRU: Stephen C. Dapson, Ph.D., Branch Senior Scientist
Toxicology Branch II
Health Effects Division (7509C) Stephen C. Dapson 2/19/98

CC: Barbara Briscoe/Franklin Rubis, PM Team #81
Reregistration Branch
Special Review and Reregistration Division (7508W)

I. Conclusions:

The acute oral toxicity study (MRID 41482502) and the 13-week subchronic inhalation toxicity study (MRID 41544701) are Acceptable/Guideline and satisfy the requirements for guideline series 81-1 and 82-4 toxicity studies. The remaining 3 studies (MRID's 40647502, 40647504 and 40647505) are being returned because they have previously been reviewed (see TOX Doc. #007060).

II. Requested Action:

The Special Review and Reregistration Division has requested that TOX II evaluate the following Studies on octhilinone:

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Citations:

1) Romanello, A.S., Krywicki, K.M. and G.A. Hazleton (1987) Skane M-8 Microbicide. Acute oral toxicity study in male and female rats. Rohm and Haas Company, Spring House, PA 19477 Laboratory Project ID 86R-178 A and B. March 18, 1987. MRID 41482502. Unpublished.

2) Hagan, J., B. Kulwich, and J. Fisher (1989) Skane® M-8 HQ microbicide thirteen-week inhalation toxicity study in rats. Toxicology Department, Rohm and Haas Company, 727 Norristown Road, Spring House, PA 19477. Report No. 87R-013, June 29, 1989. MRID 41544701. Unpublished.

3) Sames, J.L. and J.P. Frank (1987) Skane M-8 HQ in vivo cytogenetic study in rats. Rohm and Haas Company, 727 Norristown Road, Spring House, PA 19477. Report No. 86R-218, March 30, 1987. MRID 40647504. Unpublished.

4) Foxall, S. (1986) Skane M-8 HQ Microbicide CHO/HGPRT gene mutation assay guideline reference 84-2. Rohm and Haas Company, 727 Norristown Road, Spring House, PA 19477. Report No. 86R-055, August 11, 1986. MRID 40647502. Unpublished.

5) Muller, G. (1986) Skane M-8 HQ Microbiocide in vitro unscheduled DNA synthesis assay. Rohm and Haas Company, 727 Norristown Road, Spring House, PA 19477. Report No. 86R-0018, August 12, 1986. MRID 40647505. Unpublished.

III. Results/Discussion:

Three of the studies have previously been reviewed and are therefore being returned. They are MRID's 40647502, 40647504 and 40647505 (TOX Doc. #007060). The results of the remaining two studies are as follows:

1) Acute Oral Toxicity

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 41482502), groups of fasted, young adult Charles River CD rats (10/sex) were given a single oral dose of Skane M-8 HQ Microbicide (46.7% a.i.) in propylene glycol at doses of 300, 500, 800, 1200 or 2000 mg/kg (representing 126, 210, 336, 504 or 839 mg/kg a.i.) and observed for 14 days.

Oral LD50 (Skane M-8 HQ) Males = 760 (603-937) mg/kg
(Skane M-8 HQ) Females = 767 (603-987) mg/kg
(a.i.) Males = 318 (251 - 396) mg/kg
(a.i.) Females = 324 (254-418) mg/kg

Toxicity Category: ~~II~~ III

Clinical signs included passiveness, ataxia, abdominal

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breathing and distension, moribundity, pale extremities, salivation, respiratory noise, cool to touch, lacrimation, scant droppings, diarrhea, tan or red stained muzzle and/or brown or yellow stained anogenital area occurring within the first 4 days of dosing. One female showed signs of toxicity at days 8-14. Signs observed at necropsy included reddened stomach mucosae or intestines, yellow or white fluid-filled stomach or intestines, red or tan stained muzzle and/or brown or yellow stained anogenital area. All other findings were considered incidental or post mortem changes and not treatment related. The changes in body by treatment might be significant based on the less body weight gain in the treated males vs. controls, however, no fair judgement could be made due to the poor copy of the report and missing raw data.

The acute oral toxicity study is classified as acceptable/guideline. This study does satisfy the guideline requirement for an acute oral toxicity study (81-1) in rats.

2) 13-Week Subchronic Inhalation Toxicity

EXECUTIVE SUMMARY: In a subchronic aerosol inhalation (nose-only) toxicity study (MRID 41544701), eleven Crl:CD®BR rats/sex/exposure group were exposed by inhalation (6 hours/day, 5 days/week) for 13 weeks to aerosolized Skane® M-8 HQ Microbicide (octhilinone, a.i. 42%, Lot No. SW 85-0311) at exposure concentrations of 0 (air), 0 (propylene glycol, 123 mg/m^3), 0.05, 0.64, and 6.39 mg of octhilinone/m^3. An additional eleven rats/sex/exposure group were assigned to a fourteen-week recovery period.

The mean mass median diameter and geometric mean were 2.5 μm and 9.2, respectively, for the propylene glycol exposure group and were 1.4 μm and 5.5, respectively, for all exposure groups of octhilinone. Three deaths occurred during the study but were not considered related to the exposures. No clinical signs were observed in the 0, 0(PG), 0.05, and 0.64 mg/m^3 groups. Clinical signs in the 6.39 mg/m^3 exposure group included: rales [males and females: 5-22/22: weeks 1-13]; dyspnea [females: 3/22: week 4; 3-9/22: weeks 7-10]; thriftless [(males: 3/22: weeks 8 and 10) and (females: 9-22/22: weeks 7-10)]; and red staining of the dropping sheet [(males: 11/22: week 2) and (females: 6/22: week 8)]. There were statistically significant decreases ($p<0.05$) in body weights (3.3 to 8.8% for weeks 1, 7, and 13) and body weight gains (11.3 to 68.9% for weeks 1, 7, and 13) in male and female rats in the 6.39 mg/m^3 group. No clinical chemistry and organ weight changes and deaths were related to the exposures. There were no gross pathological findings in exposed males or females. Histopathological findings in the male and/or females from the 6.39 mg/m^3 group consisted of secretory cell hyperplasia, squamous metaplasia, inflammation, and eosinophilic droplets in the nasal cavity at the 13-week sacrifice.

During the recovery period, rales were present in the males and females from the 6.39 mg/m^3 group.

Based upon the clinical signs, the decreased body weights, fluid in the uterus, and the pulmonary histopathological findings at the terminal sacrifice for males and females in the 6.39 mg/m^3 group, the **LOEL for 13-week inhalation exposure to octhilinone is 6.39 mg/m^3. The NOEL is 0.64 mg/m^3.**

The study is classified as Acceptable/Guideline, satisfying the requirements for a subchronic inhalation toxicity study in rats (82-4).

EPA Reviewer: William B. Greear, M.P.H. William B. Greear 1/23/98
Toxicology Branch II (7509C)
EPA Secondary Reviewer: Ching-Hung Hsu, Ph.D. C-H Hsu 1/23/98
Toxicology Branch II (7509C)

012498

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity
OPPTS 870.1100 OPP 81-1

DP BARCODE: D227387 SUBMISSION CODE: S506628

PC CODE: 099901 TOX. CHEM. NO. 613 C

TEST MATERIAL (PURITY): Skane M-8 HQ Microbicide, (46.7%)

SYNONYMS: 2-Octyl-3(2H)-isothiazolone, Kathon, Octhilinone, Microbicide M-8, RH-893, CAS# 26330-20-1.

CITATION: Romanello, A.S., Krywicki, K.M. and G.A. Hazleton (1987) Skane M-8 Microbicide. Acute oral toxicity study in male and female rats. Rohm and Haas Company, Spring House, PA 19477 Laboratory Project ID 86R-178 A and B. March 18, 1987. MRID 41482502. Unpublished.

SPONSOR: Rohm and Haas Company

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 41482502), groups of fasted, young adult Charles River CD rats (10/sex) were given a single oral dose of Skane M-8 HQ Microbicide (46.7% a.i.) in propylene glycol at doses of 300, 500, 800, 1200 or 2000 mg/kg (representing 126, 210, 336, 504 or 839 mg/kg a.i.) and observed for 14 days.

Oral LD50 (Skane M-8 HQ) Males = 760 (603-937) mg/kg
(Skane M-8 HQ) Females = 767 (603-987) mg/kg
(a.i.) Males = 318 (251 - 396) mg/kg
(a.i.) Females = 324 (254-418) mg/kg

Toxicity Category: ~~II~~ III

Clinical signs included passiveness, ataxia, abdominal breathing and distension, moribundity, pale extremities, salivation, respiratory noise, cool to touch, lacrimation, scant droppings, diarrhea, tan or red stained muzzle and/or brown or yellow stained anogenital area occurring

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within the first 4-5 days of dosing. One female showed signs of toxicity at days 8-14. Signs observed at necropsy in both sexes included reddened stomach mucosae or intestines, yellow or white fluid-filled stomach or intestines, red or tan stained muzzle and/or brown or yellow stained anogenital area. All other findings were considered incidental or post mortem changes and not treatment related. Necropsy of the survivors in both sexes revealed no treatment related changes. The changes in body weights by treatment might be significant based on the less body weight gain in the treated males vs. controls, however, no fair judgement could be made due to the poor copy of the report and missing raw data.

The acute oral toxicity study is classified as acceptable/guideline. This study does satisfy the guideline requirement for an acute oral toxicity study (81-1) in rats.

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

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Skane M-8 HQ Microbicide
Description: yellow liquid
Lot/Batch #: SW85-0311
Purity: 46.7%
CAS#: 26330-20-1

2. Vehicle and/or Positive Controls: propylene glycol 53.3%

Test Animals: Species: Rat
Strain: Charles River CD
Age and/or weight at dosing: 211-225 for males (mean wts.)
162-171 for females (mean wts.)
Source: not reported
Acclimation period: not reported
Diet: not reported
Water: not reported

B. STUDY DESIGN AND METHODS:

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1. In life dates and start: August 4, 1986; end: August 18, 1986

2. Animal Assignment and treatment: Animals were assigned to the test groups noted in Table 1. Rats were fasted overnight and given a single dose of the test substance at a constant volume of 10 ml/kg by gavage and then observed daily for signs of toxicity and mortality. Body weights were taken initially and at termination. Survivors were sacrificed and a necropsy was performed.

Table 1. Doses, Mortality/Animals Treated

Dose Skane M-8 HQ (mg/kg)	Dose a.i. (mg/kg)[1]	Males	Females	Combined
0	0	0/10	0/10	0/20
300	126	0/10	1/10	1/20
500	210	1/10	1/10	2/20
800	336	7/10	4/10	11/20
1200	504	8/10	9/10	17/20
2000	839	10/10	10/10	20/20

1. Data provided in a memorandum of W. Greear dated August 26, 1993.

3. Statistics: not reported.

II. RESULTS AND DISCUSSION:

A. Mortality is given in Table 1. Deaths occurred within the first 3 days of dosing. One female died between days 8-14.

The oral LD50 for: Skane M-8 HQ in males is 760 (603-937) mg/kg.
Skane M-8 HQ in females is 767 (603-987) mg/kg.
a.i. in males in 318 (251-396) mg/kg
a.i. in females is 324 (254-418) mg/kg

B. Clinical Observations: Toxic signs included passiveness, ataxia, abdominal breathing, moribundity, salivation, distended abdomen, pale extremities, respiratory noise, cool to touch, lacrimation, scant droppings, diarrhea, tan or red stained muzzle and/or brown or yellow stained anogenital

areas. Recovery was generally with 4 days of dosing.

C. Body Weight: The changes in body weights by treatment might be significant based on the less body weight gain in the treated males vs. Controls, however, no fair judgement could be made due to poor copy of the report and missing raw data.

D. Necropsy: Signs included reddened stomach mucosae and intestines, yellow or white fluid filled stomach or intestines, red or tan stained muzzle and/or brown a yellow stained anogenital area. Necropsy of survivors revealed no treatment related changes.

E. Deficiencies: The most serious deficiency was that the TGAI was not tested. However, the study is still adequate. The onset of signs was not observed for each toxic sign, rather a general indication of onset of "toxic signs" was provided. Although parts of the report was illegible, the information provided was satisfactory. Lack of detail regarding source of animal, diet, etc., were minor deficiencies which did not seriously detract from the study.

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DATA EVALUATION REPORT

012498

OCTHILINONE

STUDY TYPE: SUBCHRONIC INHALATION TOXICITY - RAT (82-4)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 96-14

Primary Reviewer:
James C. Norris, Ph.D., D.A.B.T.

Signature: Robert N. Ross for J.C. Norris
Date: 9-15-97

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C. Scott Jamison, Ph.D.

Signature: for C. Scott Jamison
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Robert H. Ross, M.S., Group Leader

Signature: RHR
Date: Robert H. Ross 9-15-97

Quality Assurance:
Susan S. Chang, M.S.

Signature: for S.S. Chang
Date: 9-15-97

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under Contract No. DE-AC05-96OR22464

EPA Reviewer:
W. Greear, M.P.H., D.A.B.T. W. Greear, Date 9/26/97
Toxicology Branch 2 (7509C)
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M.P. Copley, D.V.M., D.A.B.T. M P Copley, Date 10/4/97
Registration Action Branch 1 (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Inhalation Toxicity - Rat
OPPTS 870.3465 [§82-4]

DP BARCODE: D227387 SUBMISSION CODE: S506628
P.C. CODE: 099901 TOX. CHEM. NO.: 613C

TEST MATERIAL (PURITY): Skane® M-8 HQ Microbicide (Octhilinone, 42%)

SYNONYMS: 2-N-octyl-4-isothiazolin-3-one, octylthinone

CITATION: Hagan, J., B. Kulwich, and J. Fisher (1989) Skane® M-8 HQ microbicide thirteen-week inhalation toxicity study in rats. Toxicology Department, Rohm and Haas Company, 727 Norristown Road, Spring House, PA 19477. Report No. 87R-013, June 29, 1989. MRID 41544701. Unpublished.

SPONSOR: Rohm and Haas, 727 Norristown Road, Spring House PA, 19477

EXECUTIVE SUMMARY: In a subchronic aerosol inhalation (nose-only) toxicity study (MRID 41544701), eleven Crl:CD®BR rats/sex/exposure group were exposed by inhalation (6 hours/day, 5 days/week) for 13 weeks to aerosolized Skane® M-8 HQ Microbicide (octhilinone, a.i. 42%, Lot No. SW 85-0311) at exposure concentrations of 0 (air), 0 (propylene glycol, 123 mg/m^3), 0.05, 0.64, and 6.39 mg of octhilinone/m^3. An additional eleven rats/sex/exposure group were assigned to a fourteen-week recovery period.

The mean mass median diameter and geometric mean were 2.5 μm and 9.2, respectively, for the propylene glycol exposure group and were 1.4 μm and 5.5, respectively, for all exposure groups of octhilinone. Three deaths occurred during the study but were not considered related to the exposures. No clinical signs were observed in the 0, 0(PG), 0.05, and 0.64 mg/m^3 groups. Clinical signs in the 6.39 mg/m^3 exposure group included: rales [males and females: 5-22/22: weeks 1-13]; dyspnea [females: 3/22: week 4; 3-9/22: weeks 7-10]; thriftless [(males: 3/22: weeks 8 and 10) and (females: 9-22/22: weeks 7-10)]; and red staining of the dropping sheet [(males: 11/22: week 2) and (females: 6/22: week 8)]. There were statistically significant decreases ($p<0.05$) in body weights (3.3 to 8.8% for weeks 1, 7, and 13) and body weight

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gains (11.3 to 68.9% for weeks 1, 7, and 13) in male and female rats in the 6.39 mg/m^3 group. No clinical chemistry and organ weight changes and deaths were related to the exposures. There were no gross pathological findings in exposed males or females. Histopathological findings in the male and/or females from the 6.39 mg/m^3 group consisted of secretory cell hyperplasia, squamous metaplasia, inflammation, and eosinophilic droplets in the nasal cavity at the 13-week sacrifice.

During the recovery period, rales were present in the males and females from the 6.39 mg/m^3 group.

Based upon the clinical signs, the decreased body weights, fluid in the uterus, and the pulmonary histopathological findings at the terminal sacrifice for males and females in the 6.39 mg/m^3 group, the **LOEL for 13-week inhalation exposure to octhilinone is 6.39 mg/m^3. The NOEL is 0.64 mg/m^3.**

The study is classified as Acceptable, satisfying the requirements for a subchronic inhalation toxicity study in rats (82-4).

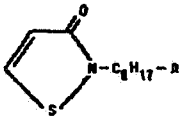
COMPLIANCE: Signed and dated Quality Assurance, Good Laboratory Practices, Data Confidentiality, and Flagging Statements were present.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test substance: Skane® M-8 HQ Microbicide

   Description: yellow liquid
   Lot/Batch #: SW 85-0311 (TD 86-60)
   Purity: The active ingredient, 2-N-octyl-4-isothiazolin-3-one, was 42% of the Skane® M-8 HQ Microbicide.
   Stability of compound: stable at room temperature
   CAS #: 26530-20-1
   Structure:



2. Vehicle control

   The solvent for the octhilinone in Skane® M-8 HQ Microbicide was propylene glycol. Additional propylene glycol (TD 86-136; Lot No. 0132; manufactured by Union 76 and supplied by American Chemical Company, Wilmington, DE) was used to dilute

the Skane® M-8 HQ Microbicide in order to achieve the desired exposure concentration for each group.

3. Test animals

Species: rat
Strain: Crl:CD®BR
Age and weight at study initiation: age not specified, males (227.7-289.3 g), females (155-196.5 g)
Source: Charles River Kingston, Kingston, NY (The city was Kingston, NY according to the report, but Protocol Amendment # 6 stated Stone Ridge, NY.)
Housing: wire-mesh cages suspended over absorbent paper, one/cage during non-exposure periods, individually in restraining tubes made of PVC during exposure.
Diet: Purina Rodent Laboratory Certified Chow® (type 5002), ad libitum, except during exposure
Water: water provided, ad libitum, except during exposure
Environmental conditions:
Temperature: 21-27°C
Humidity: 40-70%
Air changes: not provided
Photoperiod: 12 hour light/dark cycle
Acclimation period: 2 weeks

B. STUDY DESIGN

1. In life dates

Start: 5/28/86; end: 12/10/86

2. Animal assignment

Animals were randomly assigned to the exposure groups (Table 1).

TABLE 1: Study design

Test Group	Exposure concentration (a.i., mg/m^3)	Exposure duration (weeks)	Main study (Animals/sex/ Exposure group)	14-Week Recovery group (Animals/sex / Exposure group)
Control (air)	0	13	11	11
Vehicle Control (propylene glycol)	0	13	11	11
Low	0.05	13	11	11
Medium	0.64	13	11	11
High	6.39	13	11	11

Data taken from p.10, MRID 41544701.

3. Exposure concentrations selection rationale

The study did not describe the reasons for the selection of the exposure concentrations, however there was a reference (MRID 41544701, p. 30) to a previous 2-week range-finding study, [Hall, W. (1986) Pathology Report-Skane M-8: Two-week Inhalation Range-Finding Toxicity Study in Rats. Report No. 86RC-003. Rohm and Haas Company, Toxicology Department, Spring House, PA].

4. Exposure chamber/aerosol generation

During the exposure, rats were housed individually in 2 inch x 7 inch or 2.5 inch x 8 inch PVC restraining tubes attached to the front of the exposure chamber. Tube positions were rotated daily. The presentation of the test atmosphere to the animals was by nose-only. The 1250 L exposure chamber was made of stainless steel, Plexiglas®, and glass.

The aerosolized octhilinone was generated within an all-glass nebulizer (PGC Scientifics Corp., Rockville, MD or Custom Scientific Glass, Inc., Elkton, MD). The Skane® M-8 HQ Microbicide was diluted with the appropriate amount of propylene glycol so as to achieve the desired exposure concentration of octhilinone. The resulting solutions were pumped with

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an FMI pump (Fluid Metering, Inc., Oyster Bay, NY) into the fluid port of the nebulizer, and dispersed after contact with compressed air entering the nebulizer at a 90° angle to the liquid stream. The aerosolized octhilinone was directed into the exposure chamber by a glass manifold (Custom Scientific Glass, Inc., Elkton, MD). The exposure chamber was supplied additionally with room air conditioned by passage through a 3-stage filter system (rough, absolute, and charcoal filters).

5. Analysis of test atmosphere

Chamber airflow rates were 400 L/minute. Chamber temperatures during the exposure ranged from 20.8 to 22.4°C. Chamber humidities during the exposure ranged from 71 to 80%.

The analytical concentration of octhilinone in the exposure chambers was determined by sampling the exposure chamber at 30-minute intervals during exposures for the rats exposed to 0(PG), 0.64, and 6.39 mg/m^3 octhilinone. For the air control and the 0.05 mg/m^3 groups, one sample was taken beginning after the t_{99} to the end of the six-hour exposure. Samples of the test atmosphere at a flow rate of 0.31 L/minute were collected along a train of impingers (SKC, Inc., Eighty Four, PA) containing 10 or 15 mL of methanol. The collecting solution was quantitatively transferred to vials, weighed, and then analyzed in duplicate by HPLC for RH-893 (RH-893 was assumed by the reviewer to be octhilinone).

Particle size distributions, mass median diameter (MMD), and geometric standard deviation (GSD) were determined from gravimetric analysis of samples drawn from the test atmosphere through a QCM cascade impactor (California Measurements, Inc., Sierra Madre, CA). Samples were obtained once/week.

6. Statistics

Body weights and body weight changes were analyzed for normality and homogeneity of variance by plotting data, then analyzed by a 2-way ANOVA. Dunnett's t-test was used to compare group means. Bartlett's test was used to compare variances. Hematology and differential counts were analyzed for normality and homogeneity of variance by stem leaf, boxplot, and normal probability plots. If the data were considered continuous, then Dunnett's t-test and Bartlett's tests were used. If the ANOVA assumptions were not satisfied, then Chi-squared and Jonckheere tests were