

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
OCTHILINONE

Chemical Code # 001881, Tolerance # 00366
SB 950 # 315
Original date: 2/14/01

I. DATA GAP STATUS

| | |
|------------------------|--|
| Chronic Toxicity, rat: | Data gap, no study on file (13-week studies using inhalation and dermal routes of administration have been reviewed with no adverse effects indicated) |
| Chronic Toxicity, dog: | Data gap, no study on file |
| Oncogenicity, rat: | Data gap, no study on file |
| Oncogenicity, mouse: | Data gap, inadequate study, no adverse effect indicated |
| Reproduction, rat: | Data gap, no study on file |
| Reproduction, mouse: | Data gap, no study on file |
| Teratology, rat: | No data gap, no adverse effect |
| Teratology, rabbit: | No data gap, no adverse effect |
| Gene mutation: | No data gap, no adverse effect |
| Chromosome: | No data gap, possible adverse effect |
| DNA damage: | No data gap, no adverse effect |
| Neurotoxicity: | Not required at this time |

Toxicology one-liners are attached.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T010214

Reviewed by: J. Kishiyama and J. Gee, 2/14/01

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

CHRONIC TOXICITY, RAT

Subchronic:

018 114816 Hagan, J. V., B. A. Kulwich, and J. R. Fisher. "Skane® M-8 HQ Microbiocide Thirteen-Week Inhalation Toxicity Study in Rats." (Rohm & Haas Company, Toxicology Department, Report No. 87R-013, June 29, 1989.) Skane® M-8 HQ Microbiocide (lot SW 85-0311, 42% a.i. in propylene glycol) was administered via nose-only inhalation 6 hours/day, 5 days/week for thirteen weeks at concentrations of 0 (filtered air), 0 (vehicle: propylene glycol), 0.05, 0.64, and 6.39 mg/m³ to 22 CrI:CD® BR rats/sex/group, with a t₉₉ of 23 minutes. Doses were adjusted for purity. The MMD was 1.4 µm, GSD, 5.5 µm and respirable fraction, 68%. Eleven/sex/group were necropsied at the end of the thirteen weeks of treatment and the remainder after a fourteen-week recovery period. Inhalation of Skane® M-8 (6.39 mg/m³) during a 13 week treatment period produced irritation of the nasal cavity. A mild irritant effect was noted at the end of the treatment period in both sexes, with histopathologic signs of squamous metaplasia of the nasal epithelium, secretory cell hyperplasia and minimal to mild acute inflammation. NOEL = 0.64 mg/m³. Nasal cavity irritation was still present after the 14-week recovery, especially at the high dose. Body weight and weight gains were reduced for the high-dose groups, particularly for males. Body weight recovered in the 14-week post-treatment period.

UNACCEPTABLE (no

rationale for dose selection, no food consumption data and no ophthalmological examination). Probably not upgradeable. (Kishiyama and Gee, 2/8/01).

017 114815 Bernacki, H. J. and J. D. Hamilton. "RH-893 HQ Technical Three-Month Dermal Toxicity Study in Rats". (Rohm & Haas Company, Toxicology Department, Report No. 90R-031, August 19, 1991.) RH-893 HQ Technical (batch no 3192, 99.1%) was administered by non-occluded dermal application at concentrations of 0 (untreated), 0 (propylene glycol), 2.97, 5.95 and 14.87 mg/kg in 1 ml/kg, 5 days/week for 13 weeks to 10 CrI:CD®BR rats/sex/group. Body weight was reduced in high dose males. Systemic NOEL = 5.95 mg/kg/day. Skin irritation was observed for all RH-893 HQ groups and was dose-related. Dermal NOEL = <2.97 mg/kg/day. UNACCEPTABLE (dosing was non-occluded and the differential blood smear counts were not reported). Upgradeable. (Kishiyama and Gee, 2/14/01) See record 129298 below.

020 129298 Shindel, B. "Data evaluation report: RH-893 HQ technical." (Clement International Corporation, prepared for Office of Pesticide Programs, US EPA, 1/10/92). This record is a copy of an evaluation on the above study, "RH-893 HQ Technical Three-Month Dermal Toxicity Study in Rats". The conclusion of the evaluation was that the dermal NOEL < 2.97 mg a.i./kg/day (skin irritation) and the systemic NOEL = 5.95 mg/kg/day (decreases in hematological parameters, glucose, total protein in females and decrease in body weight and weight gain in males). The study was classified as Core minimum because the test site was not occluded and data for differential leukocyte count were not

provided. Page of the review states that "...not applying an occlusive dressing is a minor deviation from the Guidance which did not appear to affect the outcome of the study." Supplemental information. No worksheet. (Gee, 2/14/01)

CHRONIC TOXICITY, DOG

No study submitted.

ONCOGENICITY, RAT

No study submitted.

ONCOGENICITY, MOUSE

005 038052 Piccirillo, V. J. and J. Smith. "Eighteen Month Study on the Carcinogenic Potential of RH-893 in Mice". (Medical College of Virginia, Report No. C-1, May 15, 1975.) RH-893 (purity not reported) at concentrations of 0, 500 and 1000 ppm admixed with feed was fed to 125 hybrid mice/sex/group (C57BL/6 females x C3H/Anf males) for 18 months. Body weights were reduced at 1000 ppm in both sexes, especially early in the study. At 6 months, 25/sex/dose were sacrificed. No oncogenic response was reported with octhilinone. Apparent systemic NOEL = 500 ppm (reduced body weight). UNACCEPTABLE (numerous deficiencies with respect to recent guidelines). Not upgradeable. No adverse effect identified. (Kishiyama and Gee, 1/31/01).

REPRODUCTION, RAT

No study submitted.

TERATOLOGY, RAT

009 038056 Powers, M. B. "Teratology Study - Rats RH-893 (Technical). Final report". (Hazleton Laboratories, Project No. 417-349, May 21, 1971.) RH-893 (Technical, SW 70/0293, purity not given) was admixed with the feed at concentrations of 0, 200, and 1000 ppm, days 6 through 15 of gestation. There were 18, 18 and 17 albino female rats per group. There were no maternal deaths, clinical signs, effects on body weight or food consumption reported. There were 18, 16 and 14 litters at C-section for evaluation. Fetal effects presented as summary data only with no treatment-related findings.

Maternal and Developmental NOEL \geq 1000 ppm. UNACCEPTABLE (inadequate number of litters per group, purity not stated, no analysis of diets for content, dose selection not justified.) Not upgradeable. (Kishiyama and Gee, 2/1/01).

** 014 114806 Nemec, M. D. "A Teratology Study in Rats with Skane M-8 HQ. Final report". (WIL Research Laboratories, Inc., Project Number WIL-91003, March 31, 1987.) Skane M-8 HQ (46.7% a.i. in 50% propylene glycol) at doses of 0 (0.5% aqueous methylcellulose), 0 (propylene glycol

in 0.5% aqueous methylcellulose), 1, 5 and 30 mg/kg/day was administered via gavage during gestation days 6 through 15 to 25 mated Sprague Dawley female rats/group. Doses were corrected for percentage of the active ingredient. The high dose group had reduced food consumption, body weight and weight gain, and decreased defecation plus an increased incidence of salivation. There was a single mortality attributed to treatment. Body weight for the mid-dose group was not statistically significantly lower but appeared slightly reduced and treatment related. Maternal NOEL = 1 mg/kg/day. No teratogenic response reported. Developmental NOEL = 5 mg/kg/day (slight increase in resorptions, not statistically significant). ACCEPTABLE. (Kishiyama and Gee, 2/5/01).

TERATOLOGY, RABBIT

001 024970: Teratology- Rabbits. Hazleton Laboratories. No date. UNACCEPTABLE (insufficient information). (J. Remsen, 8/22/85).

008 038055 M. B. Powers. "Teratology Study – Rabbits, RH-893 (Technical) Final report". Hazleton Laboratories, Project No. 417-346, December 23, 1970.) RH-893 (Technical, purity not stated, SW 70/0293) at doses of 0 (corn oil), 6 and 60 mg/kg/day was administered via gavage to New Zealand White rabbits as follows: 1) during gestation days 6 through 18 to eight females (designated for Caesarean delivery) per group and also 2) during gestation days 6 through 16 to seven female rabbits (allowed a natural delivery) per group. RH-893 was toxic at both tested doses with mortality of 6/15 at the low dose and 10/15 at the high dose. At the day 29 C-section, there were 5, 3 and 1 litters. After delivery, there were 4, 1 and 1 litters for evaluation. There were too few fetuses/litters for meaningful evaluation, although no developmental toxicity was reported. No specific cause of death was identified, although lung involvement was common. No clinical dose-related clinical signs were evaluated. Maternal NOEL < 6 mg/kg (mortality). UNACCEPTABLE. Not Upgradeable. (Kishiyama and Gee, 2/1/01).

** 015 114807, 114808 Solomon, H. M. and Lutz, M. F. "Skane™ M-8 HQ Industrial Mildewcide: Oral (Gavage) Developmental Study in Rabbits". (Rohm & Haas Company, Toxicology Department, Report No. 87R-019, 12/1/87.) Skane™ M-8 HQ (lot SW86-6155, 46.3% ai in propylene glycol) at doses of 0 (vehicle control, 0.5% aqueous methylcellulose), 0 (propylene glycol control), 5, 20, and 80 mg a.i./kg/day was administered via gavage on gestation days 7 - 19 to nineteen artificially inseminated New Zealand White female rabbits/group. Reduced body weight, primarily days 7-11, and increases in the incidence of anorexia, scant feces, abortion (5/19) and mortality (1/19) were seen for the high dose group. Maternal NOEL = 20 mg/kg. Fetal weight, especially for males, was reduced for the high dose group. Developmental NOEL = 20 mg/kg. No adverse developmental effect. ACCEPTABLE. (Kishiyama and Gee, 2/8/01).

GENE MUTATION

SUMMARY: Considering that there are three separate studies with *Salmonella typhimurium* conducted over a number of years, all with negative results, the data gap is considered filled, despite the deficiency of a lack of positive controls without activation. It is believed that requesting another study would not contribute significantly to the database for gene mutation. (Gee, 2/14/01)

016 114809 Fisher, P. M. and J. P. Frank. "Skane[®] M-8 HQ: *Salmonella typhimurium* Gene Mutation Assay". (Rohm and Haas Company, Toxicology Department, report No. 88R-203, February 1, 1989.) Skane[®] M-8 HQ (lot SW-87-7064, 45.1% purity for ai) was evaluated for mutagenic activity using *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100, with and without activation with Aroclor-induced rat liver S9. There were triplicate plates per concentration with two trials. Skane[®] M-8 HQ was toxic at concentrations from 50 to 5000 µg/plate in the first test. Therefore, a second test at concentrations from 3 to 30 µg/plate was performed. No toxicity or significant increase in the number of histidine revertants for *Salmonella typhimurium* strains was reported for Test #2. No positive controls without activation, therefore, UNACCEPTABLE, and not upgradeable. (Kishiyama and Gee, 2/8/01)

006 038053 Lohse, K. L. "Skane[®] M-8 Microbial Mutagen Test". (Rohm and Haas Company, Report No.: 82R-207, 11/8/1982.) Skane[®] M-8, lot 2-6714, 45% ai, was tested at concentrations ranging from 0.1 to 7500 nanoliters/plate with and without Aroclor-induced rat liver metabolic activation using *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100. There were apparently two (or three) trials. The number of plates for each concentration was not specified. Skane[®] was tested to concentrations which were noted as inhibiting the test strains. Positive controls with activation were functional. There were no positive controls used for non-activation plates. There was no significant increase in revertants. UNACCEPTABLE (no positive controls without activation, missing information on the conduct of the study). Not upgradeable. (Kishiyama and Gee, 2/1/01).

007 038054 Chism, E. M. and E. Kunz. "RH-893 Process Variation; Microbial Mutagen Test". (Rohm and Haas Company, Toxicology Department, Report No.: 84R-0144, 10/2/84.) RH-893, lot 7KDR42-1, purity not stated, was tested at concentrations ranging from 0.5 to 7500 nanoliters/plate with and without Aroclor-induced rat liver metabolic activation using *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100. There were no details of the conduct of the study including the number of plates per concentration. Positive controls for activation were functional. There were no appropriate positive controls used for the non-activated plates. The test material was not technical grade. No significant increase in revertants was reported. UNACCEPTABLE (no appropriate positive controls without activation, inadequate description of study conduct). Not upgradeable. (Kishiyama and Gee, 2/1/01).

CHROMOSOME EFFECTS

** 016 114811, 114812 Ivett, J. L. "Clastogenic Evaluation of Skane M-8 Micobiocide in an *In Vitro* Cytogenic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells". (Hazleton Biotechnologies, HB Project No.: 20990, March 27, 1987.) Skane M-8 (46.7% ai with 53.3% propylene glycol) was tested at concentrations of 400 ng/ml to 8 µg/ml without activation and at 750 ng/ml through 20 µg/ml with metabolic activation for the potential to induce chromosomal aberrations in Chinese hamster ovary cells (CHO-WBL). There were duplicate cultures per concentration and several trials both with and without Aroclor-induced rat liver S9 activation. Exposure times were approximately 17.5 hours without activation and a harvest time of 20 hours after the initiation of exposure in both trials. With activation, treatment was for two hours with either a 10 or a 20-hour harvest time. The higher concentration(s) both with and without activation depressed the % relative

growth. Mitotic indices were also lower. The aberrations included complex chromatid types (e.g., triradials, quadriradials). **Significant increases in chromosomal aberrations (with and without S9 Mix) occurred in both the initial and repeat tests . ACCEPTABLE.** (Kishiyama and Gee, 2/9/01)

DNA DAMAGE

** 016 114813, 114814 Muller, G. "Skane M-8 HQ Microbiocide *In Vitro* Unscheduled DNA Synthesis Assay". (Rohm & Haas Company Toxicology Department, Laboratory Project ID Report No. 86R-0018, August 12, 1986.) Skane M-8 HQ (lot SW 85-0311, 46.7% ai and 53.3% propylene glycol) was evaluated at concentrations of 0.05 to 100 µg/ml (uncorrected for ai content) for the potential to induce unscheduled DNA synthesis in CRCD male rat hepatocytes by autoradiography. Hepatocytes were incubated for 18 – 19 hours. Six wells with coverslips were set up per concentration. One coverslip was used for cytotoxicity (by trypan blue dye exclusion) and 3/5 for determination of UDS. There were two trials with the second trial testing a closer range of concentrations (1.0 to 10 ug/ml). Octhilineone was tested to > 50% toxicity. No individual cell data. No significant increase in net nuclear grains/cell reported. **ACCEPTABLE.** (Kishiyama and Gee, 2/13/01).

NEUROTOXICITY

Not required at this time.