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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
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Prepared by

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OCTHILINONE Subchronic Inhalation Toxicity (82-4)

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DATA EVALUATION RECORD

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

DP BARCODE: D227387
P.C. CODE: 099901

SUBMISSION CODE: S506628
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 Unpublished.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).

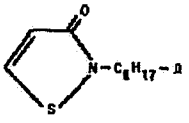
COMPLIANCE: Signed and dated Quality Assurance, Good Laboratory Practices, Data Confidentiality, and Flagging Statements were present.

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

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

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used. Histopathologic data were analyzed using a categorical modeling procedure.

C. METHODS

1. Observations

Rats were observed for mortality and clinical signs twice daily (prior to and after exposure during the week) or once daily on weekends and during the 14-week recovery period.

2. Body weight

Rats were weighed on the day prior to the first exposure and then weekly until study termination.

3. Test atmosphere

Listed below are the particle sizes for the aerosolized PG and octhilinone (Table 2).

TABLE 2: Mean particle sizes, respirable fraction, and active ingredient (a.i.) concentrations for male and female rats exposed to aerosolized octhilinone.

Exposure group (mg/m^3)	MMD (μm)	GSD	Respirable fraction (%)	a.i. Concentration (mg/m^3)	a.i. Respirable (mg/m^3)
0 (air)	ND	ND	ND	ND	ND
0 (PG[a])	2.5 ± 2.9	9.20 ± 3.9	58 ± 17%	0	0
0.05	1.5 ± 0.6	9.5 ± 5.0	60 ± 14%	0.053 ± 0.034	0.031 ± 0.017
0.64	1.4 ± 0.9	4.2 ± 2.0	72 ± 14%	0.64 ± 0.10	0.47 ± 0.11
6.39	1.4 ± 0.6	2.9 ± 1.1	72 ± 14%	6.39 ± 1.80	4.52 ± 1.55

Data taken from Appendices B1-B5, pp. 178-186, MRID 41544701.
ND=Not determined, MMD=Mass Median Diameter, GSD=Geometric Standard Deviation
[a]Propylene glycol

4. Ophthalmoscopic examinations were not performed.

5. Blood was collected just prior to exsanguination from 11 rats/group. Hematologic evaluations were performed

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using an ELT-8/ds hematology analyzer (Ortho Instruments, Westwood, MA). Erythrocyte morphology and leukocyte differentials were determined microscopically for the rats exposed with air, propylene glycol, and 6.39 mg/m^3 octhilinone. The CHECKED (X) parameters were examined. Clinical chemistry evaluations were performed using a CentrifiChem System 400 (Baker Instruments, Allentown, PA).

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential
X	Hemoglobin (HGB)*	X	count*
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)*	X	Mean corpusc. HGB
X	Platelet count*		conc.(MCHC)
	Blood clotting		Mean corpusc. volume (MCV)
	measurements*		Reticulocyte count
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic studies based on Subdivision F Guidelines

b. Clinical chemistry

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
	Chloride*	X	Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
X	Phosphorus*	X	Total Cholesterol*
	Potassium*	X	Globulins
	Sodium*	X	Glucose*
	ENZYMES	X	Total bilirubin
		X	Total serum protein (TP)*
X	Alkaline phosphatase (ALK)	X	Triglycerides
	Cholinesterase (ChE)		Serum protein
	Creatine phosphokinase*		electrophores
	Lactic acid dehydrogenase		
X	(LDH)*		
	Serum alanine amino-		
X	transferase (also SGPT)*		
	Serum aspartate amino-		
	transferase (also SGOT)*		
	Gamma glutamyl transferase		
	(GGT)		
	Glutamate dehydrogenase		

* Required for subchronic studies based on Subdivision F Guidelines

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6. Urinalysis was not performed.

7. Sacrifice and pathology

At the scheduled time, each animal was anesthetized with sodium pentobarbital (50 mg/kg, ip) and killed by exsanguination from the dorsal aorta. The necropsy was then performed. The CHECKED (X) tissues were collected for histological examination. The tissues listed below were examined from the 0, 0 (PG), and 6.39 mg/m^3 groups, except for gross lesions, larynx, lungs, lymph nodes, nasal cavity, and trachea which were also examined from the 0.05 and 0.64 mg/m^3 groups. The (XX) organs, in addition, were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
	Tongue (oral cavity)	X	Aorta*	X	Brain*
	Salivary glands*	XX	Heart*	X	Periph. nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*	X	Eyes (optic n.)
X	Jejunum*	X	Thymus*		
X	Ileum*		UROGENITAL		GLANDULAR
X	Cecum*	XX	Kidneys*+	X	Adrenal gland*
X	Colon*	X	Urinary	X	Lacrimal gland
X	Rectum*	XX	Bladder*	X	Mammary gland
XX	Liver*+	X	Testes*+	X	Parathyroids*
X	Gall bladder*	X	Epididymides	X	Thyroids*
	Pancreas*	X	Prostate	X	OTHER
		XX	Seminal	X	Bone
XX	RESPIRATORY	X	vesicle	X	Skeletal muscle
X	Trachea*	X	Ovaries		Ears
X	Lung*		Uterus*	X	Skin
	Nose		Vagina	X	All grosslesions
X	Pharynx			X	and masses*
	Larynx			X	
				X	

* Required for subchronic studies based on Subdivision F Guidelines
+ Organ weight required in subchronic and chronic studies.

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II. RESULTS

A. OBSERVATIONS

1. Clinical signs of toxicity

There were no exposure-related clinical signs of toxicity in animals exposed to 0.05 or 0.64 mg/m^3. For males and females exposed to octhilinone at 6.39 mg/m^3, clinical signs 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)] (apparently due to nasal discharge).

During the recovery period, the incidences of dyspnea, thriftlessness, and red staining on the drop sheets were not observed. For the animals in the 6.39 mg/m^3 group, the rales were observed in 3/11 males and 3/11 females at week 14. By week 20, no male displayed rales, while one female exhibited rales throughout the recovery period.

2. Mortality

Two males in the propylene glycol-exposed group were sacrificed (one in week 7 and one in week 11) due to moribund condition. One female exposed to octhilinone at 0.64 mg/m^3 died in week 9 due to being too tightly restrained during exposure. During the recovery period, one male from the control group died in week 17. The histopathological examination revealed a tooth abscess with acute inflammation of the oral mucosa/palate and acute necrotizing inflammation of the nasal cavity. These deaths were not due to the octhilinone exposure.

B. BODY WEIGHT AND WEIGHT GAIN

Body weights (Table 3) for males exposed to octhilinone at 6.39 mg/m^3 were statistically significantly decreased ($p<0.05$) from week 1 of the study period to termination. Body weights for high exposure group females were statistically significantly ($p<0.05$) decreased during week 7. Body weight gains (Table 4) for males exposed with octhilinone at 6.39 mg/m^3 were significantly decreased from weeks 1-13. Body weight gains for high exposure females were statistically significantly decreased during weeks 1 and 7.

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TABLE 3: Mean body weights (g) (± SD) for male and female rats exposed to octhilinone for 13 weeks

Study week	Exposure group (mg/m^3)									
	Males					Females				
	0	0 (PG[a])	0.05	0.64	6.39	0	0 (PG)	0.05	0.64	6.39
0	258.8 ± 3.0	258.1 ± 2.9	256.9 ± 2.9	255.8 ± 3.5	260.6 ± 3.1	174.5 ± 1.8	171.8 ± 1.7	173.7 ± 2.0	173.0 ± 1.8	173.3 ± 1.9
1	294.0 ± 2.8	290.2 ± 2.6	291.8 ± 3.3	288.9 ± 3.7	271.5 * ± 2.6 (7.8%[b])	192.1 ± 2.1	189.2 ± 2.0	193.1 ± 2.2	190.3 ± 1.9	185.8 ± 1.5 (3.3%)
7	422.0 ± 4.4	410.4 ± 6.1	417.4 ± 6.7	411.6 ± 7.1	385.7 * ± 4.1 (8.5%)	239.4 ± 3.6	240.8 ± 3.3	242.2 ± 2.9	240.7 ± 2.7	225.9* ± 2.5 (5.6%)
13	480.6 ± 9.8	483.6 ± 4.5	486.3 ± 7.3	471.9 ± 7.4	448.8 * ± 6.6 (8.2%)	265.5 ± 4.7	270.3 ± 4.0	270.8 ± 3.6	265.7 ± 3.6	254.1 ± 3.0 (4.3%)

Data taken from Tables 5A, 5B, 5C, and 5D, pp. 47-50, MRID 41544701.
[a]Propylene glycol-exposed control group
[b]Parentheses: percent decrease of the exposed group's body weight as compared to the air control group's body weight (calculated by the reviewer).
*Significantly different from air control, $p<0.05$.

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TABLE 4: Mean body weight gains (g) (± SD) for male and female rats exposed to octhilinone for 13 weeks

Study week	Exposure group (mg/m³)									
	Males					Females				
	0	0 (PG[a])	0.05	0.64	6.39	0	0 (PG)	0.05	0.64	6.39
1	35.1 ± 1.8	32.1 ± 1.5	34.9 ± 1.0	33.1 ± 1.3	10.9* ± 2.4 (68.9%[b])	17.6 ± 1.6	17.4 ± 1.3	19.4 ± 1.6	17.2 ± 1.1	12.4* ± 1.2 (29.6%)
7	163.1 ± 3.7	152.3 ± 5.8	160.5 ± 5.1	155.8 ± 6.3	124.4* ± 3.5 (23.7%)	64.9 ± 3.6	69.0 ± 3.0	68.5 ± 2.4	67.7 ± 2.4	52.6* ± 2.6 (19.0%)
13	221.8 ± 8.8	225.0 ± 4.9	229.5 ± 5.8	216.1 ± 6.5	180.7* ± 5.9 (18.5%)	91.0 ± 4.1	98.5 ± 3.7	97.0 ± 2.9	92.5 ± 3.2	80.7 ± 2.8 (11.3%)

Data taken from Tables 6A, 6B, 6C, and 6D, pp. 55-58, MRID 41544701.
[a]Propylene glycol-exposed control group
[b]Parentheses: percent decrease of the exposed group's body weight gain as compared to the air control group's body weight gain (calculated by the reviewer).
*Significantly different from air control, $p<0.05$.

The recovery groups did not have any differences in body weight or body weight gains.

C. FOOD CONSUMPTION

Food consumption was not reported by the study authors.

D. OPHTHALMOSCOPIC EXAMINATION

Ophthalmoscopic examinations were not performed.

E. CLINICAL PATHOLOGY

1. Hematology

There were no exposure-related findings.

2. Clinical chemistry

There were statistically significant ($p<0.05$) decreases in triglycerides (33.8%) and glucose (17.6%) levels for high exposure males (Table 5). However, these decreases are likely due to decreased

food consumption as exhibited by the decreased body weights and body weight gains in high exposure males. There were statistically significant ($p<0.05$) reductions in creatinine values (12.7%) for females in the high exposure group and in SGOT values (23.5%) for females in the low exposure group (0.05 mg/m^3). Since the SGOT decrease was only in the low exposure group, this change was considered spurious and not related to octhilinone exposure. Generally, an increase in creatinine is indicative of a toxicologically significant effect, therefore, the decrease in creatinine in the high exposure group was not considered toxicologically significant.

TABLE 5: Mean clinical chemistry values (± SD) in male or female rats exposed to octhilinone for 13 weeks

Parameter	Sex	Exposure group (mg/m^3)				
		0	0 (PG[a])	0.05	0.64	6.39
Triglycerides (mg/dL)	Male	77 ± 9	59 ± 7	59 ± 6	61 ± 5	51 ± 3* (33.8%)
Glucose (mg/dL)	Male	125 ± 7	117 ± 5	123 ± 4	110 ± 6	103 ± 5* (17.6%)
SGOT (U/L)	Female	115 ± 9	92 ± 3	88 ± 7* (23.5%)	95 ± 7	99 ± 8
Creatinine (mg/dL)	Female	0.71 ± 0.03	0.69 ± 0.02	0.68 ± 0.02	0.68 ± 0.03	0.62* ± 0.02 (12.7%)

Data taken from Tables 8A-D, pp. 71-74, MRID 41544701.
[a]Propylene glycol-exposed control group
[b]Parentheses: percent decrease of the exposed group's clinical chemistry value as compared to the air control group's clinical chemistry value (calculated by the reviewer).
*Significantly different from air control, $p<0.05$

In the recovery groups, a statistically significant decrease in the total protein concentration was found in the 0 (PG) mg/m^3 group, and a statistically significant increase in the SGPT values was observed in the 0.05 mg/m^3 group. However, these were not

considered exposure-related changes since the higher exposure groups did not exhibit these changes.

F. URINALYSIS

Urinalysis was not performed.

G. SACRIFICE AND PATHOLOGY

1. Organ weight

At the 13-week sacrifice, statistically significant ($p<0.05$) decreases in the absolute weights of the liver, kidneys, and spleen for males in the 6.39 mg/m^3 group were noted (Table 6). The absolute weight of the adrenals in the males from the 0 (PG), 0.64, and 6.39 mg/m^3 groups were statistically significantly decreased. Also, the relative adrenal (organ weight to body weight) weights were also statistically significantly decreased in the 0 (PG) and 0.64 mg/m^3 groups (Table 7). The relative brain (organ weight to body weight) weights were statistically significantly increased. No statistically significant differences in organ weights of the females were observed.

TABLE 6: Mean organ weights (g) (± SD) of male rats exposed to octhilinone for 13 weeks

Organ	Exposure groups (mg/m^3)				
	0	0 (PG[a])	0.05	0.64	6.39
Liver	11.993 ± 0.303	12.162 ± 0.213	12.438 ± 0.465	11.770 ± 0.337	10.176* ± 0.403 (15.2%)[b]
Spleen	0.803 ± 0.032	0.763 ± 0.029	0.773 ± 0.042	0.750 ± 0.052	0.665* ± 0.032 (17.2%)
Kidneys	3.248 ± 0.043	3.267 ± 0.066	3.353 ± 0.097	3.049 ± 0.085	2.897* ± 0.092 (10.8%)
Adrenals	0.064 ± 0.004	0.053* ± 0.003 (17.2%)	0.056 ± 0.003 (12.5%)	0.048* ± 0.002 (25.0%)	0.053* ± 0.003 (17.2%)

Data taken from Tables 7A and 7B, pp. 63 and 64, MRID 41544701.
[a]Propylene glycol-exposed control group
[b]Parentheses: percent decrease of the exposed group's organ weight as compared to the air control group's organ weight (calculated by the reviewer).
*Significantly different from air control, $p<0.05$

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TABLE 7: Mean relative (organ to body weights) organ weights (g) (± SD) of male rats exposed to octhilinone for 13 weeks

Organ	Exposure groups (mg/m^3)				
	0	0 (PG[a])	0.05	0.64	6.39
Liver	2.602 ± 0.061	2.650 ± 0.044	2.789 ± 0.065	2.600 ± 0.059	2.530 ± 0.093
Spleen	0.175 ± 0.008	0.167 ± 0.007	0.168 ± 0.007	0.166 ± 0.012	0.166 ± 0.008
Kidneys	0.706 ± 0.015	0.712 ± 0.016	0.731 ± 0.013	0.674 ± 0.015	0.722 ± 0.024
Adrenals	0.014 ± 0.001	0.011* ± 0.000 (21.4%)[b]	0.012 ± 0.001	0.010* ± 0.001 (28.6%)	0.013 ± 0.001

Data taken from Tables 7A and 7B, pp. 63 and 64, MRID 41544701.
[a]Propylene glycol-exposed control group
[b]Parentheses: percent decrease of the exposed group's relative organ weight as compared to the air control group's relative organ weight (calculated by the reviewer).
*Significantly different from air control, $p<0.05$

At the sacrifice of the recovery groups, relative lung (organ weight to body weight) weights were statistically significantly decreased in the 0 (PG) group, while absolute lung weights were statistically significantly decreased in the females from the 0.05 mg/m^3 group.

All of these organ weight changes (at the terminal and recovery sacrifices) were not considered to be related to the animals' exposure to octhilinone, because (1) the changes were not reflected in the relative organ weights, (2) they were spurious, or (3) the changes were also present in the PG-exposed animals.

2. Gross pathology

The only exposure-related finding at the terminal sacrifice was fluid in the uterus body and horns (4/11) of the females in the 6.39 mg/m^3 group as compared to 1/11 females in the 0 mg/m^3 group, and 1/11 females in the 0 (PG) mg/m^3 group.

No exposure-related changes were noted in the recovery groups.

3. Microscopic pathology

a) Non-neoplastic - Statistically significant histopathologic findings for the nasal passages in the 6.39 mg/m^3 group at the terminal sacrifice included: secretory cell hyperplasia in the nasal septum (females: 7/11), squamous metaplasia in the lateral wall of the nasal cavity (males and females: 3/11 and 5/11, respectively), squamous metaplasia in the maxilloturbinate (females: 4/11), acute inflammation of the nasal mucosa (males and females: 4/11 and 4/11, respectively), eosinophilic intraepithelial droplets in the nasal cavity III (males and females: 7/11 and 10/11, respectively), eosinophilic intraepithelial droplets in the nasal cavity IV (females: 8/11), and lung intra-alveolar macrophages, focal/ multifocal (males and females: 9/11 and 10/11, respectively). This latter finding was also observed in the 0 (PG), 0.05, and 0.64 mg/m^3 groups, and consequently, it was not attributed to the octhilinone exposure due to the effect in the 0 (PG) group. No exposure-related findings were observed in the 0.05 mg/m^3 group.

At the end of the recovery period, the octhilinone-exposed females in the 0.05, 0.64, and 6.39 mg/m^3 groups had incidences (8/11, 10/11, and 10/11, respectively) of eosinophilic intraepithelial droplets in the nasal cavity that were more prevalent than in the 0 and 0 (PG) groups (3/11 and 3/11, respectively). However, this finding in the 0.05 and 0.64 mg/m^3 groups at the recovery sacrifice was not considered toxicologically significant: (1) the males in all groups had high incidences of this finding, (2) some females in the 0 and 0(PG) groups were observed to display this same finding, and (3) no exposure-related response was present.

b) Neoplastic - No neoplastic lesions were reported in any of the exposure groups at the terminal or recovery sacrifices.

III. DISCUSSION

A. DISCUSSION

There were no deaths attributable to octhilinone exposure. Clinical signs in rats exposed to octhilinone at 6.39 mg/m^3 included rales, dyspnea, thriftless appearance, and red nasal discharge. Body weights and body weight gains in male and female rats of the 6.39 mg/m^3 group were decreased 4.3%-18.5%. The clinical chemistry and organ weight changes were not considered to be related to the octhilinone exposures but related

to the decreased body weights. The only gross pathological finding (fluid in the uterus) was in the female rats from the 6.39 mg/m^3 group. Histopathologic findings in the 6.39 mg/m^3 group were consistent with irritation to the nasal and upper airway passages.

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

Consequently, the data were consistent with a NOEL of 0.64 mg of octhilinone/m^3 and a LOEL of 6.39 mg of octhilinone/m^3 in a subchronic (13 week) inhalation (nose-only) exposure of male and female Crl:CD®BR rats.

B. STUDY DEFICIENCIES

Major: None.

Minor: The rationale for selection of the propylene glycol concentration (123 mg/m^3), the vehicle control, was not provided. No data were presented to substantiate the selection of the exposure concentrations. In the "Aerosol Concentration" section, impinger samples from the test atmosphere were analyzed for RH-893. This was presumably octhilinone, however, no statement to that effect was provided.

A number of the tables had some problems or missing data. Table 11F was illegible. In Table 8E, some unusual and undefined markings were in the location for the number of animals for the propylene glycol group in the "BUN" and "CREA" columns. Table 11F illustrated the findings in the larynx at the terminal sacrifice, however, these data were illegible. Tables 11II and 11JJ were missing the nasal cavity nares and the nasal cavity tooth section data, respectively, for the females from the recovery groups. Also, in tables 11II (nasal cavity nares) and 11JJ (nasal cavity tooth section) and in tables 11KK (lung), 11LL (trachea), and 11MM (peribronchial lymph node), the 0.05 and 0.64 mg/m^3 groups for the males and females were not examined. In table 11NN (lacrimal gland), the 0.05 and 0.64 mg/m^3 groups for the males and all of the female groups were not examined. These omissions should have been explained in the report, and depending on the explanation protocol deviations should have been written.

Several inhalation specifications for the study were missing. The chamber dimensions were not provided. In addition, the homogeneity of the aerosol distribution within the chamber was not documented which includes the sampling locations and number of sampling locations tested. These sampling locations should have been

provided demonstrating that they were in the breathing zone of the animals. Also, no documentation was provided that the sampling during the animal exposures was conducted in the breathing zone of the animals.