9-26-91

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

008637

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Kathon 886F Biocide: Submission of an Acute Inhalation Study in Rats; 6(a)(2) Study.

TO: Christine Rice/Tom Myers
Product Manager (52)
Registration Division (H7505C)

FROM: Linda L. Taylor, Ph.D.
Toxicology Branch II,
Health Effects Division (H7509C)

THRU: K. Clark Swentzel
Section II Head, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D.
Chief, Toxicology Branch II/HFAS/HED (H7509C)

Registrant: Rohm & Haas Company
Chemical: 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one
Synonym: Kathon 886F Biocide
Project No.: 1-2349
Caswell No.: 195C
Record No.: Case: 816020; Submission: S402232
Identifying No.: 107103-000707
MRID No.: 419635-01
Action Requested: Please review the following 6(a)(2) study for methylisothiazolinone (chemicals 107103 and 107104).

Comment: There was no cover memo submitted to TB II with this study to explain why this acute inhalation study is being submitted. The study has been reviewed and the DER is attached.

Kathon® 886F Biocide Acute Inhalation Toxicity Study in Rats, FJ Wanner and JV Hagan, dated July 10, 1991.

CONCLUSION: Under the conditions of the study, the LC_{50} for Kathon 886F Biocide (containing 13.71 or 13.99% ai) is 2.36 mg/L (combined sexes). When calculated for active ingredient, which consists of two active ingredients (5-chloro-2-methyl-4-isothiazolin-3-one and

2-methyl-4-isothiazolin-3-one). the LC_{50} is 0.33 mg/L.

TOXICITY CATEGORY: Test material: III; active ingredient: II.

CLASSIFICATION: Core-supplementary. This study does not satisfy the guideline requirements (§81-.) for an acute inhalation toxicity study in rats, but it can be upgraded with the submission of data/information on the percentage of the particles that were ≤ 1 um. NOTE: It is not clear to this reviewer why this is thought to be a 6 (a)(2) study when there are similar studies listed in the CASWELL file for this ai, which list the Toxicity Category as II and III. This study does not present anything new and is not, therefore 6 (a)(2) data, as defined in the CFR (153.65).

Primary Reviewer: Linda L. Taylor, Ph.D. 9/26/91
Review Section II, Toxicology Branch II / HED (H7509C)
Secondary reviewer: K. Clark Swentzel 9/26/91
Section Head, Review Section II, Toxicology Branch II / HED (H7509C)

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DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation-Rats (§81-3)

LABORATORY NUMBER: 195C

MRID NUMBER: 419635-01

TEST MATERIAL: Kathon® 886F Biocide

SYNONYMS: 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one

STUDY NUMBER: Protocol/Report # 91P-018

SPONSOR: Rohm and Haas Company
Spring House, PA

TESTING FACILITY: Toxicology Department, Rohm and Haas Company

TITLE OF REPORT: Kathon® 886F Biocide Acute Inhalation Toxicity Study in Rats

AUTHOR(S): FJ Wagner and JV Hagan

REPORT ISSUED: July 10, 1991

QUALITY ASSURANCE: A quality assurance statement was provided.

CONCLUSION: Under the conditions of the study, the LC_{50} for Kathon 886F Biocide (containing 13.71 or 13.99% ai) is 2.36 mg/L (combined sexes). When calculated for active ingredient, which consists of two active ingredients (5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one), the LC_{50} is 0.33 mg/L.

TOXICITY CATEGORY: Test material: III; active ingredient: II.

CLASSIFICATION: Core-supplementary. This study does not satisfy the guideline requirements (§81-3) for an acute inhalation toxicity study in rats, but it can be upgraded with the submission of data/information on the percentage of the particles that were ≤ 1 um.

I. MATERIALS

1. Test compound: Kathon® 886F Biocide; Description: amber liquid; Batch #: Lot #'s J59098 (Group 1) and 60047 (Groups 2-6); Purity: 13.71% and 13.99%, respectively.

2. Test animals: Species: rat; Strain: Crl:CD®BR; Age: not given; Weight: 184-230 grams (males)/193-230 grams (females); Source: Charles River-Kingston (Stone Ridge, NY).

II. METHODS

A. Atmosphere Generation: The Kathon® aerosol was generated by using a single nebulizer for the three lowest dose levels, a second one for the next highest dose level, and a third one for the two highest dose levels. The test material was pumped into the nebulizer, and a compressed air source served to aerosolize a portion of the test material into the chamber intake. The various chamber concentrations were achieved by varying the dilution of the test material being fed into the nebulizer. In the multiple nebulizer chambers, the test material that was not aerosolized by the first nebulizer was drained into the second one, which further served to aerosolize the test material. The test material not aerosolized was directed to a waste container. The chamber was supplied with conditioned air drawn through an absolute filter located on the chamber air inlet. The chamber air flow rate, temperature, and humidity were monitored. For the highest exposure group, the chamber was operated at an airflow of 60 L/min, which gave a calculated 99% aerosol equilibrium time (t_{99}) of 18.4 minutes, or less than 7.7% of the exposure duration. For the other 5 groups, the airflow rate was 75 L/min., which gave a calculated t_{99} of 14.7 minutes, or less than 6.1% of the exposure duration.

B. Exposure: Six groups of rats (6/sex each) were exposed to an aerosol of the test material (see table below) during a single four-hour nose-only inhalation exposure period. There was no control group. The animals were randomly assigned and individually housed in suspended wire-mesh cages except during the exposure period. During exposure, animals were housed individually in nose-only restraining tubes (6" x 2" PVC pipe), which were placed into exposure 240-L Plexiglas® and stainless steel exposure chambers. Feed (Purina Rodent Laboratory Chow Checkers®) and water were available ad libitum, except during the exposure period. Atmospheric concentrations of the aerosol were determined 3 times during exposure. Particle size analysis was conducted twice during exposure using a QCM Cascade Impactor (California Measurements Inc., Sierra Madre, CA).

Conc.* (mg/L)	GROUP					
	1	2	3	4	5	6
a.i.	0.026	0.045	0.070	0.177	0.314	0.423
TM	0.19	0.32	0.05	1.26	2.24	3.02

* a.i. = active ingredient; TM = test material

C. Observations: Rats were examined for clinical signs of toxicity and mortality during exposure (unless the aerosol obscured observation), upon removal from the chamber, and then twice daily thereafter up to day 14 [exception: onc· daily on weekends, Holidays and on Day 14 (terminal sacrifice)]. Body weights were recorded immediately prior to exposure, and on Days 1, 7, and 14 post dose. All surviving animals were necropsied on Day 14, and the following organs were examined macroscopically: adrenals, cervical lymph nodes, eyes, gonads, heart, intestinal tract, kidneys, liver, lungs, pancreas, salivary glands, spleen, stomach, thymus, thyroids, trachea, urinary bladder, and uterus.

III. RESULTS

A. Atmosphere Generation: Exposure to the various test material concentrations occurred on 6 different days. A summary of the results is shown below.

Group	Nom.conc. (mg/L)	Anal. conc. (mg/L)	Particle Size MMD* (µm)	GSD**	RF (%)***
1	4.3	0.19	1.5	4.4	66
2	5.3	0.32	2.4	3.9	58
3	4.3	0.50	2.2	4.1	58
4	10.8	1.26	4.0	4.5	44
5	13.2	2.24	3.5	3.2	48
6	13.4	3.02	2.6	2.7	66

*Mass Median Diameter; ** Geometric Standard Deviation;
***Respirable Fraction

Calculation of the mass median diameter (MMD) and the geometric standard deviation (GSD) was performed by computer using a log-probit regression analysis program (Hagan, 1980). The respirable fraction was calculated from the MMD and the GSD using the RFB program (Moss & Baldwin, 1983), which defines "respirable fraction" as that fraction of an aerosol that would pass a size-selector described by the American Conference of Governmental Industrial Hygienists (ACGIH), with the following characteristics: 90% of ≤ 2.0 µm particles, 75% of 2.5 µm

particles, 50% of 3.5 um particles, 25% of 5.0 um particles, and 0% of ≥ 10 um particles will pass through the selector. NOTE: There is no information on what percent of the particles were ≤ 1 um.

B. Animal Observations: Mortality was observed as shown below. Signs of respiratory irritation, including rales, gasping, hyperpnea, dyspnea, and vocalization were observed in some animals of all groups immediately after exposure, with the number of animals displaying signs and the severity increasing with increasing dose. The signs of respiratory irritation disappeared within 2 to 12 days in all survivors. Additionally, small red droplets (expired nasal exudate) were observed in the cages of the animals in the 4 highest dose groups, which was considered to be the result of nasal irritation; the irritation disappeared within 6-12 days in all survivors. All other signs were unrelated to treatment.

GROUP	Mortalities	Survivors	
		Males	Females
1	0/12	6/6	6/6
2	1/12	6/6	5/5
3	0/12	6/6	6/6
4	3/12	5/6	4/6
5	4/12	3/6	5/6
6	9/12	0/6	3/6

Body Weight and Body-Weight Changes

All dose groups lost weight during/after exposure, with the Day 1 body weight being 2-15% lower than that measured prior to treatment. With the exception of the highest dose group animals, all animals had gained weight by the next weighing period (Day 7). None of Group 6 males survived to Day 7. Group 6 females had not attained their starting body weight by Day 7; by day 14, there was a gain of 23 grams.

GROUP	Overall Body-Weight Gain (g)	
	MALES	FEMALES
1	125	63
2	113	25
3	120	23
4	124	33
5	111	53
6	-	23

Gross Pathology

The only treatment-related observation was the occurrence of gas in the stomachs and/or intestines of the three highest dose groups, which was attributed by the author to be the result of swallowing air in an attempt to breath.

LC_{50} Calculation

The LC_{50} for the test material (combined sexes) was 2.36 mg/L, with confidence limits of 1.60 to 4.82 and a slope of 2.2. With respect to the active ingredient, an LC_{50} of 0.33 mg a.i./L was calculated, with confidence limits of 0.22 to 0.67, and a slope of 2.2.

IV. CONCLUSIONS

The LC_{50} for Kathon 886F Biocide (containing 13.71 or 13.99% ai) is 2.36 mg/L (combined sexes). With respect to the active ingredient, which consists of two active ingredients (5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one), the LC_{50} is 0.33 mg/L.

Page_____ is not included in this copy.

Pages 9 through 12 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

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

____ The document is not responsive to the request.

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