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

TOXR 010852

MAR 30 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Kathon® 287T Industrial Microbicide (707-EEU)
Response to Agency Letters dated 5/1/91 and
12/2/92 Re: Data Requirements

TO: John Lee/Valdis Goncarvos
Product Manager/PM Team Reviewer (31)
Registration Division (H7505C)

FROM: Linda L. Taylor, Ph.D. 3/7/94
Toxicology Branch II, Section II,
Health Effects Division (7509C)

THRU: K. Clark Swentzel 3/28/94
Section II Head, Toxicology Branch II
Health Effects Division (7509C)

and

Marcia van Gemert, Ph.D. 3/29/94
Chief, Toxicology Branch II/HFAS/HED (7509C)

Registrant: Rohm & Haas Company
Chemical: 4,5-dichloro-2-n-octyl-3-(2H)-isothiazolone
Synonym: Kathon 287T Industrial Microbicide; XB3
Technical HQ(RH-287)
Caswell No.: 314B
Submission No.: S452045
DP Barcode: D196244
Identifying No.: 000707-EEU KATHON 287T
Case No.: 192535
MRID No.: 429777-01

Action Requested: Review the data and comment on the waivers outlined in the cover letter; also itemize the remaining data requirements for this product.

Comment: The Registrant has submitted an acute oral toxicity study: XB3 Technical HQ(RH-287) Acute Oral Toxicity Study in Male and Female Rats (Rohm and Haas Report No. 92R-066) to fulfill a data requirement to support the registration of Kathon® 287T Industrial Microbicide. The study has been reviewed, and the DER is appended. Additionally, the Registrant responded to the request for studies on the technical grade active ingredient by either committing to perform the required study or requesting a data waiver, as follows:

REQUIRED STUDIES

(1) **acute oral toxicity study**-[submitted study MRID #429777-01].
(2) **acute dermal toxicity study**-[requested waiver-agrees to Toxicity Category I].
(3) **acute inhalation study**-[performing method development work to determine if respirable droplets, suitable for testing, can be generated; if not, will provide data to support a waiver request].
(4) **90-day dermal or 90-day feeding study** [if dermally corrosive]. Because Kathon® 287T is dermally corrosive, has committed to perform a 3-month dietary study in rats, a dermal absorption study in rats and an oral pharmacokinetics study in rats.
(5) **90-day inhalation study** [if respirable or a gas at room temperature]. Since Kathon® 287T is a low melting solid at room temperature, it is stated that use would not result in exposure to respirable droplets; a waiver is requested
(6) **developmental toxicity study** [in one species]-[has committed to perform a rat study].
(7) **mutagenicity battery**-[has committed to perform an Ames test, a CHO point mutation assay, an in-vitro cytogenetic assay, an in vivo cytogenetic assay or a mouse micronucleus assay.

MRID # 429777-01 - Acute Oral Toxicity Study: Under the conditions of the study [6 Crl:CD®BR rats/sex/group; dose groups of 500, 750, 1000, 1500, and 2000 mg/kg], **the acute oral lethal dose [LD_{50}] of XB3 Technical (RH287) in both sexes was 1636 mg/kg,** with 95% confidence limits of 1322 and 2469 mg/kg and a slope of 4.3 probits per log dose unit. This study is classified Core minimum, and it satisfies the guideline requirements (§81-1) for an acute oral toxicity study in rats.

With regard to the request for a waiver for the acute dermal toxicity study, this may be granted since the main purpose of the study is to assign a Toxicity Category for dermal exposure and the Registrant agrees to a TOXICITY CATEGORY I.

Also forwarded to TB II under this "bean" is a risk assessment ["Human Health Risk Assessment of Kathon® 930 Biocide in Millwork and Joinery Applications"], which is not the purview of TB II. The toxicology data cited address mainly studies on various products containing the active ingredient. With regard to the request for a waiver of the 90-day inhalation study on the technical grade active ingredient, the Registrant argues that the data available indicate that the significant human health hazards associated with the active ingredient are its potential for local tissue response [respiratory tract and skin irritation] and skin sensitization, and all other responses observed are attributable to these overriding and controlling effects. Given that respiratory irritation and skin sensitization occur at relatively low levels of exposure, it is argued that limiting contact to prevent these

toxicological responses will control all other risks to human health from exposure to the active ingredient. Two 3-month inhalation studies on two isothiazolin-3-one chemicals [Kathon 886 MW and Kathon®893] are cited, which displayed NOEL's of 0.34 and 0.64 mg a.i./m^3, and a recently completed study on Kathon® 930 Biocide [in-life portion completed; final report to be submitted in support of this waiver request], shows a NOEL of 0.02 mg/m^3. TB II reiterates that a study with the technical active ingredient will be required **if** the active ingredient is a gas at room temperature or use of the product results in respirable droplets. An assessment by OREB of whether the use is likely to result in inhalation exposure is required before TB II can determine whether a waiver can be granted. With regard to whether the toxicology data discussed in the risk assessment of Kathon® 930 Biocide are appropriate for comparison with worker exposure, for inhalation exposure the to-be-submitted study on Kathon®930 is. The data cited for Kathon 886 MW and Kathon®893 are not. KATHON 886 MW biocide is comprised of 5-chloro-2-methyl-4-isothiazolin-3-one (8.6-12.1%) and 2-methyl-4-isothiazolin-3-one (2.6-4.6%); KATHON®893 is comprised of 45% a.i.: 2-n-octyl-4-isothiazolin-3-one.

The Registrant has committed to perform the other studies required for the technical active ingredient, except as noted above. There are no **new** data requirements.

Reviewed by: Linda L. Taylor, Ph.D. Linda Lee Taylor 3/10/94
Section II, Tox. Branch II (7509C)
Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 3/28/94
Section II Head, Tox. Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral - Rats (§81-1) TOX. CHEM. NO.: 314B

MRID NO.: 429777-01 Shaughnessy #: 128101

TEST MATERIAL: XB3 Technical HQ(RH-287)

SYNONYMS: Kathon®287T Industrial Microbicide

STUDY NUMBER: Report # 92R-066; Protocol # 92P-066

SPONSOR: Rohm and Haas Company

TESTING FACILITY: Rohm and Haas Company Toxicology Department

TITLE OF REPORT: XB3 Technical HQ(RH-287) Acute Oral Toxicity Study in Male and Female Rats

AUTHORS: RD Morrison and ME Kyle

REPORT ISSUED: December 11, 1992

QUALITY ASSURANCE: A quality assurance statement and a Good Laboratory Practice compliance statement were provided.

EXECUTIVE SUMMARY: Under the conditions of the study [6 Crl:CD®BR rats/sex/group; dose groups of 500, 750, 1000,1500, and 2000 mg/kg], **the acute oral lethal dose for combined sexes (LD_{50}) of XB3 Technical HQ(RH-287) is 1636 mg/kg [1322-2469 mg/kg].** This study is classified Core Minimum, and it satisfies the guideline requirements [§81-1] for an acute oral toxicity study in rats.

TOXICITY CATEGORY: III

A. MATERIALS

1. Test compound: XB3 Technical HQ(RH-287); Description: light brown solid; Batch #: Lot #: SW5097; Purity: 96.9% 4,5-dichloro-2-n-octyl-3(2H) isothiazolone.

2. Test animals: Species: rat; Strain: Crl:CD®BR; Age: ♂♂ ≈ 55 days old, ♀♀ ≈ 65 days old; Weight: ♂♂: 206-229 g, ♀♀: 187-230 g; Source: Charles River Kingston, Stone Ridge, NY.

B. STUDY DESIGN

1. Methodology: Six male and six female rats per dose level were administered the test material [corn oil solution] via gavage [dose level: 500, 750, 1000, 1500, and 2000 mg/kg] in a dosage volume of 10 mL/kg, following an overnight fast. The rats were selected from a healthy stock population and assigned to the groups using a computer-generated sequence of random numbers. Rats were housed 2 per cage and were quarantined for ≈ one week. Water was available ad libitum, and Purina Certified Rodent Chow 5002(C) was provided. All rats were observed for signs of toxicity at 1, 2, and 4 hours post dose and once a day thereafter for 14 days. Body weight was recorded on day 0 prior to dosing and on Days 7 and 14, and for found-dead rats if they survived beyond the day of dosing. All surviving rats were sacrificed on day 14, and necropsies were performed on all found-dead and surviving rats. The necropsy consisted of a gross examination of all organs in situ.

2. Dose preparation: The test material and corn oil were heated in an oven [60°C], and an appropriate amount of test material was mixed in corn oil, with stirring to obtain homogeneous solutions. The solutions were cooled to 40°C and maintained at this temperature to prevent the test material from solidifying. The doses were administered within 90 minutes of preparation. No data were provided with respect to stability, homogeneity, or concentration of the test material.

3. Statistical procedures: The mortality incidences of both sexes were compared with a categorical data modeling procedure using SAS CATMOD [SAS Institute Inc., SAS User's Guide: Statistics, Version 5 edition, pp 171-253 (1985)]. The LD_{50}, 95% confidence limits, and slope were calculated from the logarithm of the doses and the incidences of death using a SAS PROBIT procedure [ibid. pp 639-645], based on the method of DJ Finney [Probit Analysis, 3rd Edition, London: Cambridge University Press, 1971].

C. RESULTS

Deaths occurred in both sexes at dose levels of 1000 mg/kg and

above and in males at the 750 mg/kg dose level also [Table 1]. All deaths were considered related to treatment and occurred within 6 days of dosing. Clinical signs of irritation around the anal-genital area were observed at all dose levels, and passiveness, no feces and/or tan-stained muzzle were observed in survivors at dose levels of 750 mg/kg and above in males and at 1000 mg/kg and above in females. Signs judged secondary to dying included somnolence, ptosis, labored breathing, tremors, and ataxia, which were observed only in those rat dying on test. Signs attributed to the corn oil were brown-stained anal-genital area and diarrhea. Decreased body-weight gain was observed in males at dose levels of 750 mg/kg and above compared to the lowest dose group [Table 2]. Female body- weight gains were comparable among the groups. Decedents displayed a high incidence of viscous material in the cecum, intestines, and stomach; black material or black foci adhered to stomach mucosa; and reddened stomach mucosa at necropsy. Survivors displayed thickened stomach walls. Because no statistically significant difference was observed between the sexes, the LD_{50} was calculated from the combined mortality incidence data.

Dose [mg/kg] sex	Table 1. Mortality [# of deaths/# dosed]				
	500	750	1000	1500	2000
males	0/6	1/6	1/6	2/6	4/6
females	0/6	0/6	2/6	1/6	5/6

Day Dose [mg/kg] Sex	Table 2. Body Weight/Change [grams]				
	500	750	1000	1500	2000
Males					
0	222	217	215	220	219
7	280	258	249	243	229
14	346	321	319	304	305
0-14	124	105(85)♦	105(85)	86(69)	84(68)
Females					
0	201	205	201	201	199
7	240	240	231	230	229
14	255	261	257	259	255
0-14	54	56	62	57	55

♦ % of 500 mg/kg dose group

D. CONCLUSIONS

Under the conditions of the study, **the acute oral lethal dose [LD_{50}] of XB3 Technical (RH287) in both sexes was 1636 mg/kg,** with 95% confidence limits of 1322 and 2469 mg/kg and a slope of 4.3 probits per log dose unit. This study is classified Core minimum, and it satisfies the guideline requirements (§81-1) for an acute oral toxicity study in rats.