UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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004799

DATE: June 13, 1978

SUBJECT: Registration No. 707 - RUG

FROM: J.D. Doherty, Toxicology Branch John Doherty

TO: J.H. Lee, Product Manager #22

Registrant: Rohm and Haas
Philadelphia, Pennsylvania

Product: KATHON 893T, Binder IV. (Industrial Microbiocide)

Active Ingredient	
2-n-octyl-3-isothiazolin-3-onc	85%
Inerts	15%

Caswell No: 613c

Action sought: New Product registration, for industrial use only.

Remarks

1. The active ingredient is listed as the octyl-3-isothiazolin-3-one. This apparently with a misprint or other error. The correct compound should be octyl-4-isothiazolin-3-one.

2. This chemical is a possible skin sensitizer in humans although the test with guinea pigs was negative. An appropriate warning statement to this effect is included on the label.

Recommendation:

TOXICOLOGY BRANCH has no objection to the registration of this product for manufacturing purposes only.

The registrant should be advised that supporting teratology, oncogenisis and reproduction studies may have to be submitted or referenced for products that contain this compound.

Review of Toxicological Studies Submitted

Summary

		CORE
Acute Oral (rats) LD_{50}	794 mg/kg males III 681 mg/kg females III	MINIMUM
Acute Dermal (rabbit) LD_{50}	1.78 ml/kg II	MINIMUM
Acute Eye Irritation (rabbit)	CORROSIVE I	MINIMUM
Acute Inhalation	4 mg/l III	MINIMUM
Primary Skin Irritation	4.12 I	MINIMUM
Skin sensitization	probably not a sensitizer	

All studies were conducted by Hazelton Laboratories, Incorporated

A. Acute Oral (rats) LD_{50} (417-306, August 6, 1970)

The test material was administered by oral intubation to five groups of five male and five female rats at dosage levels of 100, 215, 464, 1000 and 2150 mg/kg. The rats were fasted overnight prior to dosing.

Results: an LD_{50} of 794 (584- to 1080) mg/kg 95% confidence limits was calculated for males.

An LD_{50} of 681 (no confidence limits) mg/kg was calculated. All the females at 1000 mg/kg or above died. All deaths for both sexes occured within 24 hours.

Toxic effects noted at the lowest dose tested included diarrhea unkempt fur, depression, labored respiration and a red rust on the nose.

Major necropsy findings included - molted liver, stomach and intestinal distention on the poisoned rats. At sacrifice no observable gross pathology was observed. This test is CORE MINIMUM.

B. Acute Dermal LD_{50} (417-307, August 6, 1970).

A single 24 hour dermal application of the undiluted test material (RH-893, technical) was made to the lipped intact (half of the rabbits) and abraded (half of the animals) abdominal skin of four groups of 4 animals. Also a single, 24 hour, dermal application of the test material as a 50 ppm dilution in water was also applied to a similar set of rabbits. Dosage levels included 0.316, 1.0, 3.16, and 10 ml/kg. The test material was held in place with binders for 24 hours.

Results

An LD_{50} of 1.78 ml/kg was determined. All 4 rabbits died at the 3.16 and 10 ml/kg dose. Deaths occured as late as 5 days post application.

Necropsy showed no significant findings in the visceral organs. The rabbits lost weight following treatment.

For the dilute preparation. No deaths resulted. This test is CORE MINIMUM

C. Acute Eye Irritation (Rabbits) (417-308)

A single application of 0.1 ml of undiluted RA-893 technical was made into the conjunctival sac of the left eye of each of six albino rabbits. In a separate experiment a single application of 0.1 ml of a 50 ppm dilution of test material in water was made. Untreated eyes served as controls, no attempts to wash the eyes following instillation were made.

All six rabbits that were treated with the technical grade of RH-893 developed corneal opacity that was not reversed in 7 days.

No corneal opacity developed in any of the rabbits receiving the 50 ppm dose.

This test is CORE MINIMUM.

D. Acute Inhalation Exposure - Rats (417-310)

10 male and 10 female albino rats were exposed under dynamic conditions in a 100 liter stainless steel and glass inhalation chamber for 1 hour to an aerosol of a 0.5% aqueous solution of RH-893 (technical) at a nominal concentration of 200 mg/l of air. The test material was metered by a Harvard infusion pump into a nebulizer which aerosolized the liquid into the chamber.

No deaths occured in any of the test animals. Some increased activity among the rats was noted. No gross alnormalities, were noted by autopsy.

A second acute inhalation study (Hazelton 417-281) reports using 10 male and 10 female Charles River rats exposed to 4 mg/ml for 1 hour under dynamic conditions in a 1000 - liter chamber.

3/10 of the male rats died and 8/10 females rats died at this concentration as a result of exposure. The exposed rats lost weight when compared with controls. No differences are reported between control and exposed animals revealed by necropsy of the survivors. This test is CORE MINIMUM.

E. Primary Skin Irritation (417-325)

A single 24 hour dermal application of 0.5 ml of the test material was made under a one-inch square gauze patches to clipped intact (three animals) or abraded (three animals) skin on the back of each albino rabbit (New Zealand White). The rabbits were wrapped with binders of rubber dam and were immobilized in animal strainers.

A primary irritation score of 4.12 was determined. Eythema and edema that was not reversed in 72 hours developed. Dark green areas at the sight of application were observed in all animals at 24 hours, accompanied by blanching which persisted through seven days in all abraded and one intact animal. Thickening and necrosis of the application area were observed in all animals from 72 hours through day 7.

This test is CORE MINIMUM.

F. Skin sensitization, guinea pigs (Hazelton, 417-326, Oct. 7, 1970)

A. 0.1% weight per volume suspension of the test material in saline was injected into the right side of each of eight test animals. The control and test materials were injected intradermally three times per week until a total of 9 were given. Following the last sensitizing treatment, the animals were set aside for a period of two weeks after which a challenge dose was administered.

The sensitizing injections of RH-893-50% produced slight to moderate erythema generally from 24 to 48 hours following each injection. Following the challenge dose, slight to moderate erythema was observed in all animals. No evidence that RH-893 was a skin sensitizer was obtained.

A Rohm and Hass report states that "a few cases of skin rash occurred as a result of inadvertant skin contact with Kathon 893 T. Improved handling procedures to prevent such contact were instituted and no further problems developed.

R/D init: G.E. Whitmore 6/20/78
gjl
E for GEW 6/28/78