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

JUN 23 1981

SPECIAL

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: May 21, 1981

SUBJECT: EPA Reg.#707-133; 707-128; Application for KATHON WT and
KATHON WT 1.5%, for use in Air Washer Systems to
control microbial fouling.
CASWELL#195C Accession#244707, 244708

FROM: William S. Woodrow, Ph.D.
Toxicology Branch, HED (TS-769)

TO: John Lee (31)
Registration Division (TS-767)

WAB

Registrant: Rohm and Haas Co.
Independence Mall
Philadelphia, PA 19105

Action Requested:

Rohm and Haas KATHON is registered as an Industrial Microbicide and
Slimicide under various formulations:

- KATHON 886 CT EPA Reg.#707-128
- KATHON 886 MF EPA Reg.#707-129
- KATHON 886 F EPA Reg.#707-130
- KATHON 886 WT EPA Reg.#707-133
- KATHON 886 MW EPA Reg.#707-134

The present applications (Reg.#707-128, 707-133) propose the addition
of two different KATHON WT concentrations for use in Air Washer
Systems to control microbial fouling under two product labels; KATHON
WT, and KATHON WT 1.5%.

Recommendations:

1. The use of KATHON WT microbicide in Air Washer Systems is not toxicologically supported.

A number of volatile organic compounds were stripped from a 100 ppm solution of KATHON WT in simulated Air Washer experiments designed to detect any materials whose inhalation toxicity has not been defined. Since humans working in enclosed areas could potentially be exposed to these compounds by treated air from Air Washers, additional toxicity tests must be conducted to assess the hazard potential of some of the volatile compounds stripped experimentally from KATHON WT prior to registration of KATHON WT for use in Air Washers:

- A. Subchronic inhalation toxicity tests must be conducted using the following compounds that were stripped from KATHON WT treated water:
 - a. Nitrous oxide;
 - b. Carbonyl sulfide;
 - c. Propionaldehyde;
 - d. Hydrocarbon (C₆);
 - e. Chlorotoluene; and
 - f. Malonic acid

Subchronic inhalation toxicity tests using each of the above compounds should be conducted according to Section 163.82-4, Subpart F (p. 37371) of the August 22, 1978, Proposed Guidelines for Registering Pesticides in the U.S.

- B. Separate oncogenicity studies must be conducted with benzene, toluene and chlorotoluene which are known or suspected carcinogens stripped from KATHON WT treated water by bubbled air; according to Section 163.83-2 (page 373379), Subpart F of the August 22, 1978, Proposed Guidelines for Registering Pesticides in the U.S.

Consideration of KATHON WT for use in Air Washer Systems will be reassessed following EPA evaluation of data generated by the studies outline above.

2. Label signal word and precautionary statements are satisfactory.
3. Previously Reviewed Data: (KATHON 886; equivalent to KATHON WT)
 - a. L. Anderson, August 22, 1978

Acute inhalation toxicity, rat

LC₅₀ = > 4.62 mg/L
Toxicity Category - III
Classification: Core-Minimum Data

- b. W. Greear, November 16, 1977

Acute oral, rat

LD₅₀ = 3.81 (3.53 - 4.22) g/kg
Toxicity Category - III
Classification: Core-Minimum Data

Acute dermal, rabbit

LD₅₀ = 5.0 g/kg
Toxicity Category - III
Classification: Core-Minimum Data

Primary skin irritation, rabbit

P.I. = 7.5/8.0
Toxicity Category - II
Classification: Core-Minimum Data

Primary eye irritation, rabbit

Persistent corneal opacity through day 7.
Toxicity Category - I
Classification: Core-Minimum data

Acute inhalation toxicity, rat (IBT)

LC₅₀ = > 9.73 mg/L
Toxicity Category - III
Classification: Core-Minimum Data
(Study repeated; #3 above)

- c. Robert Coberly, February 23, 1976 (See R. Engler memo, August 26, 1974).

Acute oral, rat

LD₅₀ = 105 mg/kg

Acute dermal, rabbit

LD₅₀ = 200 mg/kg (intact skin)
as 10% sol. = 168 mg/kg (abraded)
as 0.1% sol. = 800 mg/kg (intact)

Acute inhalation LC₅₀, rat

LC₅₀ = 1.2 mg/L

Skin Irritation, rab.

Draize

1% sol.	6.3 (severe)
0.5% sol.	3.2 (moderate)
0.1% sol.	0

Eye Irritation (100 mg of sol. held for 2 sec.), rab.

Draize

10% sol.	86-110 (3rd day)
0.1% sol.	0

21-day dermal, rabbit (0.1% sol.)

Systemic NEL = > 50 mg/kg

Cytogenic (mutagenicity)

No chromosomal aberrations or changes in mitotic indices at highest level tested (50 mg/kg).

14-day inhalation, rat

NEL = < 0.06 mg/L

Human exposure

(10/group) were exposed to creams containing 100 and 1000 ppm test material. 15 applications (24 hr duration) performed on alternate days.

Irritation and sensitization at both dose levels - reactions dose dependent.

4. New Data (not previously reviewed) - These studies were conducted according to the attached "Protocol for Human Hazard Evaluation of Microbicides Used in Industrial Air Washing Systems to Control Biological Fouling", March 1, 1978.

Air was bubbled through an aqueous KATHON WT (100 ppm) treated solution (5:1 v/v air/water) to detect any volatile hazardous compounds stripped by air in a simulated Air Washer experiment.

- a. KATHON WT solution tested (100 ppm):
(analyzed by GC)

<u>PPM Active Ingredient (w/w)</u>		
<u>Target</u>	<u>Before Expt.</u>	<u>After Expt.</u>
2	1.7	1.6
100	104	109

- b. Volatile compounds stripped by bubbled air from KATHON WT treated solution:

Nitrous oxide
CO₂
Carbonyl sulfide
Acetaldehyde
Ethanol
Propionaldehyde
Acetone
Hydrocarbon (C₆)
Tetrahydrofuran
Benzene
Toluene
Chlorotoluene
Malonic acid

INTRODUCTION

A memo by Dr. David L. Greenman (attached), Acting Chief Pharmacologist, Registration Division, EPA, recommended suspension of new registrations for microbial control chemical products used in Industrial Air Washing Systems; due to EPA's lack of knowledge of Air Washer structure and function and consequent inability to prescribe adequate human hazard/assessment protocols for such microbicides.

Following a series of meetings in Toxicology Branch involving various personnel including: Drs. O. Paynter, William Woodrow, R. Engler, Bernard Shema of the Betz Corp., Ms. Margaret Wulf and George Paul of Dow Chemical, several steps toward reinitiation of microbicide registration for Air Washers were taken:

- a. Dr. Shema submitted a study to Toxicology Branch dated June 18, 1976, which indicated that Industrial Air Washer Systems effectively removed aqueous droplets entrained in treated air effluents from such systems (report attached; the Betz Corp. gave EPA permission to make this report public).
- b. Drs. R. Engler, B. Shema and W. Woodrow attended a meeting on Air Washers, 11/16/77. Assuming that Air Washer mist eliminating systems do effectively remove entrained water droplets according to the above (Betz) study it was agreed that human hazard toxicology protocols should determine what volatile materials would be stripped from microbicide treated water during evaporation by flowing air for each product submitted for registration on a case by case basis.
- c. Woodrow visited a large Industrial Air Washing System at a DuPont Nylon plant in Seaford, Delaware. Based on a comprehensive trip report (attached), Woodrow prepared a "Protocol for Human Hazard Evaluation of Microbicides Used in Industrial Air Washing Systems, to Control Biological Fouling", March 1, 1978; which was approved for use by Dr. R. Engler, Acting Chief, Toxicology Branch.

The present Rohm and Haas applications for use of 5-chloro-2-methyl-4-isothiazolin 3-one and 2-methyl-4-isothiazolin 3-one in Air Washing Systems contains toxicity data developed using Woodrow's protocol dated 3/1/78.

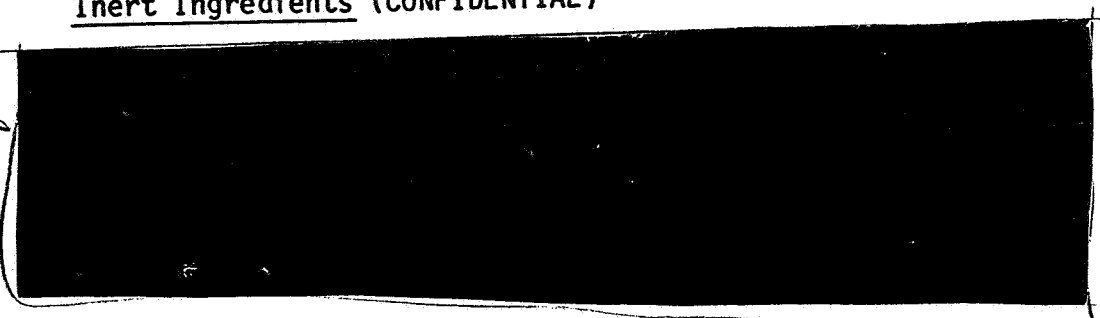
Formulations: (1) (KATHON WT 1.5%, EPA#707-133)

Active Ingredient

5-chloro-2-methyl-4-isothiazolin-3-one	1.21%
2-methyl-4-isothiazolin-3-one	0.56%

Inert Ingredients (CONFIDENTIAL)

Commercial chemical information & inert ingredients



(2) KATHON WT (EPA#707-128)

Active Ingredient

5-chloro-2-methyl-4-isothiazolin-3-one 9.7%

2-methyl-4-isothiazolin-3-one 3.4%

Inert Ingredients (CONFIDENTIAL)

Commercial formula information & inert ingredients

← [REDACTED]

Data Review: The attached Hazard Evaluation Protocol for Air Washer Microbicides March 1, 1978 requires that acute toxicity studies be performed (acute oral and dermal, primary eye and skin irritation studies).

A. Data previously submitted by Rohm and Haas:

1. L. Anderson memo of August 22, 1978.

KATHON 886 (actives-5-chloro-2-methyl-4-isothiazolin-3-one and methyl-4-isothiazolin-3-one)

Acute inhalation toxicity, rat (4 hour exposure)

LC₅₀ = > 4.62 mg/L

Toxicity Category - III

Classification: Core-Minimum Data

2. W. Greear memo of November 16, 1977.

KATHON WT 1.5%

a. Acute oral LD₅₀, rat

3.81 (3.53-4.22) g/kg

Toxicity Category - III

Classification: Core-Minimum Data

b. Acute dermal LD₅₀, rabbit

5.0 g/kg

Toxicity Category - III

Classification: Core-Minimum Data

c. Primary skin irritation, rabbit

P.I. = 7.5/8.0

Toxicity Category - II

Classification: Core-Minimum Data

d. Primary eye irritation, rabbit

Corneal opacity, iritis and conjunctivitis present in all rabbits. Corneal opacity persisting through day 7. Eye washing of little benefit.

Toxicity Category - I

Classification: Core-Minimum Data

e. Acute inhalation toxicity, rat (IBT)

LC₅₀ = > 9.73 mg/L

Toxicity Category - III

Classification: Core-Minimum Data

(Stated that study must be validated prior to registration).

3. February 23, 1976 memo, R. Coberly (See R. Engler memo, August 22, 1974). KATHON 886

a. Acute oral LD₅₀, rat = 105 mg/kg

b. Acute dermal LD₅₀, rabbit = 200 mg/kg (intact skin).

as 10% solution = 168 mg/kg (abraded)

as 0.1% solution = 800 mg/kg (intact)

c. Acute inhalation LC₅₀, rat = 1.2 mg/L

d. Skin irritation, rab.

Draize

1% sol.

6.3 (severe)

0.5% sol.

3.2 (moderate)

0.1% sol.

0

e. Eye irritation (100 mg of sol. held for 2 sec.), rab.

Draize

10% solution

86-110 (3rd day)

0.1% solution

0

f. 21-day dermal, rabbit (0.1% sol.)

Systemic NEL = > 50 mg/kg

g. Cytogenetic (mutagenicity)

No chromosomal aberration or changes in mitotic indices at highest level tested (50 mg/kg).

h. 14-day inhalation, rat

NEL = < 0.06 mg/L

- i. Humans (10/groups) were exposed to creams containing 100 and 1000 ppm test material. 15 applications (24 hr. duration) performed on alternate days; (2 days rest on weekends). At both levels irritation and sensitization were observed; reaction was dose dependent.

B. New data submitted in present request to add Air Washer Systems to product label. Rohm and Haas Report#7455, 2/9/9181.

These studies were conducted according to the attached "Protocol for Human Hazard Evaluation of Microbicides Used in Industrial Air Washing Systems to Control Biological Fouling", March 1, 1978.

The test protocol states that air should be bubbled separately through high and low concentrations of microbicide at approximately 5 volumes of air to 1 volume of water per minute, for a total of 5 hours. (to determine the presence and amounts of volatile microbicide product active ingredients and/or breakdown products in the test water reservoir and effluent air.

One liter of air/minute was bubbled separately through 200 ml of aqueous KATHON 886 (KATHON WT) at 2 ppm (2 ppm is the recommended use dilution), or 100 ppm concentrations.

Droplets entrained in exit air were trapped by a glass wool plug. Exit air flow continued through XAD-4 adsorber chambers designed to remove all organic compounds for later analysis. Air exiting from adsorbers was passed through wet test meters for flow adjustment.

- a. Analysis of Kathon WT solutions (by GC) before and after experiment:

	<u>conc. of active ingredient</u> ppm (w/w)	
<u>Target</u>	<u>Before Expt.</u>	<u>After Expt.</u>
2	1.7	1.6
100	104	109

Solutions were analyzed by GC and/or GC/MS techniques.

Results:

Following adsorption, Kathon WT was not removed from XAD-4 adsorbers by passing up to 100 L of air through them. (Preliminary tests proved XAD-4's ability to quantitatively adsorb KATHON WT, and that KATHON WT could be detected at the 1 ug level; which corresponds to a sensitivity of less than 5 ppb (v/v) in air).

- b. Determination of volatile materials stripped from KATHON WT treated aqueous solutions:

Air flow was adjusted to 1 L per minute through 200 ml of 2 ppm KATHON WT in an aeration chamber, and the effluent air passed through an XAD-4 adsorber. The XAD-4 adsorber was replaced with a clean one after each hour of the 5 hour experiment.

This process was repeated using the 100 ppm solution.

The five adsorbers used to collect volatiles from the 2 ppm solution and the 20 to 80 minute, 80-140 minute and 140-200 minute adsorbers from the 100 ppm solution were all analyzed by GC, or GC/MS, after elution of adsorbers to remove any trapped organics.

Results:

No KATHON WT was detected (2 ppm sol.); therefore less than 5 ppb (v/v) was present in air after passing through the simulated air washing system.

Volatile components eluted from the 100 ppm KATHON WT solution:

<u>Component</u>	<u>Approx. conc. (ppm)</u>	<u>ACGIH TLV 1980* ppm</u>
Nitrous oxide	1.0	----
CO ₂	1.0	5000
carbonyl sulfide	1.0	----
acetaldehyde	0.3	100
ethanol	0.1	1000
propionaldehyde	0.2	----
acetone	0.1	750
hydrocarbon (C ₆)	0.05	----
tetrahydrofuran	0.2	200
benzene	0.05	10
toluene	0.3	100
chlorotoluene	0.1	----
KATHON WT	not detected**	----
malonic acid	0.2	

**Sensitivity < 5 ppb (Rohm and Haas in-house TLV is 0.5 mg/m³ equivalent to 100 ppb).

A-TLV is a threshold limit value in air (a somewhat arbitrary value); significant additional (higher) exposure than this value may be harmful or dangerous.

*ACGIH TLV is "American Congress of Governmental Industrial Hygienists Threshold Limit Values" for workplace air set by consensus, periodically.

NOTE:

No inhalation toxicity data is available for some of the volatile compounds stripped by air bubbled through KATHON WT treated water (100 ppm KATHON), and ACGIH TLV values are not available for these materials. In addition, some of the compounds (benzene, toluene and chlorotoluene) are either known or suspected carcinogens.

Page 5 (ii) of the March 1, 1978 Air Washer Testing protocol states that if volatile materials generated from microbicides can not be identified, or are known to be toxic, 90-day subacute inhalation toxicity tests will be required (regardless of the microbicide concentration tested).

Volatile compounds were stripped by air bubbled through 100 ppm KATHON WT solutions in the experiments described above. Some of these compounds for which inhalation toxicity is unknown must be further evaluated for toxic inhalation effects prior to use in Air Washing Systems.

Classification: Core-Minimum Data

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