#613

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SUBJECT: 2-n-Octyl-4-isothiazolin-3-one and its metabolites DATE: 19 SEP 1975

FROM:

TO: PM

COPY

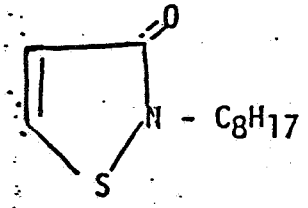
Pesticide Petition No.: 5F1632

Action Requested: Establish the tolerance of 0.01 ppm level in or on cotton seed.

Recommendation: Establish tolerance

Related Petitions: None

Structure:



Boiling Point: 142°C

Vapor Pressure: 6.8×10^{-5}

Specific Gravity: 1.042

Solubility: Infinite in benzene, acetone, ethyl ether, ethyl acetate and chloroform

FORMULATION: Kathon 893 SP-45

Active Ingredient

45-48% 2-n-octyl-4-isothiazolin-3-one

Inert Ingredients

Inert ingredients

[redacted]

EPA Form 1320-6 (Rev. 6-72)

125

004799

Use: Fungicide for seed treatment.

BACKGROUND DATA:

The following toxicity data were submitted in connection with EPA No. 7074100.

Acute Rat Oral LD_{50} (Tech.)	males 794 mg/kg females 681 mg/kg
Acute Rat Oral LD_{50} (Skane M-8)*	1470 mg/kg
Acute Rabbit Dermal LD_{50} (Tech.)	1.78 ml/kg
Acute Rabbit Dermal LD_{50} (Skane M-8)	4.22 ml/kg
Acute Rat Inhalation LC_{50} (Tech.)	<4 mg/l
Acute Rat Inhalation LC_{50} (Skane M-8)	>1.92 mg/l
Rabbit Dermal Irritation (Skane M-8)	PIS = 4.12

Guinea Pig Skin Sensitization (Skane M-8) - not a sensitizer.

PRESENT ACTION:

Summaries of acute toxicity data presented with this petition are as follows:

Acute Rat Oral LD_{50} (Kathon 893 SP-45) 550 mg/kg
Acute Rabbit Oral LD_{50} (Kathon 893 SP-45) 1200 mg/kg
Rabbit Dermal Irritation (Kathon 893 SP-45) PIS = 8.0
Eye Irritation (Kathon 893 SP-45) corrosive

Subacute toxicity data reviewed by Dr. R. Engler on 11/16/73 are as follows:

90 Day Rat Feeding (Tech.) - NEL $\geq$ 2000 ppm
90 Day Dog Feeding (Tech.) - NEL > 2000 ppm
21 Day Rabbit Dermal (Skane M-8) - 1% and 10% solutions produced mild to moderate irritation
10 Day Rat Inhalation (Skane M-8) - 2.0 mg/L producted mortality, elevated SGOT and abnormal total leukocyte counts
Rabbit Tetratogenic (Tech.) - not a teratogen at 60 mg/kg (highest level tested)

Additional toxicity data submitted in this petition are as follows:

18 Month Mice Feeding - Virginia Commonwealth University.

The material tested in this study was identified as RH-893 (2-n-octyl-4-isothiazolin-3-one).

[redacted]

The following experimental design was used: 004799

Group	Experimental Compound	Dose Levels	Number of Mice[a] Initial	6 Mo.	Sacrificed at 18 Mo.
1	negative control	Dietary (ppm) 0	250	50	all survivors
2	RH-393	500	250	50	" "
3	RH-093	1000	250	50	" "
4	AAF[b]	600	200	0	" "
		Daily Intake (mg/kg/day)			
5	DEN[c]	4	100	0	0
6	DEN[c]	6	50	50	0

a. Number of mice divided equally between sexes.

b. Positive control, 2 acetamidofluorene (AAF)

c. Positive control, diethylnitrosamine (DEN) administered in the drinking water.

The micedused were a hybrid strain (C57BL/6 x C_3H/AnF).

Observations and tests for effects included body weights, water consumption, mortality.

Terminal studies included absolute weight of the liver, organ to body ratio of the liver and histopathological examination of the liver, kidney, lung, stomach, ovary, testes, small intestine, urinary bladder, spleen, brain, lymph node, mammary gland and prostate.

Results: The positive control animals receiving DEN (diethylnitrosamine showed clear-cut malignant cytological changes in liver cells at the six month sacrifice.

The parameters for the RH 093 tested mice showed some biological variations during the 18 months which are considered unremarkable by this reviewer. The histopathological review conducted by Dr. Gordon R. Hennigar, Jr. revealed no suggestion of any pathological or cytological change in the liver or bronchial epithelium or other tissues examined.

The no-effect level is 1000 ppm.

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Conclusion:

The standard toxicological data requirements in effect prior to July 3, 1975 have been fully supplied by the petitioner. Additional data more in line with the amended requirements have not been required because of the following reasons:

1. The extremely low requested tolerance of 0.01 ppm.
2. Residues had not been found at the limit of detectability of 0.004 ppm.
3. The complete absence of neoplasms in the 18 month mice study.
4. Cotton seed is not a human food.

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Registration Division WH-567

1) not valid - when based only on the low value of 0.01 ppm
due only to lowness of number
- waiver can be based on safety factor between .1 ppm and the NEL in mice oncogenic study.

ask for mutagenic study