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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 2935-478
Agrosol T Flowable Systemic Soybean Seed Treatment

FROM: Lucy D. Markarian 10/24/90
Precautionary Review Section E 11/26/90
Registration Support Branch
Registration Division (H75-05C)

TO: Susan Lewis/Ben Chambliss (PM 21)
Registration Division (H75-05C)

APPLICANT: Wilbur Ellis Co.
Agricultural Services Corporate Office
191 Shaw Ave. Suite 107
Fresno, California 93704-2876

FORMULATION FROM LABEL:

	Active Ingredient(s):	% by wt.
256	Thiram (Tetramethyl Thiuram disulfide)	12.36
849A	2-(4-Thiazolyl) benzimidazole (Thiabendazole)	0.35
	Inert Ingredient(s):	87.29
	Total	100.0%

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BACKGROUND: Wilbur Ellis Co. has submitted Two acute studies under EPA symbol 2935-478 formerly file 935-478 changed as of 2/1/90. Acute oral & dermal Toxicity and eye & dermal irritation Tests were submitted in 1984 under accession # 254673. To complete the requirements, and as it was requested, an acute inhalation and a dermal sensitization Tests are now submitted.

RECOMMENDATION:

1- The acute inhalation test is considered core minimum data, but accepted - The reasons for core minimum rating are as follows:

a) The males and the females should have been exposed at The same Time. The receipt of inadequate number of males does not justify exposing them at a separate time

b) Too much difference exists in exposure levels of both sexes. Females were exposed at double the chamber concentration of the males, yet variation in the exposure levels for the females is ± 312.8 mg/L. If the lesser value is considered from the given concentration of 667 mg/L (667 minus 312.8) the resulting level is 355 mg/L, closer to the male chamber concentration. In estimating the LC_{50} value as required by the regulation the chamber

RECOMMENDATION: (cont)

concentration for the males is used (LC_{50} 312 mg/L) but consideration is also given to the above mentioned variation in the female chamber concentration.

2. The sensitization study is considered supplementary data. The assay does not define the sensitization potential of the test material for the following reason.

a) It is relatively easy to induce sensitization with an established sensitizer as DNCB. Baehler calls for more dilute concentrations of DNCB than used in the test for induction and elicitation. Induction is made with DNCB in 80% ETOH and elicitation at a lower concentration of DNCB in acetone. It is not explained why corn oil was used as a diluent for either purpose.

b) Challenge applications were made in 0.1 - 0.2 ml aliquots on filter paper. Since the pretest screenings were made with 0.5 ml portions, the rationale behind the reduced volume is not clear. The lower volume affords hardly any contact with skin. Baehler considers good contact of the essence to the success of the Test. The lower volume reduces the chances of good contact as well as reducing the amount of the test material applied to the skin and as a result surpasses a threshhold beyond which challenge cannot be successful. In other words not enough test material was present to either make good contact or induce a reaction. This was also demonstrated with DNCB when

RECOMMENDATION: (cont)

applications at 0.3% in corn oil at the same volume did not result in appreciable number of positive reactions at 24 hrs and the few positive results did not persist at 48 hrs.

It is Therefore recommended That the applicant Submit a new sensitization Test That follows methods more closely to offer support for the product.

Label

The signal word is "Warning" based on the inhalation Toxicity classification of II.

The precautionary statement must include:

May be fatal if inhaled. Do not breath dust, vapor or spray mist. Wear a mask or pesticide respirator jointly approved by MSHA and OSHA.

The rest of The precautionary label appears satisfactory, provided That The required sensitization study does not require precautionary measures for sensitization.

The statement of practical Treatment must include:

If inhaled remove victim to fresh air. If not breathing Give artificial respiration, preferably mouth to mouth. Get medical attention.

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: (21) Reviewer: L. Markarian
MRID No.: 416250 Report Date: ____
Testing Laboratory: ICI Central Toxicology Laboratory Report No. HR 1983
Author(s): R.W. Lewis, A.P. Mould
Species: Rat, Wistar derived Alpk:APfSD
Sex: 50♂ + 50♀ 7 weeks old Weight: ♂233-267g ♀ 194-206g
Source: Alderley Park, Cheshire, U.K.
Test Material: Thiram/Thiabendazole 125.5/3.48 g/L SL Formulation
Quality Assurance (40 CFR §160.12): included

Summary:

1. LC_{50} (mg/kg): Males = Greater Than 312 ug/L ; Females = Greater Than 667 ug/L ; Combined = greater than 312 ug/L
2. The estimated LC_{50} is Greater Than 312 ug/L
3. Mean Concentration: 312 ug for males 667 ug for females
4. Tox. Category : II . Classification: core minimum

Procedure (Deviations From §81-2): Males and females were exposed separately. Nose-only exposure was used in ICI-designed Prosper chambers equipped with Batelle (Geneva, Switzerland) restraining Tubes. The Test atmosphere was generated using a glass concentric-Jet atomizer directed into the top of the chamber. The test material was diluted to 25% V/V in deionized water and pumped into the atomizer with a Gilson Peristaltic pump. Filtered dry air was passed through the atomizer at 24 L/min to carry the aerosol into the chamber. Flow rates were measured by variable area flowmeters. Flow was altered as needed to meet concentration requirements. Chamber concentrations were measured gravimetrically at approximately half hour intervals from the breathing zone

Reported Mortality

Exposure Concentration (mg/L)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
312.0 = .312 mg	0/5	—	0/5
667.0 = .667 mg	—	0/5	0/5

at a set flow rate Through a 25 mm diameter Vinyl metricel (VM-1) filter housed in Dorlin open faced filter holder. Particle size determination was made using a Marple Cascade Impactor (Schater Instruments LTD, Wantage, Oxon, UK). All filters from the impactor were used for analysis of Thiram after weighing. Temperature and humidity were maintained using Vaisal HM131 portable monitor. Average Temperature and humidity were 19.6-22.0°C and 71-86%, respectively.

Observations were frequent during exposure. A detailed clinical examination was given at 4hrs and once a day for 14 days. Body weights were recorded at initiation, and on days 2, 3, 8 & 14. Euthanasia was by Halothane. Animals were exsanguinated prior to necropsy.

Results

The males were exposed at 312.0 mg/L (± 96.8) and the females to 667.0 mg (± 312.2) The MMAD was 2.43 μm with geometric standard deviation of 2.46 for females and 2.68 μm with geometric standard deviation of 2.42 for males.

There was no mortality. During exposure observed abnormalities included coated snouts, salivation, lacrimation, and auditory hypoesthesia. After exposure Toxic signs included hunched posture, piloerection, stains around the nose, wet fur attributed to restraining, however reduced activity, head & paw flicking, shaking, tiptoe gait ptosis and tail erection was also observed and attributed to the Test material. During the observation period, Tail erection, urinary incontinence, TipToe gait persisted intermittently, also persistent were upward curviture of the spine, ungroomed appearance and generally stained coats. There was weight loss in both males & females on days 2 & 3 That was greater than loss attributable to restraint. In females weight loss was seen on day 8, but at termination weight gains were satisfactory.

At necropsy no gross pathology was observed. The mean lung weights were within range except for one male which was above range, but in the absence of gross findings This was not judged to be Test material related.

DATA REVIEW FOR SKIN SENSITIZATION TESTING (§81-6)

Product Manager: (21)
MRID No.: 416250-03
Testing Laboratory: SafePharm Laboratories Ltd
Author(s): R.L. Guest
Species: Guinea Pig, Dunkin-Hartley
Sex: Female Weight: 323-406g (7-10wks old)
Source: David Hall Ltd, Burton-on-Trent, Staffordshire U.K.
Test Material: Thiram/Thiabendazole 125.5/3.48 g/L SC Formulation
Positive Control Material: DNCB 1% w/v cornoil
Quality Assurance (40 CFR §160.12): included

Reviewer: Lucy D. Markonen
Report Date:
Report No. 6/321

Method: Beuhler

Summary:
1. This product is / is not a dermal sensitizer.
2. Classification: Supplementary

Procedure (Deviation From §81-6): PreTest Screening was made using 100% (as received) and 30, 10, & 3% w/v dilutions in distilled water using 3 guinea Pigs for 6hr. exposures using 0.5ml of each concentration. Results from this Test prompted the use of 100% undiluted Test material for induction as it was none irritating. On day 21 of The Test Two fresh guinea pigs were again Treated with 100% 30%, 10% and 3% Test material to decide the elicitation concentration. Exposures were for 6 hrs & were occlusive. The aliquots were 0.5 ml. No irritation was observed at any concentration; Therefore 100% & 30% w/v dilution in distilled water was used as challenge Concentrations.
20 Guinea pigs were used as Test animals. Induced with undiluted (100%) Test material in 0.5ml aliquots. The patches were Lint pieced with Surgical adhesive Tape (Blenderm) and each patch was covered with aluminum foil and elastic adhesive tape (Elastoplast)
10 Guinea Pigs were used as naive controls. Patches were applied with identical wrappings to the Test group with nothing on the patches.
Reference is given to a Test run with 20 Guinea Pigs (Dec. 1989) as positive controls That used 0.5ml of 3.0% DNCB in cornoil. Naive controls were used to validate the study. Challenge was made with 1 & 3% DNCB in cornoil.
There were 3 induction applications of 6 hr duration on days 1, 7 & 14. Evaluation of induction sites were made on days 1, 7, 8, 14, & 15.
Challenge was on day 28. Test material was applied at Two concentrations (100% & 30%) at a naive site on each flank in 0.1-0.2ml aliquots on filter paper and wrapped the same way as the induction applications. The naive controls received The same Treatment. One naive control had died during the study. Therefore only 9 naive controls were challenged. Exposure was for 6 hr.

Results

At 24 hrs 18/20 1% DNCB study had been positive, but only 3/20 of 0.3% DNCB were positive. at 48 hrs only 1/20 DNCB animals was positive and none of the 0.3% DNCB animals were. This established The laboratory's ability to induce sensitization, but was disappointing because 0.3% results were negative, and at 1% all animals were not

positive as experience would dictate. This might be attributed to corn oil solvent and reduced aliquots to 0.1-0.2 ml. each

The test groups showed no positive reactions at either 24 or 48 hrs readings. Neither did the naive controls.

There had been some irritation in the test animals (3/20) during injection at 8 days.