9-2-94
433132-01
Jacket
10356-23

MEMORANDUM:

Subject: EPA File Symbol/EPA Reg. No.:10356-23

From: Lucy D. Markarian, Biologist 8/25/94
Precautionary Review Section
Registration Support Branch
Registration Division (7505W)

To: Cynthia Giles-Parker, PM 22
Fungicide-Herbicide Branch
Registration Division (7505C)

Thru: Thomas C. Ellwanger, Section Head
Precautionary Review Section
Registration Support Branch
Registration Division (7505W) E 9/2/94

Applicant: Chemical Specialties, Inc.
One Woodlawn Green
Suite 250
Chararlotte, NC 28217

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Copper as elemental	9.0 %
(from Copper ethanolamine complexes)	
Inert Ingredient(s):	
.....	91.0 %
Total:	100.0 %

D24409

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BACKGROUND

Chemical Specialties, Inc. has submitted dermal irritation and sensitization studies as 6(a)(2) data for the product ACQ-C2 under EPA 10356-23. The studies were undertaken to satisfy registration requirements in the state of California. The product is for the control of wood damaging fungi and insects, and contains the equivalent of 9 % elemental copper derived from copper ethanolamine complexes.
The registration was based on the registration of [redacted]

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

RECOMMENDATION PRODUCT INGREDIENT SOURCE INFORMATION IS NOT INCLUDED

The dermal irritation assay shows the test material to be corrosive to the skin as core minimum data. Although the presented sensitization test does not conclusively show the test material to be a sensitizer, PRS recommends that the precautionary statement about sensitization be included in the label. In addition, it is recommended that the subject product be also considered corrosive to the eyes as recommended by 40 CFR 158.340 for test materials that are corrosive to the skin. The rationale for the conclusions is given below.

Quality Assurance statements

The Quality assurance statements are not adequate. An acceptable quality assurance statement includes what was inspected, the date of the inspection, the date it was reported, and to whom the findings were reported. A generalized statement as to the routine inspection of ongoing tests does not ascertain that at least one portion of the conduct of the particular test was inspected as required. The inspection of the report is expected in addition to the inspection of the conduct of the test. The statements are accepted at this time with the stipulation that future studies include acceptable quality assurance statements as explained.

Dermal Irritation- Core minimum

1. The patch has to be better defined. It is important that the reviewer know how many layers of gauze were used. Any patch consisting of more than 4 layers of gauze are not suitable.

2. PRS does not encourage the use of elastic wrappings that exert pressure on the patch. The patch is supposed to be semiocclusive. Generally, rubber dam or plastic sheeting, loosely wrapped, are used to preclude ingestion or inhalation by the animal.

Sensitization

The test, as conducted, is inconclusive.

1. The results do not show the test material to be a sensitizer. The laboratory, by using the Draize scale to evaluate a Buehler test, has assumed that grade 1 erythema on the Draize scale is equivalent to the grade 1 reaction on the Buehler scale. Grade 1 erythema on the Draize scale translates into ± reactions on the Buehler scale, and are considered to be negative. Therefore, the reactions evaluated as grade 1 erythema are not considered positive reactions. PRS recommends and encourages the use of the scoring system devised by the author of the methodology used.

2.The presence of a large number of borderline reactions(±) is considered to be reason for rechallenge. This was not done.

3.Elicitation at the same concentration as induction, which is supposed to be a slight to moderately irritating, is not acceptable. If 5 % was considered an irritating concentration to be used for induction only, it could not, by definition, also be the highest nonirritating concentration that Buehler uses for elicitation.

4. 2 % was not the correct concentration for challenge either. Ideally, the challenge concentration should have shown 50 % ± reactions. Buehler describes the challenge concentration as the highest nonirritating concentration and defines it as that concentration that when tested in four guinea pigs results in two reactions of ± and two of 0. There was no reaction in the control group with 2 %, when ideally 50 % of the animals should have shown ± reactions.

5. The positive control test is not acceptable. According to published as well as historic data, and what is generally practiced, DNCB was induced and elicited at irritating concentrations. All concentrations used in the test are considered irritating concentrations. Generally, induction is at 0.1 % in ethanol, and elicited anywhere from 0.03 to 0.08 % in acetone. DNCB can even be induced at 0.8 %. The Laboratory must either show that the concentrations used for the positive control tests were chosen correctly, and not arbitrarily, as for the test material; or use published , and generally used concentrations for the positive control material. Whatever that is applicable to the test group is applicable to the control group. If the control group is not conducted according to the protocol used for the test group, then the control group ceases to function as control for that test.

The large number of grade 1 erythema observed with 5 % and very few of the same in with 2 %. suggests that there probably is sensitization potential. As sensitization is concentration dependent, with a corrosive test material this is extremely hard to show. Due to the irritating properties of the test material, the concentrations at which it is possible to test the product are below the threshold where sensitization can either be adequately induced or elicited. Based on this, PRS is of the opinion that conducting another sensitization study will not serve any better than the work presented at this time. It is recommended that since the subject product contains the equivalent of 9 % metallic copper, which is historically known as a sensitizer, and since certain aspects of the submitted test suggest sensitization potential, the label include a precautionary statement about the sensitization.

LABELING

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED
PRODUCT INGREDIENT SOURCE INFORMATION IS NOT INCLUDED

The registration of this product is based on the registration of [redacted] Generally cite-all method of registration has been used. PRS is of the opinion that a good set of dependable data does not exist to support any of the registration, and if there are old studies PRS cannot afford to spend the time to pusrue these without the citation of specific data, including the accession numbers. As a result the recommendation for the label is limited to the currently presented tests with the aid of the guidence 40 CFR offers.

The signal word is DANGER as it appears on the proposed label

The precautionary statement should be revised to read:

Corrosive. Causes irreversible eye damage and skin burns. The rest of the precautionary statement is acceptable. PROPOSED SENSITIZATION STATEMENT IS ACCEPTABLE. -E

The statement of practical treatment should be revised to read:

If in eyes	Call Physician. Keep eye lids open and flush with a gentle steady stream of water for 15 minutes.
If on skin	Wash thoroughly with soap and water. Get medical attention.
If swallowed	Drink promptly a large quantity of milk, egg white or gelatin mixture, or if these are not available, a large quantity of water. Do not induce vomiting or give anything by mouth to an unconscious person.

Note to the physician: probable mucosal damage may contraindicate the use of gastric lavage.

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Note to PM

Category I placement of the eye and skin irritation potential hits the trigger for restricted use classification. The PM must decide if alternative labeling language is sufficient to offset the need for restricted use classification.

PRS recommends that the registrants of similar products as [redacted] and others that PRS is not able to name, be informed of this 6(a)(2) data and be encouraged to revise their labels, as their products pose a serious threat if accidental ocular or dermal contact should occur.

PRODUCT INGREDIENT SOURCE INFORMATION IS NOT INCLUDED

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

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DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5)

Product Manager: 22
MRID No.: 433132-01
Testing Laboratory: Safepharm Labs Ltd.
Author(s): D.J.Allen
Species: Rabbit, New Zealand White
Age: Young Adult
Sex: Four male and two female
Weight: 2.28 - 2.48 kg
Source: David Percival Ltd.,Moston, Sandbach, Ceshire, U.K.
Dosage: 0.5 ml
Test Material: Copper amine complex, dark blue liquid
Batch 011494
Quality Assurance (40 CFR §160.12): Included, inadequate

Reviewer: L. Markarian
Report Date: 5/24/94
Report No.: 577/20

Summary:

1. **The Primary Irritation Index** = Corrosive,not calculated
2. **Toxicity Category:** I
3. **Classification:** Core minimum

Procedure (Deviations From §81-5):

undiluted test material was applied to the clipped skin of the animals on 2.5 X 2.5 cm gauze patch and secured with a 2.4 X 4 cm strip of Blenderm surgical tape. The trunks of the animals were wrapped in elasticized "corset" (Tubigrip). At 4 hrs the patches were removed and residue wiped with cotton dipped in distilled water. The sites were evaluated at 1, 24, 48, 72 hrs and days 7 and 14 according to Draize.

Results:

At 1 hr grade 1 or 2 erythema and edema was observed at all sites. At 24 hrs 3/6 animals showed grade 4 erythema and grade 1, 2, and 3 edema. The other sites showed grade 2 (2/6) and grade 1 (1/6) erythema with grade 2 and 1 edema. All the sites were stained light blue and 3/6 showed scattered areas of necrosis and by day 7 there was scab formation, and it is reported that adverse skin states did not permit evaluation of the skin at these sites. At 14 days encrustation or scab formation was not resolved in 1/6 animals, and 2/6 showed desquamation.

Special Comments:

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

Product Manager:22 **Reviewer:** L. Markarian
MRID No.:433132-02 **Report Date:**5/24/94
Testing Laboratory: Safepharm Labs, Ltd. **Report No.:**577/22
Author(s):D.J.Allen
Species: Guinea Pig, Hartley
Weight:349 - 427 g, 8-12 weeks old
Source: David Hall Ltd.,Burton-on-Trent, Staffordshire, U.K.
Test Material: Copper amine complex, dark blue liquid
Batch 011494
Positive Control Material: None
Quality Assurance (40 CFR §160.12): Included, inadequate

Method: Buehler

Summary:

1. **This Product is a dermal sensitizer.**

2. **Classification:** Supplementary

Procedure (Deviation From §81-6):

There was a pretest screening for the definition of the induction and elicitation concentrations. Initially, two guinea pigs were treated with four concentrations (100 %, and aqueous dilutions at 75, 50,and 25 %). This resulted in necrosis at all sites with all concentrations. Two more guinea pigs were treated with 10, 5, 2, and 1 % dilutions. At 10 % 1/2 showed necrosis, 5 % showed grade 1 erythema at both sites, 2 % showed grade 1 erythema in 1/2, and at 1 % all sites were negative. Two more guinea pigs treated with 2 and 1 % showed no reaction. All treated sites showed coloration from product.
The test was induced at 5 % and elicited at 5 % and 2 % at the same time.

All applications were made in 0.5 ml aliquots on clipped skin using patches made of 60 X 50 mm(for induction) or 40 X 50 MM (for elicitation) Blenderm surgical tape with a 15 X 30 mm felt center. The patches were covered with aluminum foil and the trunks of the animals were wrapped in elastic adhesive bandage. At six hrs the patches were removed, and the sites wiped clean of any residue. Prior to the evaluation of the induction sites, at 24 hrs the skin was clipped and shaved with razor. The skin was not shaved prior to the evaluation of the challenge reactions.

There were two groups of animals, twenty guinea pigs in the test group and ten as vehicle control. The control animals were induced with distilled water and elicited in same way as the test group.

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There were three inductions one week apart. Induction sites were moved in two cases where the responses were severe. Challenge was two weeks after the last induction at two virgin sites.

Evaluations were made at 24 and 48 hrs after applications according to Draize.

Reference has been given to a study conducted with DNCB conducted during February of 1994. The study used 0.5 DNCB in ethanol for the first two inductions and 0.25 % for the last induction. 0.1 % DNCB in acetone was used for elicitation. The actual results of the test and the reason for using the given concentrations is not stated. It is only stated that 55 % were sensitized.

Results:

There was coloration from the product during elicitation and challenge. It is reported that this in general did not interfere with the evaluations.

In the test group, during induction, the initial application could not be evaluated accurately due to coloration from product. Following the second induction two sites showed necrosis. 12/20 sites showed coloration from product, two sites showed grade 1 edema. Following the third induction 4/5 showed coloration from product. No other reaction was observed.

At challenge with 5 %, 12/20 sites showed grade 1 erythema, and all sites showed coloration from product at 24 hrs. At 48 hrs 5/20 still showed grade 1 erythema with all sites showing coloration from product.
With 2 % at 24 hrs 2/20 showed grade 1 erythema with all sites showing coloration from product. At 48 hrs no erythema was observed,but coloration from product persisted.

In the control group no reaction was observed during induction with distilled water. At challenge with 5 % 2/10 showed grade 1 erythema at 24 hrs. There was no reaction at 48 hrs. 2 % did not elicit any response at any site at any interval.

Tox Chem No: 024403 Copper Triethanolamine Complex **Current Date:** 8/24/94

Laboratory: Safepharm Laboratories, Ltd., P.O.Box 45, Derby, DE1 2BD, U.K.

STUDY	MATERIAL	MRID NO	RESULTS	TOX CAT	CORE GRADE
Dermal Irritation in Rabbits 577/20 5/24/94	ACQ-C2 Copper Amine Complex batch 011494	433132-01	Corrosive	I	Minimum
Sensitization in guinea pigs 577/22 5/24/94	" " " "	433132-02	sensitizer*		Supplementary

* PRS conclusion based on historical data and parts of the presented test