6/12/1995

MEMORANDUM:

Subject: EPA File Symbol/EPA Reg. No.: 10356-19 (10465-33)
CSI Copsol (ACQ-C)

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

6/12/95

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

Applicant: Chemical Specialties , Inc.
One Woodlawn Green
Charlotte, North Carolina 28217

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Copper Ammonium Carbonate	24.1 %
Inert Ingredient(s):	
.....	75.9 %
Total:	100.0 %

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BACKGROUND

Chemical Specialties, Inc. had requested a label amendment for the product Copsol under EPA 10356-19. The Signal word had to be changed from CAUTION to DANGER, based on the eye irritation potential. At the review of 1/27/92 the studies submitted in support of the product could not be located in the Agency. The submission of the tests or the accession numbers were requested so that the change could have documentation. It was also stated that a sensitization test should be submitted if the removal of the precautionary language about sensitization was desired , and it could be shown that the product was not a sensitizer. In addressing the area of inhalation testing, PRS had also stated that inhalation test was required when the threshold limit value (TLV) at industrial settings exceeded 1 mg/M^3. The registrant has submitted the five tests, but has not addressed the inhalation question.
The cover letter states that the test material ACQ-C used for the sensitization test is identical to Copsol used in the other four tests.

RECOMMENDATION

Submitted acute oral test is acceptable in category II toxicity. This decision is based on the wider than acceptable 95 % confidence limits in general, and particularly for the females that show an LD_{50} of 510 (236 - 1101). If this is not acceptable, the registrant has the option of defining the oral toxicity of the subject product more accurately.
The Acute dermal test is not acceptable, because the test material is not applied correctly. The dermal irritation test may be upgraded if the incongruence in reactions in the acute dermal toxicity and the sensitization test as compared with the results of this test can be explained.
The sensitization test is acceptable.
The Inhalation test is still to be addressed.

The rationale for the classification of the tests is given below.

Acute oral

> According to the guidelines the 95 % confidence limits should be within 20 % of the calculated LD_{50} values. All the confidence limits are larger. Most striking, however, is the confidence limits for the females that are larger than 50 %. At the lowest dose of 565 mg/kg there was 60 % mortality in the females. The LD_{50} for the females is calculated to be 510 mg/kg with confidence limits ranging from 236 to 1101 mg/kg. This value is arrived at using the Litchfield and Wilcoxon method where the fit of the curve on logarithmic paper can make a great deal of difference in the calculated values. Due to the wide range of the confidence limits in

the females, the oral LD_{50} of the product is placed in category II toxicity. If this is not acceptable, the registrant has the option of submitting a new acute oral toxicity test that defines the limits more closely.

Acute Dermal - Unacceptable

The test material was not applied correctly. The test material after application to the skin must be covered with gauze and the trunks of the animals should be wrapped in an impermeable material to retard evaporation and prevent ingestion and inhalation of the test material. There was no impermeable wrapping.

The test material was applied on a larger area than usual(10 % of body surface) and is described as 20 to 25 % of the body surface. This means that application was not at a constant rate per cm^2 of all animals. The area is not specified in measured units. This is reflected in the wide range of skin responses in the animals. However, even at this reduced rate of application, the majority showed necrosis and eschar.

The gauze wrapping is not adequately described. The gauze should not be so many layered as to absorb the test material completely and reduce the full impact of the test material. Application on a larger than usual area, covering with gauze of undetermined thickness, and allowing evaporation by not wrapping the trunks with an impermeable material resulted in failure to test the full hazard potential of the product.

It is unusual that with coloration from product grade 1 erythema could be discerned. Additionally, whenever necrosis or eschar is present the erythema score should be 4 and not anything less, because Draize describes grade 4 erythema as slight eschar. Obviously eschar and necrosis would qualify for this evaluation. The skin after exfoliation should also be described to fully evaluate the effects of the product. Necrosis rarely leaves the underlying skin undamaged.

A new acute dermal toxicity test needs to be submitted.

Eye Irritation

The use of pen light is not an acceptable source of auxiliary light, because it is yellow light. Eyes should be examined under white light, closely resembling daylight. The test is accepted at this time, because irreversible eye damage is clearly shown. It is recommended that future eye irritation tests be evaluated under white light and it is encouraged that magnification be also used. The case in

point is the presence of grade 1 opacity for a period of three weeks. Grade 1 opacity is not likely to last that long.
Fluorescein is generally used starting at 24 hrs. By 72 hrs some opacity not discerned without fluorescein may have resolved and completely missed.

Dermal irritation - Supplementary

In the acute dermal toxicity test 6/10 animals showed necrosis or eschar that was not resolved in two animals at 14 days. This was observed in spite of the fact that the test material was not properly applied, and was spread on a much larger area than it should have been. In the presented dermal sensitization tests conducted at a different laboratory, 12 % dilution of the formulation resulted in grade 2 to 3 erythema following a six hour exposure to 0.4 ml of test material in 10 guinea pigs that are generally known to be less sensitive to irritants. In this test, 0.5 ml of undiluted material resulted in grade 1 erythema in one animal. The difference in the reactions is very remarkable and cannot be explained by the difference in exposure time alone. The guinea pig exposure comes very close to this exposure and showed reaction of grade 2 or greater erythema in all ten animals with an almost ten times more dilute solution.

If an acceptable explanation can be given for this incongruence, the test may be upgraded.

LABEL

The signal word is changed to DANGER based on the eye irritation potential of the product
The toxicity profile as of now is:

Acute Oral	Category II
Acute dermal	To be defined
Acute Inhalation	To be defined
Eye Irritation	Category I
Dermal Irritation	To be defined
Sensitization	not sensitizer

Based on this partial profile the Precautionary statement must read:

Corrosive. Causes irreversible eye damage. May be fatal if swallowed.Do not get in eyes or on clothing. Wear goggles or face shield. Wash thoroughly after handling, and before eating drinking and using tobacco. Remove contaminated clothing and wash before reuse.

The statement of practical treatment must include:

If in eyes	Call physician. Hold eyelids open and flush with a gentle steady stream of water for 15 minutes.
If swallowed	Call physician or poison control center. Drink promptly a large quantity of milk, egg white or gelatin solution, or if these are not available a large quantity of water. Do not give anything by mouth or induce vomiting to an unconscious person.
Note to Physician:	possible mucosal damage may contraindicate the use of gastric lavage.

The precautionary label may have to be revised upon the presentation and acceptance of the outstanding data.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§ 81-1)

Product Manager:22 **Reviewer:** L. Markarian
MRID No.421233-01 **Report Date:**12/2/91
Testing Facility:WIL Research **Report No.**WIL-158006
Author(s): Gary R. Kiplinger
Species: Rat, Sprague Dawley
Age: Young adult
Weight:214 - 292 g
Source: Charles River Breeding Laboratories, Inc.,Portage, MI
Test Material: Copsol, lot 227-11-037, blue liquid, pH 9.6
Quality Assurance (40 CFR §160.12): Included, adequate
Conclusion:

1. **LD_{50} (mg/kg):** **Males =** 982 (901 - 1071)
Females = 510 (236 - 1101)
Combined = 737 (565 - 961)
2. **Tox. Category:** II **Classification:**Acceptable

Procedure (Deviations from §81-1):

Fasted animals were intubated at three levels with the test material as received. Observations were frequent on the day of intubation and daily thereafter. Body weights were recorded at initiation and on days 7 and 14. Necropsy was performed on all animals.

Results:

Dosage mg/kg (as received)	(Number Killed/Number Tested)		
	Males	Females	Combined
565	0/5	3/5	3/10
1000	3/5	4/5	7/10
1770	5/5	5/5	10/10

Symptoms & Gross Necropsy Findings:

All mortality occurred within 48 hrs of intubation. symptoms of toxicity included hypoactivity, soft stools, decreased defecation, stained and/or matted anogenital area,red encrustation around the mouth, salivation, and ataxia. Less frequently observed symptoms included clear ocular discharge, rales, labored respiration,gasping, red encrustation around the mouth, exopthalmia, prostration, and red material on the forepaws. The survivors appeared normal within five days with the exception of red encrustation around the eyes of one male at the lowest dose level. The same rat had one incisor missing. Body weight gains were normal among the survivors.
Necropsy of the decedents revealed abnormalities of the kidneys and gastrointestinal contents and mucosae, swollen livers,red adrenals, hemorrhagic thymi, and blue foamy material in the

trachea.
The necropsy of the survivors, with the exception of one female at the lowest level, showed no gross pathology. That female showed enlarged cervical lymph nodes.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

Product Manager:22
MRID No.: 421233-02
Testing Laboratory:WIL Research
Author(s): Gary R. Kiplinger
Species: Rabbit, New Zealand White
Weight:2157 -2645 g
Age: young adult
Source: Hazleton Research Products, Inc., Denver, PA
Test Material: Copsol, lot 227-1-037, blue liquid, specific gravity 1.15
Quality Assurance (40 CFR §160.12): Included, adequate

Reviewer: L. Markarian
Report Date:12/2/91
Report No.:WIL-158007

Summary:

1. **The estimated LD_{50} is**

3. **Tox. Category:** **Classification:**Unacceptable

Procedure (Deviation From §81-2):
The test material was applied to the clipped dorsum of the animals on 20 to 25 % of the body surface, the site was covered with gauze binder and secured with tape. Collars were placed around the necks. At 24 hrs the collars were removed and the sites were wiped with moist paper towels. Observations were frequent during the day of treatment and daily thereafter, and included dermal evaluations.Body weights were recorded at initiation and on days 7 and 14. Necropsy was performed on all animals.

Results:

Reported Mortality

DOSAGE	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
2000 mg/kg	0/5	0/5	0/10

Symptoms & Gross Necropsy Findings:

9/10 animals showed no adverse reactions. One female showed decreased defecation and urination and inappetence, but appeared normal on day 3. Another female did not show adequate gain in body weight at termination.
Dermal reactions included erythema and edema in all animals. 6/10 showed necrosis or eschar at least during part of the observation period. Necrosis and eschar persisted to termination in two males and to day 13 in one female. The skin of all animals was stained green. Coloration from product persisted to termination in three males and three females. There was desquamation and exfoliation. The state of the skin after exfoliation was not described.

DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (§81-4)

Product Manager:22
MRID No.: 421233-03
Testing Laboratory:WIL Research
Author(s): Gary R. Kiplinger
Species: Rabbit, New Zealand White
Sex: Female
Weight:3491 - 3868 g
Age: Adult
Source: Hazleton Research Products, Denver, PA
Dosage:0.1 ml
Test Material: Copsol, lot 227-1-037, blue liquid
Quality Assurance (40 CFR §160.12): Included, adequate

Reviewer: L. Markarian
Report Date:12/2/91
Report No.:WIL-158009

Summary:

1. **Toxicity Category:**I

2. **Classification:**Acceptable

Procedure (Deviations From §81-4):
The test material was instilled, in the conjunctival sacs of six pre examined eyes , as received. Evaluations were at 1, 24, 48, 72, hrs and days 4, 7, 14, and 21 according to Draize. Fluorescein was used to confirm corneal findings before and at 72 hrs and later intervals.

Results:

Observations	(number "positive"/number tested)							
	Hour	Days						
	1	1	2	3	4	7	14	21
Cornea Opacity	6/6	6/6	6/6	6/6	6/6	5/6	2/6	1/6
Iris	6/6	6/6	6/6	5/6	3/6	0/6	0/6	0/6
Conjunctivae								
Redness	2/6	5/6	6/6	5/6	5/6	1/6	0/6	0/6
Chemosis	5/6	6/6	6/6	5/6	5/6	0/6	0/6	0/6
Discharge	6/6	5/6	6/6	5/6	3/6	2/6	1/6	1/6

Comments:

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

Product Manager: 22
MRID No.: 421233-04
Testing Laboratory: WIL Research
Author(s): Gary R. Kiplinger
Species: Rabbit, New Zealand White
Age: Adult
Sex: Four males & two females
Weight: 3083 - 3780 g
Dosage: 0.5 ml
Test Material: Copsol, lot 227-1-037, blue liquid
Quality Assurance (40 CFR §160.12): Included, Adequate

Reviewer: L. Markarian
Report Date: 12/2/91
Report No.: WIL-158008

Summary:

1. **The Primary Irritation Index** =

2. **Toxicity Category:**

3. **Classification:** Supplementary

Procedure (Deviations From §81-5):

Test material as received was applied to the clipped skin of the animals on 6 cm^2 area, covered with 2 ply gauze patch. The trunks of the animals were wrapped with gauze binders secured with tape. Collars were placed around the necks for the duration of the test. At 4 hrs the patches were removed and the sites wiped with moist paper towels. Evaluations were at 1, 24, 48 and 72 hrs, according to Draize.

Results:

There was coloration from the product at all sites up to 48 hrs. Grade 2 erythema is recorded at one site at 1 and 24 hrs.

Special Comments:

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

Product Manager: 22
Reviewer: L. Markarian
MRID No.: 428674-01
Report Date: 7/27/93
Testing Laboratory: Product Safety Labs
Report No.: T-2257
Author(s): Ralph Shapiro
Species: Guinea Pig, Hartley
Weight: 337 - 400 g
Age: young adult
Source: Davidson's Mill Farm, S. Brunswick, NJ
Test Material: ACQ-C Lot 050692, blue liquid
Positive Control Material: DNCB
Quality Assurance (40 CFR §160.12): Included, Adequate

Method: Buehler

Summary:

1. **This Product is not a dermal sensitizer.**

2. **Classification:** Acceptable

Procedure (Deviation From §81-6):

A pre test screening was made to define induction and elicitation concentrations. Six guinea pigs and eight concentrations were used. After a preliminary screening with two animals four guinea pigs were tested at 12, 6, 3, and 1.5 % aqueous solutions. At 12 % there were two grade 2 and two grade 1 reactions and at 1.5 % there were two grades of 0 and two grades of 0.5. The test was induced at 12 % and elicited at 1.5 %.
A similar screening was made with DNCB tested at 0.05, 0.03 and 0.01 % in acetone. 0.3 % resulted in 3 grades of 0.5 and one grade of 0. The test was conducted with 0.08 % DNCB in ETOH for induction and 0.03 % in acetone for elicitation.

There were ten animals in each of the test and positive control groups. Each group had group of five naive controls. Applications were made in 0.4 ml aliquots in Hill Top Chambers on clipped skin for six hours. The chambers were affixed to the skin with hypoallergenic tape. The animals were not restrained.

Three induction applications made one week apart. Challenge was two weeks after the last induction at a virgin site. Evaluations were at 24 and 48 hrs after each application according to Buehler.

Results:

In the test and positive control groups progressively more pronounced reaction was observes with each subsequent application. Following the third induction there was eschar in the majority of the test group, and in a few of the DNCB group. At challenge 4/10 in the test animals and 3/5 in the naive

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group showed 0.5 reactions. 6/10 DNCB animals were positive, 4/10 showed 0.5 reactions. there were 2/5 0.5 scores in the naive controls for DNCB.

Tox Chem No: 022703 Copper ammonium Carbonate **Current Date:** 6/12/95

Laboratory: WIL Research Laboratories, Ashland OH 44805-9281
Product Safety Labs, 725 Cranbury Road, E. Brunswick, NJ

STUDY	MATERIAL	MRID NO	RESULTS	TOX CAT	CORE GRADE
Acute Oral LD_{50} Study(Rats) WIL-158005 12/2/91 WIL	CSI Copsol Lot 227-11-037	421233-01	LD_{50} mg/kg M 982(901-1071) F 510(236-1101) C 737(565-961)	II	Acceptable
Acute Dermal Limit Test(Rabbits) WIL-158007 12/2/91 WIL	" " "	421433-02			Unacceptable
Eye Irritation in Rabbits WIL-158009 12/2/91 WIL	" " "	421233-03	Corrosive		Acceptable
Dermal Irritation in Rabbits WIL-158008 12/2/91 WIL	" " "	421233-04			Supplementary
Sensitization In Guinea Pigs T-2257 7/17/93 PSL	ACQ-C Lot 050692	428674-01	not sensitizer		Acceptable

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