10-28-93

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: EPA Reg. # 55146-AU; Champ Plus Flowable Copper Hydroxide

TO: Cynthia Giles-Parker PM # 22. Attn.:James Stone
Herbicide-Fungicide Branch
Registration Division (H7505C)

FROM: David L. Ritter, Toxicologist DLR 8-24-93
Precautionary Review Section
Registration Support Branch
Registration Division (H7505W) Mary Waller for T.E 10/28/93

THRU:: Thomas C. Ellwanger, Jr., Section Head
Precautionary Review Section
Registration Support Branch
Registration Division (H7505W)

Registrant: Agtrol Chemical Products
7322 Southwest Freeway Suite 4000
Houston TX 77074

FORMULATION FROM LABEL:

Active Ingredient(s):	% by Wt.
Copper Hydroxide	37.5%
Inert Ingredient(s):	62.5%
Total	100.0%

Action Requested:

1. Review six acute toxicity studies.

2. Review Precautionary labeling.

Background:

A previous eye irritation study (MRID # 424706-01) using a different formulation than the present one was reviewed in the L. Markarian memo of 1/29/92, EPA Reg. # 55146-AU. The product tested, ACP Copper Hydroxide Flowable 6.0 lb/gal (EPA Reg. # 55146-41) also showed a TOX Cat. III for eye irritation. However, since it did not use the same formulation as that up for registration, it was not used to establish precautionary labeling.

The present submission uses 37.5% copper hydroxide as the Test Article in each study.

PRS Response:

Data Review:

All studies have been reviewed and the reviews are appended. All studies except the dermal sensitization were Category III or IV and were rated CORE Guideline. The sensitization study may be upgraded upon submission of results of a historical positive control study which was noted in the report but was not included.

Precautionary Labeling Review:

Signal Word: Caution.

Precautionary Statement:

Causes moderate eye injury. Avoid contact with SKIN eyes or clothing. Harmful if swallowed or absorbed through skin. Harmful if inhaled. Avoid breathing spray mist. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.

Statement of Practical Treatment:

If Swallowed: Call a physician or Poison Control Center. Drink 1 or 2 glasses of water and induce vomiting by touching back of throat with finger. Do not induce vomiting or give anything by mouth to an unconscious person.

If on Skin: Wash with plenty of soap and water. Get medical attention.

If Inhaled: Remove victim to fresh air. If not breathing, give artificial respiration, preferable mouth-to-mouth. Get medical attention.

If in Eyes: Flush with plenty of water. Call a physician if irritation persists.

Additional labeling changes may be necessary depending on the results of data submitted in support of the dermal sensitization study (MRID # 428718-06).

..3

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

Product Manager (PM): 22 EPA Reg. No.: 55146-AU

Reviewer: David L. Ritter, Toxicologist DLR 8-24-93

MRID No.: 428718-01

Testing Laboratory: Stillmeadow, Inc.
12852 Park One Drive
Sugar Land TX 77478

Title Of Report: Acute Oral Toxicity Study in Rats

Date of Report: 7/16/93

Lab. No.: 0123-93

Author(s): Janice O. Kuhn, Ph.D.

Quality Assurance (40 CFR, Section 160.12): Acceptable

Species: HSD.SD rat Sex: 20 M + 20 F Wt.: M: 188 - 288 gm
F: 188 - 235 gm

Source: Harlan Sprague Dawley, Inc.
Houston TX

Test Material: Champ Plus Flowable Copper Hydroxide

Dosage: 1000 - 5050 mg/kg

Summary:

LD_{50} mg/kg: M - 2169 mg/kg; F - 1224 mg/kg
Combined - 1697 mg/kg

Toxicity Category: III CORE Classification: Guideline

Procedure:

Standard laboratory animal husbandry and GLPs were followed.

Animals were weighed initially, at the time of death and on days 7 and 14.

Test Article Administration:

Test Article administered undiluted by oral intubation to groups of 5 males and/or 5 females each at doses of 1000 (5 F only); 1500 (5M + 5F);, 2000 (5M only): 3500 (5M + 5F) and 5000 (5M + 5F) mg/kg.

Animals were observed for mortality and signs of toxicity three times on day 0, then daily thereafter for 14 days. Gross necropsy was performed at the time of death or at termination of the study.

Results:

Body Weights: Some weight loss between day 0 and 7, then normal.

Signs of Toxicity: hypoactivity, diarrhea, polyurea, piloerection,, ptosis & occasional ataxia.

Mortality:

REPORTED MORTALITY

DOSE MG/KG	Animals Killed/Animals Tested		
	Males	Females	Combined
1000		1/5	1/5
1500	1/5	4/5	5/5
2000	1/5		1/5
3500	5/5	5/5	10/10
5050	5/5	5/5	10/10

Necropsy: Diarrhea, blue liquid in stomach, polyuria, blue nasal discharge, brown liquid in intestine.

5

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

Product Manager (PM): 22 EPA Reg. No.: 55146-AU

Reviewer: David L. Ritter, Toxicologist DLR 8-24-93

MRID No.: 428718-02

Testing Laboratory: Stillmeadow, Inc.
12852 Park One Drive
Sugar Land TX 77478

Title Of Report: Acute Dermal Toxicity Study in Rabbits

Date of Report: 6/9/93

Lab. No.: 0124-93

Author(s): Janice O. Kuhn, Ph.D.

Quality Assurance (40 CFR, Section 160.12): Acceptable

Species: New Zealand White Rabbit Sex: 5M + 5F
Wt.: M: 2.175 - 2.750 kg
F: 2.000 - 2.300 kg

Source: Ray Nichols Rabbitry, Lumberton TX

Test Material: Champ Plus Flowable Copper Hydroxide

Dosage: 2020 mg/kg

Summary:

LD_{50} mg/kg: M $\geq$ 2020 mg/kg F $\geq$ 2020 mg/kg
Combined $\geq$ 2020 mg/kg

Toxicity Category: III CORE Classification: Guideline

Procedure:

Standard laboratory animal husbandry and GLPs were followed.

Animals were weighed initially and on days 7 and 14.

Fur was clipped from the dorsal trunk one day prior to exposure.

Test Article Administration:

2020 mg/kg Test Article was introduced under a 10 x 10 cm gauze pad which was then secured with a semi-permeable dressing.

After 24 hours the dressings were removed and the test sites were cleansed with water. Observations for effects and mortality were made at ½, 3 and 6 hours and once daily thereafter for 14 days.

A gross necropsy was performed at termination on day 14.

Results:

Body Weights: normal.

Signs of Toxicity: mild diarrhea.

Mortality: None reported.

REPORTED MORTALITY

DOSE MG/KG	Animals Killed/Animals Tested		
	Males	Females	Combined
2020	0/5	0/5	0/10

Necropsy: Unremarkable.

-7

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

Product Manager (PM): 22 EPA Reg. No.: 55146-AU

Reviewer: David L. Ritter, Toxicologist DLR 8-2393

MRID No.: 428718-03

Testing Laboratory: Stillmeadow, Inc.
12852 Park One Drive
Sugar Land TX 77478

Title Of Report: Acute Inhalation Toxicity Study in Rats

Date of Report: 7/22/93

Laboratory Number: 0125-93

Author(s): Mark S. Holbert

Quality Assurance (40 CFR, Section 160.12): Acceptable.

Species: HSD:SD rat Sex: 5M + 5F/group
Wt.: M: 216 - 286 gm
F: 217 - 256 gm

Source: Harlan Sprague Dawley, Inc., Houston TX

Test Material: Champ Plus Flowable Copper Hydroxide

Dosage: Nominal Conc.: 130.9 mg/l

Gravimetric Conc.: 1.20, 1.31 and 1.84[a]

MMAD ± GSD: 2.74 ± 2.31 μm

% < 4 micron: > 40.7%

Summary:

LC_{50} (mg/L): M - 1.72 mg/l; F - 1.97 mg/l
Combined - 1.79 mg/l

Toxicity Category: III Classification: Guideline

Procedure:

Standard laboratory animal husbandry and GLPs were followed.

Animals were weighed initially and days 7 and 14.

[a] Maximum concentration attainable

Observations were made frequently on day of exposure and daily thereafter for 14 days.

Gross necropsy performed at termination or time of death.

Generation of Test Atmosphere:

Standard methods were used to produce respirable aerosols from a 60:40 aqueous dilution of Test Article. Animals were subjected to whole body exposure for four hours.

Air samples were taken hourly from the breathing zone for determination of analytical and nominal concentrations.

Determination of Particle Size:

Samples were taken twice during exposure using an Andersen cascade impactor.

Results:

Body Weights: Females lost weight at all 3 levels.

Signs of Toxicity: hypoactivity, chromodacryorrhea, diarrhea, nasal discharge, polyuria, ptosis and salivation.

Mortality:

REPORTED MORTALITY

DOSE MG/L	Animals Killed/Animals Tested		
	Males	Females	Combined
1.20	0/5	0/5	0/5
1.31	1/5	2/5	3/10
1.84	3/5	2/5	5/10

DATA EVALUATION RECORD EYE IRRITATION TOXICITY TESTING (§81-4)

Product Manager (PM): 22 EPA Reg. No.: 55146-AU

Reviewer: David L. Ritter, Toxicologist DLR 8-2493

MRID No.: 428718-04

Testing Laboratory: Stillmeadow, Inc.
12852 Park One Drive
Sugar Land TX 77478

Title Of Report: Primary Eye Irritation Study in Rabbits

Date of Report: 6/7/93

Laboratory Number: 0126-93

Author(s): Janice O. Kuhn, Ph.D.

Quality Assurance (40 CFR, Section 160.12): Acceptable.

Species: New Zealand White Rabbit

Sex: 3M + 3F, 3F for washed eyes.

Wt.: Not weighed

Test Material: Champ Plus Flowable Copper Hydroxide (undiluted)

Dosage: 0.1 ml in right lower eyelid.

Quality Assurance 40 CFR 160.12): Acceptable

Summary:

Toxicity Category: III; corneal involvement or irritation cleared by day 7.

CORE Classification: Guideline

Procedure:

Standard laboratory animal husbandry procedures were followed.

Animals were pre-examined with sodium fluorescein solution to determine suitability for testing.

0.1 ml undiluted Test Article was instilled into the lower right eyelid.

Three females were similarly treated and their eyes were washed with room temperature deionizd water for one minute thirty seconds after exposure.

All treated eyes were examined for injury at 1, 24, 48 and 72 hours, and on days 4, 7 and 10 and scored according to Draize.

All treated eyes were washed with deionized water for one minute following the 24 hour observation period.

Results:

Those animals whose treated eyes were washed showed no effects after the first hour for the remainder of the study.

OBSERVATIONS ON UNWASHED EYES

Effects on Eyes	Observations Eyes affected/Eyes tested							
	Hour	Days						
	1	1	2	3	4	7	10	21
Corneal Opacity	0/6	0/6	0/6	0/6	0/6	0/6	0/6	
Iris	0/6	0/6	0/6	0/6	0/6	0/6	0/6	
Conjunctivae								
Redness	6/6	6/6	5/6	3/6	2/6	0/6	0/6	
Chemosis	2/6	6/6	0/6	0/6	0/6	0/6	0/6	
Discharge								

-11

DATA EVALUATION RECORD DERMAL IRRITATION TOXICITY TESTING (§81-5)

Product Manager (PM): 22 EPA Reg. No.: 55146-AU

Reviewer: David L. Ritter, Toxicologist DLR 8-24-93

MRID No.: 428718-05

Testing Laboratory: Stillmeadow, Inc.
12852 Park One Drive
Sugar Land TX 77478

Title Of Report: Dermal Irritation Study in Rabbits

Date of Report: 5/27/93

Lab. No.: 0127-93

Author(s): Janice O. Kuhn, Ph.D.

Quality Assurance (40 CFR, Section 160.12): Acceptable

Species: New Zealand White Rabbit Sex: 3M + 3F
Wt.: Not weighed.

Source: Ray Nichols Rabbitry, Lumberton TX

Test Material: Champ Plus Flowable Copper Hydroxide

Dosage: 0.5 ml undiluted.

Summary:

Toxicity Category: IV CORE Classification: Guideline

PII: 0.25

Procedure:

Standard laboratory animal husbandry procedures were followed.

Animals were prepared by clipping the dorsal area clear of fur one day prior to exposure.

0.5 ml Test Article was introduced under a 2.5 x 2.5 cm gauze pad which was then secured with tape and a semipermeable dressing.

After four hours the dressings were removed and the test sites were cleansed. The sites were observed for dermal irritation and were scored according to Draize at 3/4, 24, 48 and 72 hours after cleansing.

Results:

DERMAL IRRITATION SCOREBOARD

#Rab	Eschar/Erythema					Edema						Score
	Observation times in hours											
	1.0	24	48	72		1.0	24	48	72			
34M	1	0	0	0		0	0	0	0			0.25
58M	1	0	0	0		0	0	0	0			0.25
60M	1	0	0	0		0	0	0	0			0.25
33F	1	0	0	0		0	0	0	0			0.25
35F	1	0	0	0		0	0	0	0			0.25
75F	1	0	0	0		0	0	0	0			0.25

Score = sum of numerical grades/no. observation periods at 1, 24, 48 and 72 hours.

PII = Sum of scores/No. animals = 0.25

Slight < 2.0; Moderate 2 - 5; Severe > 5

Conclusions:

This product is TOX Category IV for dermal irritation in this assay.

13

DATA EVALUATION RECORD DERMAL SENSITIZATION TESTING (§81-6)

Product Manager (PM): 22 EPA Reg. No.: 55146-AU

Reviewer: David L. Ritter, Toxicologist 8-24-93

MRID No.: 428718-06

Testing Laboratory: Stillmeadow, Inc.
12852 Park One Drive
Sugar Land TX 77478

Title Of Report: Dermal Sensitization Study in Guinea Pigs

Date of Report: 6/30/93

Lab. No.: 0128-93

Author(s): Janice O. Kuhn, Ph.D.

Quality Assurance (40 CFR, Section 160.12): Acceptable

Species: Hartley Albino Guinea Pigs

Sex: 10 M + 10 F (2M + 2F range finder test)
Wt.: M: 330 - 365 gm; F: 320 - 390 gm.

Source: SASCO Inc., The Woodlands TX

Test Material: Champ Plus Flowable Copper Hydroxide

Dosage: Induction: 100%; Challenge: 100%

Summary:

CORE Classification: Supplementary. No positive control results were provided although reference is made that positive controls were tested within six months of the test date of this study.

Procedure:

Modified Buehler assay[1].

Standard laboratory animal husbandry and GLP procedures were followed.

Test animals were weighed initially and at termination.

Animals were prepared by clipping the dorsal area clear of fur one day prior to exposure.

[1]Ritz, H.L and E. V. Buehler. Current Concepts in Cutaneous Toxicity. p. 28. Academic Press, NY, 1980.

Test Article was applied under 3.8 x 5 cm gauze pad secured by a Coverlet adhesive dressing which was then wrapped in polyethylene film. Animals were restrained for ca. six hours. The dressings were then removed and the application sites were evaluated for dermal reaction at 24 hours after each application, and 48 hours after the first induction application and 48 hours after challenge treatment.

Screen Procedure:

2 males and 2 females received 0.4 ml of 100, 50, 20 or 5% Test Article in water at either of two sites.

Induction Phase:

Two groups of 5 males and 5 females each received either no treatment (naive controls) or 0.4 ml undiluted Test Article at each of three weekly treatments.

Challenge Phase:

Two weeks after the third induction treatment all animals received 0.4 ml undiluted Test Article at a virgin application site.

Results:

Body weight-gain was normal.

Screen Procedure:

No animal showed any response to any concentration. Therefore, a 100% concentration was used.

Induction Phase:

No skin reaction was reported.

Challenge Phase:

No skin reaction was reported.

Historical Controls:

Historical control data were not supplied although the laboratory did report that such information was available.

Conclusions:

Without the positive control data we are unable to reach any conclusions as to the results of this study.

-115-

ACUTE TOX ONE-LINER

1. PC CODE: 023401; Copper Hydroxide

2. CURRENT DATE: 8/24/93

3. TEST MATERIAL: Champ Plus Flowable Copper Hydroxide

4. EPA Reg. #: 55146-AU

Study/Species/Lab/ Study#/Date	MRID No.	Results	Tox. Cat.	Core Grade
Acute Oral/Rat/ Stillmeadow/0123-93/ 7-16-93	428718-01	LD_{50} combined = 1697 mg/kg	III	G
Acute Dermal/Rabbit Stillmeadow/0124-93/ 6-9-93	" -02	$LD_{50} \geq$ 2020 mg/kg	III	G
Acute Inhal./Rat/ Stillmeadow/0125-93/ 7-22-93	" -03	LC_{50} (mg/L) combined 1.79 mg/l	III	G
Eye Irr./Rabbit/ Stillmeadow/0126-93/ 6-7-93	" -04	Non-irritating. Clear by day 7.	III	G
Dermal Irr./Rabbit/ Stillmeadow/0127-93/ 5-27-93	" -05	Non-irritating. PII = 0.25. All irritation gone by 24 hours.	IV	G
Dermal Sens./Guinea Pig/Stillmeadow/ 0128-93/6-30-93	" -06	Unable to determine. No positive control data	--	S

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Core Grade Key:

G = Guideline
M = Minimum
S = Supplementary