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

OFFICE OF
PREVENTION,

PESTICIDES

AND
TOXIC

SUBSTANCES

01/MAY/2001

MEMORANDUM

Subject: Name of Pesticide Product: Triangle Brand Copper Sulfate Crystal
EPA Reg. No.: 1278-8
DP Barcode: D273334
Case No: 024606
PC Code: 024401

From: Eugenia McAndrew, Biologist
Technical Review Branch
Registration Division (7505C)

To: C.P. Moran, PM Team 22
Fungicide Branch
Registration Division (7505C)

Applicant: Phelps Dodge Refining Corporation
P.O. Box 20001
El Paso, Texas 79998

FORMULATION FROM LABEL:

	Active Ingredient(s):	% by wt.
024401	Copper Sulfate Pentahydrate	99.0
	Inert Ingredient(s):	1.0
	Total:	100.00%

ACTION REQUESTED: PM requests review of acute toxicity data for EPA Reg. No. 1278-8.

BACKGROUND: Phelps Dodge Refining Corporation has submitted five acute toxicity studies in support of registration of EPA Reg. No. 1278-8, Triangle Brand Copper Sulfate Crystal. The studies submitted are acute oral, acute dermal, primary eye irritation, primary dermal irritation and dermal sensitization with assigned MRID numbers 453397-01 to - 05. The studies were conducted at Stillmeadow, Inc., Sugar Land, Texas. The registrant indicates that until now it has been "relying on acute toxicity data purchased nearly 20 years ago from another manufacturer" to support both Triangle Brand Copper Sulfate Crystal and Triangle Brand Copper Sulfate Instant Powder, EPA Reg. No. 1278-5. These two products are substantially similar, both containing 99% copper sulfate pentahydrate. An acute inhalation toxicity study (MRID 431470-01) was submitted for 1278-8 in 1994 and classified as toxicity category IV in an Agency memo dated March 20, 1995.

RECOMMENDATIONS: The five studies have been reviewed and are classified as acceptable. The acute inhalation toxicity study previously submitted may be used to support registration of this product.

The acute toxicity profile for EPA Reg. No. 1278-8, Triangle Brand Copper Sulfate Crystal, is as follows:

acute oral toxicity	II	Acceptable	MRID 453397-01
acute dermal toxicity	IV	Acceptable	MRID 453397-02
acute inhalation toxicity	IV	Cited	MRID 431470-01
primary eye irritation	I	Acceptable	MRID 453397-03
primary skin irritation	IV	Acceptable	MRID 453397-04
dermal sensitization	No	Acceptable	MRID 453397-05

LABELING: Based on the toxicity profile above, the following are the precautionary and first aid statements for this product as obtained from the Label Review System.

ID #: 001278-00008 COPPER SULFATE ALGICIDE-HERBICIDE

RESTRICTED USE CLASSIFICATION RECOMMENDED:

Due to eye irritation toxicity category.

The PM Team should decide if restricted use classification is necessary or if alternative labeling will allay the requirement for restricted use classification.

AGRICULTURAL USE REQUIREMENTS:

DIRECTIONS FOR USE:

For early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil, or water, wear: coveralls over long-sleeved shirt and long pants, socks, shoes goggles or face shield and waterproof gloves.

SIGNAL WORD: DANGER PELIGRO

PRECAUTIONARY STATEMENTS:

Corrosive. Causes irreversible eye damage. May be fatal if swallowed. Do not get in eyes or on clothing. Wear long-sleeved shirt and long pants, socks and shoes and goggles or face shield.

STATEMENT OF PRACTICAL TREATMENT (SOPT):

IF SWALLOWED: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to by a poison control center or doctor. Do not give anything by mouth to an unconscious person.

IF IN EYES: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN:

Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician." The following statements are suggested types of information that may be included, if applicable:

- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

The following "Note to Physician" statement is required for the subject product:

NOTE TO PHYSICIAN: Probable mucosal damage may contraindicate the use of gastric lavage.

USER SAFETY RECOMMENDATIONS:

Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet. Remove contaminated clothing and wash clothing before reuse.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (870.1100)

Product Manager: 22 **Reviewer:** Eugenia McAndrew

CITATION: Kuhn, J. (2001) Triangle Brand Copper Sulfate Crystal; acute oral toxicity in rats. Stillmeadow, Inc., Sugar Land, Texas. Laboratory Report Number 6142-00. February 13, 2001. MRID 453397-01. Unpublished.

SPONSOR: Phelps Dodge Refining Corporation, P.O. Box 20001, El Paso, Texas 79998

EXECUTIVE SUMMARY: In an acute oral toxicity study, five young adult albino Sprague-Dawley rats/sex (Weight: 201-298 g males; 155-199 g females; Source: Texas Animal Specialties, Humble, TX) were given a single oral dose of Triangle Brand Copper Sulfate Fine Diamond Crystal (99.22% Copper Sulfate Pentahydrate; Lot # 12/13/00; blue crystals) at 200 mg/kg, 500 mg/kg and 5050 mg/kg. The test substance was ground and mixed with deionized water to produce a 25% w/v concentration. Animals were observed for clinical signs of toxicity and mortality for 14 days post dosing.

Oral LD_{50} Males = 462 mg/kg (95% C.L. 406-521 mg/kg); Oral LD_{50} Females = 246 mg/kg (95% C.L. 173-308 mg/kg); Combined Oral LD_{50} = 352 mg/kg (95% C.L. 291-437 mg/kg). All values were calculated by a computer program utilizing probit analysis.

Triangle Brand Copper Sulfate Crystal is classified as Toxicity Category II based on the calculated LD_{50} value in the both sexes.

At 200 mg/kg, two females died on day 1; all males survived and gained weight during the study. Clinical signs noted were diarrhea, activity decrease, respiratory gurgle, walking on tiptoe, dark brown urine, red ocular discharge, ataxia, hunched posture, polyuria, piloerection, crusted muzzle and dark/small feces. The surviving animals recovered from these symptoms by day 3 and except for one female gained weight. At necropsy, no gross abnormalities were noted for the surviving animals; the two decedents had muzzle fur matted, lungs mottled, blue liquid in stomach, blue/green slurry in small intestine and large intestine empty.

At 500 mg/kg, three animals died within two hours and two within four hours following test substance administration and two died on day 1. Clinical signs noted were activity decrease, diarrhea, salivation, piloerection, muzzle stained red, small/dark feces, emaciation, polyuria and crust around the eyes. The surviving animals recovered from these symptoms by day 11 and gained weight. At necropsy, findings in the surviving animals included lungs pale with red spots, yellow slurry in stomach, liver herniated through diaphragm, small intestine empty and dark green solid in large intestine. Findings in the decedents included muzzle fur matted and blue, lungs pale with red spots, liver mottled, gas and blue liquid in stomach, blue/green gel in small intestine and blue gel in large intestine.

At 5050 mg/kg, all animals died within one hour following test substance administration. At necropsy, findings included face stained blue, blue patches on lungs, blue fluid in stomach and small intestine, gas and/or green paste in large intestine.

This study is classified as Acceptable (870.1100) and satisfies the guideline requirement for an acute oral study in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (870.1200)

Product Manager: 22 **Reviewer:** Eugenia McAndrew

CITATION: Kuhn, J. (2001) Triangle Brand Copper Sulfate Crystal; acute dermal toxicity in rabbits. Stillmeadow, Inc., Sugar Land, Texas. Laboratory Report Number 6143-00. February 13, 2001. MRID 453397-02. Unpublished.

SPONSOR: Phelps Dodge Refining Corporation, P.O. Box 20001, El Paso, Texas 79998

EXECUTIVE SUMMARY: In an acute dermal toxicity study, five young adult New Zealand White albino rabbits/sex (Weight: 2.8-3.2 kg males; 2.5-2.8 kg females; Source: Ray Nichols Rabbitry, Lumberton, TX) were dermally exposed to a single application of Triangle Brand Copper Sulfate Fine Diamond Crystal (99.22% Copper Sulfate Pentahydrate; Lot # 12/13/00; blue crystals) at 5050 mg/kg for 24 hours. The test substance was moistened with distilled water (0.3 mL/g of test substance) and applied to > 10% of the total body surface area. Animals were observed for clinical signs of toxicity and mortality three times on the day of dosing and once daily for 14 days.

Dermal LD_{50} Males = > 5050 mg/kg (observed); Dermal LD_{50} Females = > 5050 mg/kg (observed)

Triangle Brand Copper Sulfate Crystal is classified as Toxicity Category IV based on the observed LD_{50} values in both sexes.

All animals survived. Three animals did not gain weight during the first week but by the end of the second week all animals gained weight. Clinical signs included no defecation in two animals, decreased defecation in two animals and diarrhea in one animal. All animals recovered from these signs by day 11. Very slight erythema was noted at 4/10 test sites on day 1, resolving by day 7. At necropsy, findings included pale/mottled lungs in three animals and no gross abnormalities in the other seven animals.

This study is classified as Acceptable (870.1200) and satisfies the guideline requirement for an acute dermal study in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

DATA REVIEW FOR PRIMARY EYE IRRITATION TESTING (870.2400)

Product Manager: 22 **Reviewer:** Eugenia McAndrew

CITATION: Kuhn, J. (2001) Triangle Brand Copper Sulfate Crystal; acute eye irritation in rabbits. Stillmeadow, Inc., Sugar Land, Texas. Laboratory Report Number 6144-00. February 12, 2001. MRID 453397-03. Unpublished.

SPONSOR: Phelps Dodge Refining Corporation, P.O. Box 20001, El Paso, Texas 79998

EXECUTIVE SUMMARY: In a primary eye irritation study, a 0.125 mg portion (0.1 mL equivalent) of Triangle Brand Copper Sulfate Fine Diamond Crystal (99.22% Copper Sulfate Pentahydrate; Lot # 12/13/00; blue crystals) was placed into the conjunctival sac of the right eye of three young adult New Zealand White albino rabbits (1 male and 2 female; Source: Ray Nichols Rabbitry, Lumberton, TX). All animals were observed for ocular irritation at 1, 24, 48 and 72 hours and at 4,7,10, 14, 17 and 21 days post-installation.

Triangle Brand Copper Sulfate Crystal is classified as Toxicity Category I based on the severe ocular irritation persisting through day 21.

Corneal opacity and conjunctivitis were present in 3/3 eyes one hour after installation. The corneal opacity persisted in all three eyes until day 17. At the end of the study on day 21, corneal opacity was still present in one eye. The conjunctivitis was present in 3/3 eyes until day 14 and was still present in one eye on day 21. Necrosis or ulceration of the conjunctivae was present in all eyes from 48 hours after installation to day 14 and persisted in one eye through day 21.

This study is classified as Acceptable (870.2400) and satisfies the guideline requirement for a primary eye irritation study in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

DATA REVIEW FOR PRIMARY DERMAL IRRITATION TESTING (870.2500)

Product Manager: 22 **Reviewer:** Eugenia McAndrew

CITATION: Kuhn, J. (2001) Triangle Brand Copper Sulfate Crystal; acute dermal irritation in rabbits. Stillmeadow, Inc., Sugar Land, Texas. Laboratory Report Number 6145-00. February 12, 2001. MRID 453397-04. Unpublished.

SPONSOR: Phelps Dodge Refining Corporation, P.O. Box 20001, El Paso, Texas 79998

EXECUTIVE SUMMARY: In a primary skin irritation study, three young adult New Zealand White albino rabbits (1 male and 2 female; Source: Ray Nichols Rabbitry, Lumberton, TX) were dermally exposed to 0.5 g of Triangle Brand Copper Sulfate Fine Diamond Crystal (99.22% Copper Sulfate Pentahydrate; Lot # 12/13/00; blue crystals) for 4 hours. The test substance was moistened with 0.15 mL of deionized water and then applied to a single 6 cm^2 intact dose site on each animal. Animals were observed 1, 24, 48 and 72 hours after patch removal.

Triangle Brand Copper Sulfate Crystal is classified as Toxicity Category IV based on the resolution of dermal irritation by the 24-hour scoring.

Primary Dermal Irritation Index (PDII) = 0.25 Very slight erythema was present at 3/3 test sites one hour after patch removal. No other dermal irritation was noted. All animals were free of irritation by 24 hours.

This study is classified as Acceptable (870.2500) and satisfies the guideline requirement for an primary skin irritation study in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (870.2600)

Product Manager: 22 **Reviewer:** Eugenia McAndrew

CITATION: Kuhn, J. (2001) Triangle Brand Copper Sulfate Crystal; skin sensitization in guinea pigs. Stillmeadow, Inc., Sugar Land, Texas. Laboratory Report Number 6146-00. February 13, 2001. MRID 453397-05. Unpublished.

SPONSOR: Phelps Dodge Refining Corporation, P.O. Box 20001, El Paso, Texas 79998

EXECUTIVE SUMMARY: In a dermal sensitization study conducted with Triangle Brand Copper Sulfate Fine Diamond Crystal (99.22% Copper Sulfate Pentahydrate; Lot # 12/13/00; blue crystals), 30 young adult male and female Hartley albino guinea pigs (Source: Charles River Laboratories, Wilmington, MA) were tested using methods based on those derived by Buehler. Preliminary testing was conducted to determine the correct concentrations for induction and challenge. Twenty test animals were induced with three applications (six hours/exposure, once per week for three weeks) of 400 mg of test substance moistened with 0.15 mL of deionized water. Twenty-eight days after the first induction dose, 400 mg of test substance moistened with 0.15 mL of deionized water was applied to the twenty test guinea pigs and to ten naive control guinea pigs for a six-hour challenge exposure. Reactions were scored 24 and 48 hours after each induction and after the challenge. An additional 20 animals were tested with 1-Chloro-2, 4-Dinitrobenzene (DNCB) within six months of the main study to serve as positive controls.

Triangle Brand Copper Sulfate Crystal is classified as a non-sensitizer based on the results of this study.

Very slight erythema was noted at one test animal site during the induction phase. No dermal irritation was observed 24 or 48 hours following a single challenge exposure with the test substance to either previously induced or control animals. The positive response observed in the DNCB study validates the test system used in this study.

This study is classified as Acceptable (870.2600) and satisfies the guideline requirement for an dermal sensitization study in the guinea pig.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D273334
2. **PC CODE:** 024401
3. **CURRENT DATE:** 01/MAY/2001
4. **TEST MATERIAL:** Triangle Brand Copper Sulfate Fine Diamond Crystal (99.22% Copper Sulfate Pentahydrate; Lot # 12/13/00; blue crystals)

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat Stillmeadow, Inc. 6142-00/2-13-2001	453397-01	LD_{50} = 462 mg/kg (males) = 246 mg/kg (females) = 352 mg/kg (combined)	II	A
Acute dermal toxicity/rabbit Stillmeadow, Inc. 6143-00/2-13-2001	453397-02	LD_{50} > 5050 mg/kg (males females combined)	IV	A
Primary eye irritation/rabbit Stillmeadow, Inc. 6144-00/2-12-2001	453397-03	Severe irritant. Corneal opacity in 3/3 eyes through day 14 persisting in one eye through day 21. Conjunctivitis in 3/3 eyes through day 10 persisting in one eye through day 21.	I	A
Primary dermal irritation/rabbit Stillmeadow, Inc. 6145-00/2-12-2001	453397-04	Very slight erythema at 3/3 sites at one hour. No dermal irritation at 72 hours.	IV	A
Dermal sensitization/guinea pig Stillmeadow, Inc. 6146-00/2-13-2001	453397-05	Not a sensitizer	–	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated**