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

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DATE: May 19, 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT 1,2-BENZISOTHIAZOLIN-3-ONE [*Proxel Press Paste*]: Review of Acute Toxicity Studies.

FROM: Jess Rowland, M.S, Toxicologist, 5/19/94
Section II, Toxicology Branch II, Health Effects Division (7509C)

TO: Tom Myers / Yvonne Brown
Product Manager (51), Reregistration Division

THRU: K. Clark Swentzel, Head 5/19/94
Section II, Toxicology Branch II, Health Effects Division (7509C)
and
for Marcia van Gemert, Ph.D., Chief, 5/20/94
Toxicology Branch II, Health Effects Division (H7509C)

TASK IDENTIFICATIONS: Submission: S449585 DP Barcode: D195625
PC Code: 098901 MRID No(s): 429051-01; -02; -03

REGISTRANT: Zeneca inc, Wilmington, DE

ACTION REQUESTED: Review of acute toxicity studies with *Proxel Press Paste].*

RESPONSE: A Data Evaluation Report is attached for each study identified above [MRID No(s) 429051-01; -02; -03. The results, toxicity categories, and Core classifications are tabulated below. The Primary Eye Irritation and the Primary Dermal Irritation studies satisfy the guideline requirements § 81-4 and § 81-5, respectively, and are acceptable for regulatory purposes. A waiver is granted for an Acute Inhalation Toxicity Study [81-3] when the test material is used as the Manufacturing Use Product [i.e, the powder form]. Any aqueous based formulations made with the MP [i.e, the End-Use Products] must be tested as an aerosol to determine if an inhalation hazard exists.

Study Type	MRID No.	Results	Toxicity Category	Core Classification
Primary Eye	429051-02	Severe irritant	I	Minimum
Primary Dermal	429051-01	Slight irritant	IV	Minimum

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PRIMARY REVIEWER: Jess Rowland, M.S, Toxicologist
Section II, Toxicology Branch II

SECONDARY REVIEWER: K. Clark Swentzel, Head
Section II, Toxicology Branch II

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DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation **GUIDELINE:** § 81-3

PC CODE: 098901 **MRID No.** 429051-03

TEST MATERIAL: 1,2-Benzisothiazolin-3-one

SYNONYMS: *Proxel Press Paste*

REGISTRANT: Zeneca Inc

TESTING LABORATORY: Zeneca Central Toxicology Laboratory

STUDY IDENTIFICATION: TZ0258

TITLE OF REPORT: *"PROXEL PRESS PASTE: ASSESSMENT OF APPARENT AERODYNAMIC PARTICLE SIZE BY AIR ELUTRIATION"*

AUTHOR: R. J. Parr-Dobrzanski

REPORT DATE: May 26, 1993

EXECUTIVE SUMMARY: The Registrant requested a data waiver for an acute inhalation study based on the rationale that the test material has limited potential for penetrating an inhalation hazard from fine particles. An assessment of aerodynamic particle size distribution by air elutriation showed that only a small proportion of the test material [1.56%] had an Aerodynamic Equivalent Diameter [AED] of < 15 μM which is capable of penetrating to the lower regions of the respiratory tract. In contrast, a significant proportion of the test material [34.23% < 115 μM AED] become air borne indicating that if suspended in air and inhaled, any material which entered the respiratory tract would deposit in the nasopharyngeal region. From here, clearance to the gastrointestinal tract would probably be rapid.

Since the test material [Proxel Press Paste] is a manufacturing use product and the percentage of particles less than 15 μM is 1.56, a waiver is granted for an acute inhalation toxicity study [81-3] with "Proxel Press Paste" as a Manufacturing use Product [i.e., powder form]. However, any of the aqueous based formulations, EPs] made with the test material [i.e. End-Use Products], would have to be tested as an aerosol to determine if an inhalation hazard exists.

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I. INTRODUCTION

This Data Evaluation Report (DER) summarizes the experimental procedures and results of an assessment of aerodynamic particle size distribution by air elutriation. This study was conducted to determine the airborne hazard likely to be associated with the material in powder form.

II. MATERIALS AND METHODS

1. Test Material

Chemical Name:	1,2-benzisothiazolin-3-one
Common Name:	Proxel Press Paste
Active Ingredient:	74.3%
Batch/Lot No.	BX228
Description:	Yellow-brown moist powder

2. Test Method

Air Elutriation: A vertical elutriator was set up containing approximately 30 g Proxel Press Paste. The quantities of test material eluted from the starting material at a range of air velocities (corresponding to an appropriate range of setting velocities and hence AED), was measured on duplicate samples, allowing 30 minutes agitation at each velocity. The average of the two sets of particle size data and the corresponding cumulative size distribution was calculated.

III. RESULTS

The results derived from the mean of the two measurements taken using the elutriator are tabulated below:

AED (μM)	Weight Loss [%]		Mean Weight Loss [%]	Mean Cumulative Loss [%]
	Sample 1	Sample 2		
<15	1.56	1.56	1.56	1.56
<35	4.07	3.70	3.89	5.45
<50	0.00	1.23	0.62	6.06
<75	1.99	0.45	1.22	7.29
<115	32.00	21.90	26.95	34.23

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IV. DISCUSSION

The data shows that only a small proportion [1.56%] of the test material with an AED of < 15 μM; particles of this size range being considered capable of penetrating to the lower regions of the respiratory tract. Data also showed that a significant portion [34.23%] with AED of < 115 μM, indicating that if suspended in air and inhaled, any material which enter the respiratory tract would deposit in the nasopharyngeal region from where clearance to the gastrointestinal tract would probably be rapid.

V. CONCLUSIONS

Since the test material [Proxel Press Paste] is a manufacturing use product and the percentage of particles less than 15 μM is 1.56, a waiver is granted for an acute inhalation toxicity [81-3] with "Proxel Press Paste" as the Manufacturing use Product [powder form]. However, any of the aqueous based formulations [i.e., End-Use Products] made with the test material, would have to be tested as an aerosol to determine if an inhalation hazard exists.

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DATA EVALUATION REPORT

Proxel Press Paste

Study Type: Primary Eye Irritation in Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

Principal Reviewer	Eileen Abt, M.S.	Date 4/28/94
Independent Reviewer	Carrie Rabe, Ph.D.	Date 4/28/94
QA Reviewer	William McLellan Ph.D.	Date 4/28/94

Contract Number: 68D10075
Work Assignment Number: 3-55
Clement Number: 236
Project Officer: Caroline Gordon

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Proxel Press Paste Guideline Series 81-4: Primary Eye Irritation

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EPA Reviewer: Jess Rowland, M.S. Signature:
Review Section II, Toxicology Branch II (7509C) Date: 5/19/94

EPA Section Head: K. Clark Swentzel Signature:
Review Section II, Toxicology Branch II (7509C) Date: 5/19/94

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation - rabbits (81-4)

EPA IDENTIFICATION NUMBERS

Tox Chem. Number:

MRID Number: 429051-02

PC Number: 098901

TEST MATERIAL: Proxel press paste

SYNONYM(S): None provided

SPONSOR: ZENECA Specialties, Wilmington, Delaware

STUDY NUMBER: FB4704

TESTING FACILITY: ZENECA Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK

TITLE OF REPORT: "Proxel Press Paste: Eye Irritation to the Rabbit"

AUTHOR: P. Robinson

REPORT ISSUED: May 17, 1993

EXECUTIVE SUMMARY: In a primary eye irritation study, Proximal press paste (10 or 100 mg), a bactericide, was placed into the conjunctival sac of the left eyes of New Zealand White rabbits [1 male/dose]. The right eye of each animal served as the untreated control. Administration of 10 mg of test material produced slight discharge, slight to moderate redness, and slight to mild chemosis of the conjunctiva, which persisted up to day 4. Application of 100 mg of test material produced severe conjunctival irritation, swelling, and rupture within 3 hours. Humane sacrifice and autopsy of the animal treated with 100 mg of the test material revealed mild corneal opacity and slight iritis.

The results of this study determined that Proxel press paste was an extremely severe eye irritant, placing it in TOXICITY CATEGORY: I.

CORE CLASSIFICATION: Minimum; this study satisfies the guideline requirement [§ 81-4] for a primary eye irritation study in rabbits.

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A. MATERIALS

Test Compound

Test material: Proxel press paste
Batch number: BX228
Active ingredient: 1,2-benzisothiazolin-3-one
Purity: 74.3% w/w 1,2-benzisothiazolin-3-one
Physical description: Brown, moist powder
Storage condition: Not reported
Stability: Reported as being stable by sponsor
Vehicle: None
Dose levels: 10 mg; 100 mg

Test Animals

Species: Rabbit
Strain: New Zealand White
Source: Conventional Animal Breeding Unit, Alderley Park, Macclesfield, Cheshire, UK
Number and sex of animals: 2 males
Age: Young adults
Body weight: 3937 g (low volume application); 4089 g (high volume application)
Temperature: 17±2°C (target range)
Relative humidity: 55±15% (target range)
Photoperiod: 12 hours
Air Changes: 25-30/hour
Food: BELKAY Rabbit Maintenance Diet; *ad libitum*
Water: Tapwater, *ad libitum*
Identification: Label on inner side of one ear and cage cards
Selection: Only rabbits without any apparent eye defects or ocular irritation were used
Housing: Individual
Acclimation: Minimum of 6 days

B. TEST PERFORMANCE

Pretest Eye Examination

Eyes were examined with fluorescein stain within 24 hours prior to the start of the study.

Test Material Application

Approximately 10 mg of the test sample was placed in the conjunctival sac of the left eye of one animal. The lids were then held together for 1-2 seconds, after which the animal was released. The right eye of the animal served as the untreated control. About one week later, another animal was dosed in a similar manner with a 100 mg application of test material.

Observation Period

Immediately after the application, an assessment of the initial pain reaction was made. Ocular reaction was assessed 1-3 hours and 1, 2, 3, 4, and 11 days after application.

Scoring System: Initial pain evaluation was based on six-point scale (0-5). Eyes were scored for corneal opacity, iridial effects, conjunctival redness, chemosis, and discharge using the Draize scoring system. Fluorescein staining also was used to assess corneal damage.

C. REPORTED RESULTS

A summary of ocular effects is presented in the tables below:

Eye Irritation Scores in the Rabbit Treated with 10 mg[a]

	Observation Intervals					
	Hours		Days			
	1.3	1	2	3	4	11
Cornea						
Opacity	0	0	0	0	0	0
Iris	0	0	0	0	0	0
Conjunctivae						
Redness	1	2	2	1	1	0
Chemosis	2	1	1	0	0	0
Discharge	1	1	1	0	0	0

[a] The following grades for each tissue are considered positive:

Opacity (Density) - Grades 1, 2, 3, and 4
Iris - Grades 1 and 2
Conjunctivae (Redness) - Grades 1 and 2
(Chemosis) - Grades 2, 3, and 4
(Discharge) - Grades 2 and 3

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Eye Irritation Scores in the Rabbit Treated with 100 mg[a]

	Observation Intervals[b]	
	Hours	
	1.5	2.9
Cornea		
Opacity	-[c]	2
Iris	-[c]	1
Conjunctivae		
Redness	3	3
Chemosis	4	4
Discharge	3	3

[a] The following grades for each tissue are considered positive:

Opacity (Density) - Grades 1, 2, 3, and 4
Iris - Grades 1 and 2
Conjunctivae (Redness) - Grades 1 and 2
(Chemosis) - Grades 2, 3, and 4
(Discharge) - Grades 2 and 3

[b] This animal was sacrificed after 2.9 hours; corneal and iridial observations were made at autopsy.

[c] Unable to assess due to severe chemosis scores.

Administration of 10 mg of the test material produced moderate initial pain. No corneal or iridial effects were observed Conjunctival effects included slight to moderate redness, slight to mild chemosis, and slight discharge. Chemosis and discharge were observed up to day 2, while redness persisted until day 4. Other observations included erythema, mucoid discharge, hemorrhaging of nictitating membrane, and superficial erosion of the corneal epithelium.

Application of 100 mg of test material also caused moderate initial pain. Corneal and iridial effects could not be assessed at 1.5 hours because of severe swelling of the conjunctival sac. Other conjunctival effects included severe redness, chemosis, and severe discharge. After about 3 hours, the degree of conjunctival swelling increased and resulted in the rupturing of the conjunctival sac. The severe redness and discharge persisted. The animal was removed from the study and sacrificed. Autopsy findings revealed mild corneal opacity affecting the whole cornea and slight iritis. Additional signs of irritation included erythema on

the eyelids, hemorrhaging of the nictitating membrane, constricted pupil, and red staining around the eye.

Based on these findings, Proxel press paste is classified as Toxicity Category I (Danger).

D. REVIEWERS' COMMENTS

Proxel press paste was severely irritating to rabbit eyes under these study conditions. This corresponds to Toxicity Category I (Danger).

E. DEFICIENCIES

The guidelines (81-4) recommend that at least 6 animals be used. Only one animal was used at each dose level. Nevertheless, this study clearly identifies the severe eye irritation caused by the test material, and therefore is classified Acceptable for regulatory purposes.

F. QUALITY ASSURANCE

The test was performed under Good Laboratory Practice standards. A quality assurance statement, signed May 13, 1993, was provided.

FINAL

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DATA EVALUATION REPORT

Proxel Press Paste

Study Type: Primary Dermal Irritation in Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

Principal Reviewer: Eileen Abt — Eileen Abt, M.S. — Date 4/29/94

Independent Reviewer: Carrie Rabe — Carrie Rabe, Ph.D. — Date 4/28/94

QA Reviewer: William McLellan — William McLellan, Ph.D. — Date 4/28/94

Contract Number: 68D10075
Work Assignment Number: 3-55
Clement Number: 235
Project Officer: Caroline Gordon

Proxel Press Paste Guideline Series 81-5: Primary Dermal Irritation

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EPA Reviewer: Jess Rowland, M.S. Signature: Jess Rowland
Review Section II, Toxicology Branch II (7509C) Date: 5/13/94

EPA Section Head: K. Clark Swentzel Signature: K. Clark Swentzel
Review Section II, Toxicology Branch II (7509C) Date: 5/17/94

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation - rabbits (81-5)

EPA IDENTIFICATION NUMBERS

Tox Chem. Number:

MRID Number: 429051-01

PC Number: 098901

TEST MATERIAL: Proxel press paste

SYNONYM(S): Not reported

SPONSOR: ZENECA Specialties, Wilmington, Delaware

STUDY NUMBER: EB4147

TESTING FACILITY: Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK

TITLE OF REPORT: "Proxel Press Paste: Skin Irritation to the Rabbit"

AUTHOR: P. Robinson

REPORT ISSUED: May 17, 1993

EXECUTIVE SUMMARY: In a primary dermal irritation study, New Zealand white rabbits [6 males] were treated with 500 mg Proximal press paste, a bactericide containing 74.3% w/w 1,2-benzisothiazolin-3-one, moistened with 0.5 mL deionized water, on shaved skin for 4 hours. All animals exhibited very slight to well-defined erythema, and 5 of 6 rabbits exhibited very slight edema within 30-60 minutes of removal of the dressings. Slight erythema persisted in 3 rabbits until observation day 3, while very slight edema persisted in 1 animal for 3 days. The overall mean erythema and edema scores were 0.8 and 0.3, respectively. Proximal press paint was shown to be a slight irritant to the rabbit skin.

The results of this study determined that Proximal press paste was a slight irritant, placing it in TOXICITY CATEGORY: IV.

CORE CLASSIFICATION: Minimum; this study satisfies the guideline requirement [§ 81-5] for a primary dermal irritation study in rabbits.

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A. MATERIALS

Test Compound

Test material: Proxel press paste
Sample reference: EX228
Purity: 74.3% w/w 1,2-benzisothiazolin-3-one
Physical description: Brown, moist powder
Storage condition: Not reported
Stability: Reported as being stable by sponsor

Test Animals

Species: Rabbit
Strain: New Zealand White
Source: Conventional Animal Breeding Unit, Alderley Park, Macclesfield, Cheshire, UK
Number of animals: 6
Sex: Male
Age: Young adult
Body weight: 3587-4825 g (at beginning of study)
Temperature: 17±2°C (target range)
Relative humidity: 55±15% (target range)
Photoperiod: 12 hours
Air Changes: 25-30/hour
Housing: Individual
Feeding: BEEKAY Rabbit Maintenance Diet, *ad libitum*
Water: Tapwater, *ad libitum*
Identification: Labelled on inner side of one ear and cage cards
Selection: Not reported
Acclimation: Minimum of 6 days

B. TEST PERFORMANCE

Skin Preparation
Approximately twenty-four hours prior to testing, the hair on the left flank of each animal was clipped (7 cm x 13 cm) with veterinary clippers.

Test Material Application
Approximately 500 mg of the test material was moistened with 0.5 mL of deionized water, applied to a 2.5 square centimeter area of the left flank with a metal spatula, and held in contact with the test site using surgical gauze, surgical tape, and impermeable rubber sheeting. After 4 hours of exposure, the dressings were removed, and the test site was wiped with cotton wool soaked in warm water and dried with tissue paper to remove residual test material. The application site was identified using a black waterproof marker-pen.

Observation Period: 30-60 minutes and 1, 2, 3, and 4 (3 animals only) days after removal of the dressings

Scoring System

Application sites were examined, and reactions at each site were scored for erythema and edema using the Draize scale. Any other signs of skin irritation also were noted.

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C. REPORTED RESULTS

A summary of the irritation scores is presented in the table below.

Mean Skin Irritation Scores

	Time					
	Minutes	Days				
	30-60	1	2	3	4	Overall
Erythema Mean Score	1.3	1.0	1.0	0.5	0.0	0.8
Edema Mean Score	0.8	0.3	0.3	0.2	0.0	0.3

Very slight to well-defined erythema was observed in all rabbits within 30-60 minutes following removal of the dressings and persisted in 3 animals through day 3. Very slight edema also was observed in 5 of 6 rabbits within 30-60 minutes after removal of the dressings and persisted in 1 animal for 3 days. No other signs of irritation were observed. The overall mean erythema and mean edema scores (determined by averaging the individual scores from observation days 1, 2, and 3) were 0.8 and 0.3, respectively, indicating that the compound is a slight irritant.

On this basis, Proxel press paste was classified as Toxicity Category IV (Caution).

D. REVIEWERS' COMMENTS

Proxel press paste was slightly irritating to rabbit skin under these study conditions.

E. QUALITY ASSURANCE

The test was performed under Good Laboratory Practice standards. A quality assurance statement, signed May 13, 1993, was provided.