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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Reference:	DP Barcode D215036
Subject:	EPA File Symbol: 000264-EUP-OO
Chemical:	123000 (Isoxaflutole, RPA 201772)
Test Material:	EXP31130A, 75% Water Dispersible Granule
From:	S.E. Oonnithan 6/13/95 Precautionary Review Section Registration Support Branch (H7505W) Registration Division
To:	Joanne I. Miller, PM 23 Fungicide-Herbicide Branch (H7505C) Registration Division
Applicant:	Rhone-Poulenc Ag Company P.O. Box 12014 Research Triangle Park, NC.

FORMULATION FROM LABEL:

Active Ingredient(s)	% by wt.
RPA 201772 (Isoxaflutole)	75.0
Inert Ingredient(s)	25.0
Total	100.0

BACKGROUND

Rhone-Poulenc Ag Company submitted acute oral toxicity (MRID No. 435732-25), acute dermal toxicity (MRID No. 435732-26), acute inhalation toxicity (MRID No. 435732-27), primary eye irritation (MRID No. 435732-28), primary skin irritation (MRID No. 435732-29), and dermal sensitization (MRID No. 435732-30) studies on RPA 201772 WDG herbicide. The acute toxicity studies were performed by Bushy Run Research Center, Export, PA.

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RECOMMENDATION

1. Acute Oral: Category IV. The submitted study is acceptable.

2. Acute Dermal: Category III. The submitted study is acceptable.

3. Acute Inhalation: Category IV. The submitted study is acceptable.

4. Eye Irritation: Category III. The submitted study is acceptable.

5. Skin Irritation: Category IV. The submitted study is acceptable.

6. Dermal Sensitization: Not a sensitizer. The submitted study is acceptable.

LABELING

The appropriate signal word is **CAUTION.**

Recommended Precautionary Statements

Causes moderate eye irritation. Harmful if absorbed through skin. Avoid contact with skin, eyes, or clothing. Wash thoroughly with soap and water after handling.

Recommended Statements of Practical Treatment

IF IN EYES: Flush eyes with plenty of water. Call a physician if irritation persists.

IF ON SKIN: Wash with plenty of soap and water. Get medical attention.

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

Product Manager: 23
MRID No.: 435732-25
Author: S.M. Christopher
Testing Facility: Bushy Run

Reviewer: S. Oonnithan
Report No.: 94N1402A
Report Date: 07/28/94

Species: Rat, Sprague Dawley
Age: Young adults
Weight: Males 235-260 g; Females 203-233 g
Source: Harlan Sprague Dawley, Inc., Indianapolis, IN.

Test Material: EXP31130A in water (50%; w/v).
Dosage: 1 ml/100 g body wt.

Conclusion:
LD_{50}: **Males:** 5 g/kg; **Females:** 5 g/kg
Combined: 5 g/kg
Tox. Category: IV
Classification: Acceptable

Quality Assurance (40 CFR §160.12): Included
Procedure (Deviations from §81-1): None

Results:

Dosage	Number Dead/Tested		
	Males	Females	Combined
5 g/kg	0/5	0/5	0/10

Symptoms & Gross Necropsy Findings:
The observed signs of toxicity included diarrhea and a brown stain on the perianal fur. All animals gained weight during the observation period. In survivors, no gross lesions were evident at necropsy.

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

Product Manager: 23
MRID No.: 435732-26
Author: S.M. Christopher
Testing Facility: Bushy Run

Reviewer: S. Oonnithan
Report No.: 94N1402B
Report Date: 07/28/94

Species: Rabbit, New Zealand White
Age: Young adult (12-18 weeks)
Weight: Males 2.7-3.0 kg; Females 2.5-3.0 kg
Source: HRP Inc., Denver, PA.

Test Material: EXP31130A
Dosage: 2 g/kg
Test method: The test substance was moistened with water (at the rate of 0.4 ml/g) and applied to the dorsal surface at 81-82 mg/cm^2 surface area. The test area was occluded with a double layer of gauze sheeting, wrapped with polyethylene, and secured with plastic ties or rubber bands.

Conclusion:
LD_{50}: **Males:** >2 g/kg; **Females:** >2 g/kg
Combined: >2 g/kg
Tox. Category: III
Classification: Acceptable

Quality Assurance (40 CFR §160.12): Included
Procedure (Deviations from §81-2): None

Results:

Dosage	Number Dead/Tested		
	Males	Females	Combined
2 g/kg	0/5	0/5	0/10

Symptoms & Gross Necropsy Findings:
Moderate dermal irritation (erythema, edema, and ecchymoses) and a brown chemical residue and stain were observed in all animals for 1-14 days. There were no signs of systemic toxicity, except for rapid breathing. Some animals exhibited a weight loss for up to 7 days, but recovered by 14 days. Necropsy revealed light or bright red lungs, tan kidneys, pitted kidney surface, and red adrenal glands.

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

Product Manager: 23
MRID No.: 435732-27
Author: D.J. Nachreiner
Testing Facility: Bushy Run

Reviewer: S. Oonnithan
Report No.: 94N1401
Report Date: 08/10/94

Species: Rat, Sprague Dawley
Age: Young adult (8 weeks)
Weight: Males 265-275 g; Females 177-190 g
Source: Harlan Sprague Dawley, Inc., Indianapolis, IN.

Test Material: EXP31130A; air-milled by the registrant.
Dosage: 21.0 mg/l (Nominal concentration)
Test Conditions: In a plexiglass/stainless steel rectangular chamber (≈120 liter volume), test animals were exposed in a stainless steel wire mesh cage (5/cage). Chamber concentration was measured 8 times gravimetrically and particle size distribution was measured twice using a cascade impactor. The chamber air flow was maintained at 29.5 l/min (14.8 air exchange/hr).

Conclusion:
LD_{50}: **Males:** >5.26 mg/l; **Females:** >5.26 mg/l
Combined: >5.26 mg/l
Tox. Category: IV
Classification: Acceptable
Quality Assurance (40 CFR §160.12): Included
Procedure (Deviations from §81-3): None

Results:

Exposure Concentration	Number Dead/Tested		
	Males	Females	Combined
5.26 mg/l MMAD = 2.3 μm; GSD = 2.6	0/5	0/5	0/10

The registrant reported that approximately 19% of the dust particles were ≤1 μm and 80% of the dust particles were ≤5 μm, based on particle mass distribution data.

Symptoms & Gross Necropsy Findings:
The clinical signs observed during exposure were blepharospasm and that during post-exposure were perinasal encrustation and unkempt fur. At necropsy one male rat had a dark red punctate color change of the lungs (judged as incidental); no other gross pathologic findings were observed.

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

Product Manager: 23
MRID No.: 435732-28
Author: S.M. Christopher
Testing Facility: Bushy Run

Reviewer: S. Oonnithan
Report No.: 94N1402D
Report Date: 07/27/94

Species: Rabbit, New Zealand White
Age: 12-18 weeks
Weight: 2.0-3.3 kg
Source: HRP Inc., Denver, PA.

Test Material: EXP31130A
Dosage: ≈80 mg; 0.1 ml
Test Conditions: The test substance was ground with a mortar and pestle and 0.1 ml of the powder was placed into the conjunctival sac of one eye. Fluorescein staining was performed on day one and on subsequent examinations.

Summary: Mild irritation cleared in 72 hours.
Tox. Category: III
Classification: Acceptable

Quality Assurance (40 CFR §160.12): Included
Procedure (Deviations from §81-4): None

Results:

Observations		Number "positive"/tested at			
		1 Hr	24 Hrs	48 Hrs	72 Hrs
Cornea Opacity		2/6	0/6	1/6	0/6
Iris		3/6	3/6	0/6	0/6
Conjunctivae:	Redness	1/6	3/6	0/6	0/6
	Chemosis	2/6	1/6	0/6	0/6
	Discharge	6/6	1/6	0/6	0/6

Comments:
Minor corneal irritation was apparent in two animals; in one, the irritation lasted for 48 hours. In three animals, iritis was observed for up to 24 hours. All conjunctival irritation cleared in 48 hours.

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

Product Manager: 23
MRID No.: 435732-29
Author: S.M. Christopher
Testing Facility: Bushy Run

Reviewer: S. Oonnithan
Report No.: 94N1402C
Report Date: 07/27/94

Species: Rabbit, New Zealand White
Age: 12-19 weeks
Weight: 2.0-3.5 kg
Source: HRP Inc., Denver, PA.

Test Material: EXP31130A
Dosage: 0.5 g
Test method: The test substance was moistened with water (0.2 ml/0.5 g) and applied directly to an 1 inch square gauze patch. The patch was placed over the dose site, and secured by adhesive tape. Polyethylene sheeting was wrapped loosely around the trunk and secured.

Summary: Very slight irritation cleared in 7 days.
Tox. Category: IV
Classification: Acceptable

Quality Assurance (40 CFR §160.12): Included
Procedure Deviations from §81-5: None

Results: At 72 hour post-treatment, 1-2 test animals had very slight erythema/edema, which cleared in 7 days.

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

Product Manager: 23
MRID No.: 435732-30
Author: S.M. Christopher
Testing Facility: Bushy Run

Reviewer: S. Oonnithan
Report No.: 94N1403
Report Date: 09/07/94

Species: Guinea Pig, Dunkin Hartley Albino
Age: 6.0-7.5 weeks
Weight: Males: 367-425 g; Females: 402-487 g
Source: HRP Inc., Denver, PA

Test Material: EXP31130A

Summary: The product formulation tested at 40% (w/v) indicated that it is not a sensitizer to guinea pigs.
Classification: Acceptable

Quality Assurance (40 CFR §160.12): Included
Procedure Deviations from §81-6: None

Test Procedure:
The Buehler test was used for this study. Based on a preliminary skin irritation test using 65%, 50%, and 40% (w/v) solutions of the test substance in 0.25% (w/v) aqueous methyl cellulose, the 40% concentration was selected for induction and challenge tests. Even though there was no erythema evident at 24 and 48 hours posttreatment with 40% (w/v) concentration, this dose was picked, because higher concentrations of the test substance caused the non-woven cotton pad (used for loading the test material), to disintegrate and dehydrate during the 6-hour exposure period.

As a positive control, dinitrochlorobenzene (DNCB) was used at 0.3% (w/v) and 0.1% (w/v) concentrations for induction challenge tests, respectively. The DNCB solutions were prepared in 0.25% (w/v) aqueous methyl cellulose. A vehicle control was not included in the test, because of the availability of extensive data at Bushy Run, demonstrating the lack of any skin irritation with 0.25% aqueous methyl cellulose.

Groups of 10 guinea pigs (5 male and 5 female) were used for the tests. Each test animal was subjected to an induction treatment, once a week for three weeks. Following a two week rest period, a single challenge application was made. The test animals were examined at 24 and 48 hours after induction and challenge tests. Two naive control tests were also performed by applying a single application of the challenge dose of the test substance or positive control.

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Results:
Summary of the induction and challenge test.

Observations	Number positive/tested at 24 and 48 hours			
	EXP31130A		DNCB	
Induction 1st Application	1/10	2/10	5/10	4/10
2nd Application	0/10	3/10	10/10	10/10
3rd Application	4/10	4/10	10/10	10/10
Challenge	2/10	1/10	10/10	10/10
Naive control	3/10	2/10	6/10	5/10

After three consecutive induction treatment with the test material, 4/10 animals had slight to solid erythema at 48 hours. Following challenge application, 1/10 had slight patchy erythema at 48 hours. At the 24 and 48 hour readings, red to brown foci and/or excoriations (not given in the table) were observed on/around the test site of 5 test animals, extending beyond the test area in 2 animals. The application of 40% (w/v) test substance to naive control animals, resulted in slight patchy erythema in 3/10 and 2/10 animals at 24 and 48 hours, respectively. Red to brown foci and/or excoriations (not given in the table) were also observed on/around the test site of 5/10 animals.

The three induction treatments with positive control indicated slight patchy erythema to moderate erythema in 10/10 animals. Edema with desquamation at the dose site was also evident in 6/10 animals. The challenge application produced moderate to severe erythema in all test animals; 3/10 had eschar and 5/10 had slight edema at the dose site. The application of 0.1% (w/v) DNCB to naive control animals, resulted in slight to solid erythema in 6/10 and 5/10 animals at 24 and 48 hours, respectively.

ACUTE TOX ONE-LINER

1. **DP BARCODE:** D215036

2. **PC CODE(S):** 123000 Isoxaflutole (RPA 201772)

3. **CURRENT DATE:** June 12, 1995

4. **TEST MATERIAL:** EXP31130A, 75% Water dispersible granule

Study/Species/ Lab/Study#/Date	MRID No.	Results	Tox. Cat.	Core Grade [a]
81-1, Rat, Bushy Run, 94N1402A, 07/28/94	435732-25	LD_{50} >5 g/kg	IV	A
81-2, Rabbit, Bushy Run, 94N1402B, 07/28/94	435732-26	LD_{50} >2 g/kg	III	A
81-3, Rat, Bushy Run, 94N1401, 08/10/94	435732-27	LD_{50} >5.26 mg/l	IV	A
81-4, Rabbit, Bushy Run, 94N1402D, 07/27/94	435732-28	Mild irritation cleared in 72 hours.	III	A
81-5, Rabbit, Bushy Run, 94N1402C, 07/27/94	435732-29	Very slight irritation cleared in 7 days.	IV	A
81-6, Guinea Pig, Bushy Run, 94N1403, 09/07/94	435732-30	Not a sensitizer	--	A

[a] Core Grade Key: A = Acceptable, S = Supplementary, and U = Unacceptable.