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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: 2,4-DP Butoxyethyl Ester - Evaluation of Acute Data: Primary Eye and Dermal Studies in Rabbits; and Dermal Sensitization Study in Guinea Pigs

ToxChem No.: 320A

Accession (MRID) Nos. 421099-01, -02, and -03
HED Project No.: 2-1028

FROM: Susan L. Makris, M.S. Susan L Makris 2/6/92
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Review Section III
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and

Marcia van Gemert, Ph.D., Branch Chief Marcia van Gemert 2/7/92
Toxicology Branch II
Health Effects Division (H7509C)

Registrant: Rhone-Poulenc Ag Company
2 T.W. Alexander Drive
P.O. Box 12014
Research Triangle Park, North Carolina 27709

Action Requested: Review the following studies conducted on the chemical 2,4-DP Butoxyethyl Ester:

1. Primary Eye Irritation in Rabbits
2. Primary Dermal Irritation in Rabbits
3. Dermal Sensitization in Guinea Pigs

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Conclusions:

1. Primary Eye Irritation in Rabbits (Guideline 81-4) - MRID 421099-02, Caswell No. 320A; HED Project No. 2-1028

   Nine New Zealand White rabbits were exposed to a single 0.1 ml dose of the test material in the conjunctival sac of one eye. Conjunctival irritation (redness) noted at 24 hours postdose was reversed within 72 hours.

   Toxicity Category: III

   CORE Classification: Guideline

2. Primary Dermal Irritation in Rabbits (Guideline 81-5) - MRID 421099-01, Caswell No. 320A, HED Project No. 2-1028

   Six New Zealand White rabbits (3/sex) received a single 0.5 ml dermal dose of the test material, with exposure lasting 4 hours. No dermal irritation was observed.

   Toxicity Category: Greater than IV

   CORE Classification: Guideline

3. Dermal Sensitization in Guinea Pigs (Guideline 81-6) - MRID 421099-03, Caswell No. 320A, HED Project No. 2-1028

   For the induction phase, the test material was administered, by 3 single weekly dermal applications, to 10 Hartley guinea pigs (5/sex). A single challenge dose, was administered dermally 14 days after the last induction treatment.

   The test material was determined not to be a sensitizing agent.

   CORE Classification: Guideline

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Secondary reviewer: James N. Rowe, Ph.D. James N Rowe 2/6/92
Supervisor, Section III, Toxicology Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Primary Eye Irritation in Rabbits (Guideline 81-4)
EPA IDENTIFICATION NOS.:	MRID NO.: 421099-02 HED PROJECT NO.: 2-1028 CASWELL NO.: 320A
TEST MATERIAL:	2,4-DP Butoxyethyl Ester
SYNONYMS:	2,4-dichlorophenoxyacetic acid, butoxyethyl ester CAS No.: 1929-73-3
STUDY NUMBER:	50-604
SPONSOR:	Rhone-Poulenc Ag Company 2 T.W. Alexander Drive P.O. Box 12014 Research Triangle Park, North Carolina 27709
TESTING FACILITY:	Bushy Run Research Center R.D. #4, Mellon Road Export. Pennsylvania 15632
TITLE OF REPORT:	2,4-DP Butoxyethyl Ester Primary Eye Irritancy Study
AUTHOR:	R.C. Myers
DATE REPORT ISSUED:	October 1, 1987
CONCLUSION:	
Toxicity Category:	III; conjunctival irritation cleared within 7 days or less.
Core Classification:	Guideline

MATERIALS:

1. Test compound: Description: Brown, slightly viscous liquid
Purity: 65.6% a.i.
Sample ID: RTS-7813-AA
Source: Union Carbide Agricultural Products Co.
Research Triangle Park, NC

2. Test animals: Species: Rabbit
Strain: New Zealand White
Source: Hazleton-Dutchland, Inc.
Denver, Pennsylvania
Age: 12-18 weeks
Weight: 2.0-3.0 kg

METHODS:

Six young adult rabbits, three of each sex, confirmed to be free of ocular defects/irritation, received a 0.1 ml single dose of the undiluted test material in the conjunctival sac of one eye. The lids of the treated eye were held closed for one second following test substance administration. The remaining eye of each rabbit was left untreated and served as the control.

The eyes were examined 1, 24, 48, and 72 hours after test material application, and at Day 7. Fluorescein dye was instilled at 24-hours and at each subsequent ocular examination. Lesions in the cornea, iris, or conjunctiva were graded numerically according to the EPA FIFRA Guideline 81-4 recommendations. The study was terminated 7 days post-treatment.

RESULTS:

Individual animal ocular irritation scores are presented in Table 1. At the one-hour observation interval, redness of the conjunctivae was noted in five of six rabbits. By 24 hours postdose, the conjunctival redness was reversed in all but two rabbits, and by 48 hours postdose it was reversed in all but one rabbit. The conjunctival redness was no longer observed in any animal at 72 hours postdose.

STUDY DEVIATIONS: None noted.

COMPLIANCE:

The following signed and dated statements were included:
Statement of No Data Confidentiality
GLP Compliance Statement
Quality Assurance Statement

DISCUSSION:

According to 40 CFR Part 156.10, observations noted on this study, specifically conjunctival irritation which was reversible within 7 days or less, would place the test substance into Toxicity Category III.

Table 1. Individual Ocular Irritation Gradings[a,b]

Observation Time	Cornea	Iris	Conjunctivae		
	Opacity	Inflammation	Redness	Chemosis	Discharge
One hour	0	0	1	1	0
	0	0	1	1	0
	0	0	1	0	0
	0	0	1	1	3
	0	0	2	1	1
	0	0	0	0	0
24 hours	0	0	0	0	0
	0	0	0	0	0
	0	0	0	0	0
	0	0	1	0	0
	0	0	1	0	0
	0	0	0	0	0
48 hours	0	0	0	0	0
	0	0	0	0	0
	0	0	0	0	0
	0	0	0	0	0
	0	0	1	0	0
	0	0	0	0	0

a All scores at the 72-hour and 7-day observations were zeros.
b Examinations performed following installation of fluorescein dye at 24-, 48-, and 72-hours and at 7 days all yielded scores of 0%.
Note: Data were extracted from report No. 50-604, page 8.

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DATA EVALUATION REPORT

STUDY TYPE:	Primary Dermal Irritation in Rabbits (Guideline 81-5)
EPA IDENTIFICATION NOS.:	MRID NO.: 421099-01 HED PROJECT NO.: 2-1028 CASWELL NO.: 320A
TEST MATERIAL:	2,4-DP Butoxyethyl Ester
SYNONYMS:	2,4-dichlorophenoxyacetic acid, butoxyethyl ester CAS No.: 1929-73-3
STUDY NUMBER:	50-603
SPONSOR:	Rhone-Poulenc Ag Company 2 T.W. Alexander Drive P.O. Box 12014 Research Triangle Park, North Carolina 27709
TESTING FACILITY:	Bushy Run Research Center R.D. #4, Mellon Road Export. Pennsylvania 15632
TITLE OF REPORT:	2,4-DP Butoxyethyl Ester Primary Skin Irritancy Study
AUTHOR:	R.C. Myers
DATE REPORT ISSUED:	October 1, 1987
CONCLUSION:	
Toxicity Category:	Greater than IV (no irritation)
Core Classification:	Guideline

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MATERIALS:

1. Test compound: Description: Brown, slightly viscous liquid
Purity: 65.6% a.i.
Sample ID: RTS-7813-AA
Source: Union Carbide Agricultural Products Co.
Research Triangle Park, NC

2. Test animals: Species: Rabbit
Strain: New Zealand White
Source: Hazleton-Dutchland, Inc.
Denver, Pennsylvania
Age: 12-18 weeks
Weight: 2.0-3.0 kg

METHODS:

Six young adult rabbits (3/sex) were clipped and trimmed free of fur (over a dorsal area of unspecified size). Approximately 24 hours after the last trim, the intact clipped skin was treated with a single 0.5 ml dose of undiluted test material. The test material was applied under a 1-inch^2 gauze patch held in place with adhesive tape, and plastic sheeting loosely covered the area. The test material was allowed to remain in contact with the skin for 4 hours, after which time the coverings and excess test substance were removed from the skin.

The skin was examined at 5, 24, 48, and 72 hours after initiation of treatment. Erythema, eschar formation, and edema were graded numerically according to the EPA FIFRA Guideline 81-5 recommendations. The rabbits were also examined for any other dermal changes. The study was terminated 72 hours post-treatment.

RESULTS:

There were no signs of erythema, eschar formation, or edema at any examination period for any of the rabbits tested; all scores for the 5, 24, 48, and 72 hour examination intervals were zero. No indication of irritation, other dermal effects, or systemic toxicity were noted.

STUDY DEVIATIONS: None noted.

COMPLIANCE:

The following signed and dated statements were included:
Statement of No Data Confidentiality
GLP Compliance Statement
Quality Assurance Statement

DISCUSSION:

Based upon the criteria presented in 40 CFR Part 156.10, the Toxicity Category for skin effects following dermal administration of the test material, 2,4-DP Butoxyethyl Ester, is greater than IV (no irritation noted through 72 hours).

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DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization in the Guinea Pig (Guideline 81-6)

EPA IDENTIFICATION NOS.:
MRID NO.: 421099-03
HED PROJECT NO.: 2-1028
CASWELL NO.: 320A

TEST MATERIAL: 2,4-DP Butoxyethyl Ester

SYNONYMS: 2,4-dichlorophenoxyacetic acid, butoxyethyl ester
CAS No.: 1929-73-3

STUDY NUMBER: 50-623

SPONSOR: Rhone-Poulenc Ag Company
2 T.W. Alexander Drive
P.O. Box 12014
Research Triangle Park, North Carolina 27709

TESTING FACILITY: Bushy Run Research Center
R.D. #4, Mellon Road
Export, Pennsylvania 15632

TITLE OF REPORT: 2,4-DP Butoxyethyl Ester Dermal Sensitization Study in the Guinea Pig

AUTHORS: R.C. Myers
S.M. Christopher

DATE REPORT ISSUED: November 13, 1987

SUMMARY/CONCLUSION: A 0.3 ml aliquot of the test material, 2,4-DP Butoxyethyl Ester, was applied once weekly for 3 weeks to the shaved skin of 10 Hartley albino guinea pigs (5/sex). After a 14-day rest, a challenge dose (0.3 ml of the test substance) was applied, and dermal reactions were scored. The test material produced no signs of dermal irritation or toxicity and was not judged to be a sensitizing agent under the conditions of this study.

CORE Classification: Guideline

MATERIALS:

1. Test compound: Material: 2,4-DP Butoxyethyl Ester
Description: Brown, slightly viscous liquid
Purity: 65.6% a.i.
Source: Union Carbide Agricultural Products Co.
Research Triangle Park, NC
Lot No.: Ref. RTS-7813-AA
BRRC Sample No.: 50-164

2. Vehicle control: Material: Methyl cellulose
Description: White powder
Source: Sigma Chemical, St. Louis, MO
Lot No.: 46F-0722
BRRC Sample No.: 50-30
CAS No.: 9004-67-5

Material: Distilled water
Source: Prepared at BRRC
CAS No.: 7732-18-5

3. Positive control: Material: 2,4-dinitro-1-chlorobenzene (DNCB)
Description: Yellow, crystalline solid
Purity: Not provided
Source: Eastman Kodak Company, Rochester, NY
Lot No.: A11L
BRRC Sample No.: 50-34
CAS No.: 97-00-7

4. Test animals: Species: Guinea pig
Strain: Hartley albino
Source: Hazleton Dutchland, Inc., Denver, PA
Age at arrival: Males=4-5 weeks; Females=6-7 weeks
Weight at study start: Males=423-478g; Females=392-459g

METHODS:

Test substance preparation and administration:

The test substance, 2,4-DP butoxyethyl ester, was diluted as appropriate in 0.25% aqueous methyl cellulose, and the resulting solution was homogenized before each dose. The positive control material, DNCB, was also mixed in appropriate amounts with the methyl cellulose solution to yield 0.3% and 0.1% (w/v) concentrations for the induction and challenge phases, respectively. Test suspensions were mixed on a magnetic stirrer before and during dosing.

On the day before each application, the dorsal treatment areas of each guinea pig were clipped free of hair. At application, the test or positive control substance was placed in a Hilltop Chamber onto the clipped area of the restrained guinea pigs, then covered with adhesive tape and rubber damming. After a 6-hour exposure, the animals were removed from the restrainers, all coverings were taken off, and any residual test substance was wiped off and then washed off with warm tap water.

Initial and final body weight values were recorded.

Range-finding primary irritation study:

Dose selections for the induction and challenge phases were based on the results of a range-finding test in which 0.3 ml aliquots of either 100%, 50%, or 25% 2,4-DP butoxyethyl ester in methyl cellulose were topically applied to the skin of 10 guinea pigs (5/sex) for 6 hours. In the same manner, 0.3 ml aliquots of either 0.3% or 0.1% DNCB in methyl cellulose were applied to the skin of 8 guinea pigs (4/sex) for 6 hours. The treated skin was examined for erythema and edema approximately 24 and 48 hours posttreatment.

Induction phase:

A 0.3 ml aliquot of neat 2,4-DP butoxyethyl ester was applied to the left scapular area of ten guinea pigs (5/sex). A 0.25% aqueous methyl cellulose solution and a 0.3% solution of DNCB in methyl cellulose were applied in a similar manner to two other groups of 10 guinea pigs (5/sex) each, serving as the negative and positive controls, respectively. The test sites were examined at 24 and 48 hours after each induction application. The treatment regimen was repeated once weekly for a total of three consecutive weeks.

Challenge phase:

Approximately two weeks after the last induction application, a single 0.3 ml dose of the neat test substance, 0.25% aqueous methyl cellulose solution, or 0.1% DNCB was applied to the previously untreated right scapular area of the guinea pigs in the same manner as in the induction phase. The application sites were depilated the day after the challenge treatment. Observations and gradings for sensitization response were conducted approximately 24 and 48 hours postchallenge and at least 2 hours after depilation.

RESULTS:

Range-finding primary irritation study:

At 24-hours posttreatment, no erythema was observed in guinea pigs treated with 0.3 ml of undiluted 2,4-DP butoxyethyl ester, nor did solutions of 50%, 25%, and 10% produce signs of erythema. Based upon the lack of irritation observed following dermal exposure to the test substance, undiluted test material was selected for induction treatment in the main sensitization study.

Application of 0.1 and 0.3% solutions of DNCB in methyl cellulose resulted in no significant dermal irritancy. For the main study, 0.3% DCNB in methyl cellulose was selected for the induction dose and 0.1% was chosen for the challenge dose.

Main test for sensitization:

Body weight data:

Mean body weight values were similar between control and treated animals (Table 1). All animals gained weight during the duration of the study.

Table 1. Mean body weight values (g)

Dose group		Males		Females	
		Initial	Final	Initial	Final
Negative control: 0.25% methyl cellulose	Mean	460	705	442	610
Test material: 2,4-DP butoxyethyl ester	Mean	443	643	435	576
Positive control: 0.3%/0.1% DNCB	Mean	452	712	439	624

Note: Data were extracted from report No. 50-623, page 16.

Dermal observations:

Dermal scores are presented in Table 2.

During the induction phase of the study, no signs of dermal irritation were noted after application on Weeks 1-3 in guinea pigs treated with the test substance. Slight to moderate erythema was noted on the DNCB-treated skin.

Following challenge treatment, examination at 24 and 48 hours posttreatment showed slight to severe erythema on the treatment sites of guinea pigs treated with the positive control material. Scabbing and dark foci were also observed. In guinea pigs challenged with the test substance, the study authors attributed some signs of dark foci and scratches to the depilation procedure and/or to self-inflicted injury and judged these observations to be non-treatment-related. No signs of sensitization potential were observed in guinea pigs induced and challenged with the test substance, 2,4-DP butoxyethyl ester.

STUDY DEVIATION: - None noted.

COMPLIANCE:

The following signed and dated statements were included:
Statement of No Data Confidentiality
GLP Compliance Statement
Quality Assurance Statement

Table 2. Individual dermal observations (erythema)

Treatment Group	After Induction						After Challenge		Animal Response
	Week 1		Week 2		Week 3				
	24 Hrs	48 Hrs	24 Hrs	48 Hrs	24 Hrs	48 Hrs	24 Hrs	48 Hrs	
Negative Control:	0	0	0	0	0	0	0	0	-
	0	0	0	0	0	0	0	0	-
	0	0	0	0	0	0	0	0	-
0.25% Methyl Cellulose	0	0	0	0	0	0	0	0	-
	0	0	0	0	0	0	0	0	-
	0	0	0	0	0	0	0	0	-
	0	0	0	0	0	0	0	0	-
	0	0	0	0	0	0	0	0	-
	0	0	0	0	0	0	0	0	-
	0	0	0	0	0	0	0	0	-
Test Substance:	0	0	0	0	0	0	0	0	-
	0	0	0	0	0	0	0	0	-
	0	0	0	0	0	0	0	0	-
2,4-DP Butoxyethyl Ester	0	0	0	0	0	0	0	0	-
	0	0	0	0	0	0	0	0	-
	0	0	0	0	0	0	0	0	-
	0	0	0	0	0	0	0	0	-
	0	0	0	0	0	0	0	0	-
	0	0	0	0	0	0	0	0	-
	0	0	0	0	0	0	0	0	-
Positive Control:	0	0	2	2	1	1	2	2	+
	0	0	2	1	2	2	2	2	+
	0	0	2	1	2	1	2	2	+
0.3%/0.1%a DNCB	0	0	2	2	2	2	3	3	+
	0	0	2	2	2	1	[illegible]	2	+
	0	0	2	2	2	2	2	2	+
	0	0+	2	2	[illegible]	2	2	2	+
	0	0	2	2	2	2	2	1	+
	0	0	2	2	2	2	2	2	+
	0	0	2	2	2	2	2	1	+

Erythema
0 = No reaction
0+ = Slight, patchy erythema
1 = Slight, solid erythema or moderate patchy erythema
2 = Moderate erythema
3 = Marked erythema

Response
- = Negative
+ = Positive

a A 0.3% solution of the positive control (DNCB) material in 0.25% methyl cellulose was applied for the induction phase; this was decreased to 0.1% for the challenge phase.
Note: Data were extracted from report No. 50-623, pages 17-22.

DISCUSSION:

Neither the negative control substance, 0.25% methyl cellulose, nor the test material, 2,4-DP butoxyethyl ester, were shown to be positive sensitizing agents in the guinea pig under the conditions of this study. DNCB, the positive control material, demonstrated clear evidence of sensitization in the guinea pig following induction and challenge treatments, thereby validating the procedures used to detect sensitization potential