2-18-92

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

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FEB 18 1992

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 2-(2,4-dichloro-5-methylsulfonylamidophenyl)-4-difluromethyl-2,4-dihydro-5-methyl-3H-1,2-4-triazol-3-one

HED Project No.: 1-1765
Tox. Chem No.: Not available
Chem. No.: 129081

FROM: Ray Landolt 2/3/92
Review Section I
Toxicology Branch II
Health Effects Division (H7509C)

TO: Joanne Miller, PM 23
Fungicide-Herbicide Branch
Registration Division (H7505C)

THRU: Mike Ioannou, Section Head Mi Ioannou 2/4/92
Review Section I
Toxicology Branch II
Health Effects Division (H7509C)

and

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

Registrant: FMC Corporation, letter of June 12, 1991

Action Requested: 1. Application for experimental use of FMC 97285 herbicide on soybeans with the restriction for food or feed derived from experimental program will not be used or offered for consumption or sale.

2. Review acute toxicity studies on the technical and 39.6% use formulation.

3. Request for a waiver of an acute inhalation toxicity study on the 96.6% use formulation of FMC 97285 based on the minimal exposure of researchers investigating the efficacy of this herbicide.

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Conclusion: The acute toxicity studies submitted on the technical and use formulation do not support the requested experimental use of FMC 97285.

1. The technical material of batch No. E5857:19, a white solid with a purity of 94.0%, used in the acute oral toxicity studies is different from the technical of batch No. 31-89-0478, a tan solid with an unknown purity, used in the dermal toxicity, eye and dermal irritation, and sensitization studies.

    a. The registrant is requested to justify the use of a different batch of the technical material in these four studies rather than the material used in the acute oral toxicity studies.

    b. The registrant is requested to provide the purity of batch No. 31-89-0478.

2. An acceptable acute inhalation toxicity study is requested for registration of the use formulation of this new chemical.

3. The Confidential Statement of Formula for the use formulation (39.6%) did not accompany this request. Does this formulation contain inert ingredients that would require additional precautionary labeling, such as methanol or petroleum distillates?

4. Positive control data was not included in the guinea pig sensitization studies conducted with the technical or use formulation.

Reviewed By: Ray Landolt 2/3/92
Section I, Toxicology Branch II - HFAS (H7509C)
Secondary Reviewer: Mike Ioannou 2/4/92
Section I, Toxicology Branch II - HFAS (H7509C)

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DATA EVALUATION REPORT

Study Type: Acute Oral Toxicity Study Rats (81-1)

Project No.: 1-1765
MRID No.: 419116-05
Chem. No.: 129081

Test Material: Technical, 94.0%

2-(2,4-dichloro-5-methylsulfonylamidophenyl)-4-difluolmethyl-2,4-dihydro-5-methyl-3H-1,2,4-triazol-3-one

Classification: Herbicide

Synonym: FMC 97285 and F6285

Study No.: A88-2587

Date of Study: August 22, 1988

Sponsor: FMC

Testing Facility: FMC Toxicology Laboratory

Title of Report: Acute Oral Toxicity Study in Rats

Author: Jane D. McCarty

Quality Assurance: Luann R. Seaman

Conclusion: This study is acceptable and satisfies the guideline data requirement (81-1) for an acute oral toxicity study.

Classification of Data: Guideline

This study supports Toxicity Category-III precautionary labeling for oral toxicity and the signal word Caution.

Experimental Design

Animals - Young adult Sprague Dawley (Tac:N[SD] fBR rats weighing between 227 to 294 g for males and 222 to 285 g for females were fasted overnight prior to dosing.

Test material - The technical material (94%) of a white solid of batch number E5857:19, was dissolved in several drops of acetone then prepared as a 15% (weight/volume) suspension in corn oil.

Procedure - Five male and five female rats per level were dosed by gavage at 2, 3 and 4 g/kg. All animals were observed at 0.5, 1, 2, 3, 4, and 6 hours on the day of dosing then twice daily for 13 days. Body weights were recorded initially then on days 7 and 14 of the study. Gross necropsy was performed on all animals.

Results

LD_{50} male - 3034.4 (2101.9 - 3966.8) mg/kg Slope 8.9
female - 2688.9 (2008.1 - 3369.8) mg/kg Slope 11.5
combined - 2854.8 (2282.5 - 3427.1) mg/kg Slope 9.8

Signs of Toxicity - At the 4000 mg/kg level ataxia, dyspnea and hypersensitivity to touch were reported followed by chronic convulsions and decreased locomotion within two hours lasting for 6 hours. Chromodacryorrhea, chromorhinorrhea and death were recorded at 6 and 24 hours. Body weight gain was normal during the 14-day observation period.

Necropsy - Blood in the intestines was reported for those animals that died during the 24 to 48 hr period after dosing.

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DATA EVALUATION REPORT

Study Type: Acute Oral Toxicity Study - Mice (81-1)

Project No.: 1-1765
MRID No.: 419116-06
Chem. No.: 129081

Test Material: Technical, 94.0%

2-(2,4-dichloro-5-methylsulfonylamidophenyl)-4-difluromethyl-2,4-dihydro-5-methyl-3H-1,2,4-triazol-3-one

Classification: Herbicide

Synonym: FMC 97285 and F6285

Study No.: A88-2598

Date of Study: July 12, 1988

Sponsor: FMC

Testing Facility: FMC Toxicology Laboratory

Title of Report: Acute Oral Toxicity Study in Mice

Author: Jane D. McCarty

Quality Assurance: Luann R. Seaman

Conclusion: This study is acceptable and satisfies the guideline testing requirement (81-1) for an acute oral toxicity study.

Classification of Data: Guideline

Toxicity Category: III , for oral toxicity

Experimental Design

Animals - Young adult $B_6C_3F_1$ mice weighing between 22.8 to 28.5 g for males and 22.6 to 28.0 g for females were fasted four hours prior to dosing.

Test material - The technical material (94%), a white solid of batch number E5857:19 was dissolved in a few drops of acetone then prepared as a 5.0% (w/v) suspension in corn oil.

Procedure - Five male and five female mice per level were dosed by gavage at 500, 600, 700, 800, and 1000 mg/kg. Five male mice were dosed at 650 mg/kg. All animals were observed for mortality and signs of toxicity at 0.5, 1, 2, 3, 4, and 6 hours on the day of dosing then twice daily for 14 days. Body weights were recorded initially then on days 7 and 14 of the study. Gross necropsy was performed on all animals.

Results

LD_{50} male - 751.9 (644.7 to 859.1) mg/kg Slope 15.7
female - 701.8 (579.6 to 823.9) mg/kg Slope 13.0
combined - 711.2 (586.0 to 836.3) mg/kg Slope 11.9

Signs of Toxicity - At the 700 mg/kg level ataxia and hypersensitivity to touch were observed within one hour followed by chronic convulsions, decreased locomotion, and abdominogenital staining within two hours lasting for six hours. No signs of toxicity were observed at the 24-hour interval. Death occurred within 2 to 6 hours for males and 6 to 24 hours for females. Females exhibited a slight decrease in body weight gain over the last seven days of the study.

Necropsy - No gross pathological findings were observed.

Reviewed By: Ray Landolt 2/3/92
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DATA EVALUATION REPORT

Study Type: Acute Dermal Toxicity Study - Rabbit (81-2)

Project No.: I-1765
MRID No.: 419116-07
Chem. No.: 129081

Test Material: Technical, of unknown purity

2-(2,4-dichloro-5-methylsulfonylamidophenyl)-4-diflurolmethyl-2,4-dihydro-5-methyl-3H-1,2,4-triazol-3-one

Classification: Herbicide

Synonym: FMC 97285 and F6285

Study No.: Ad9-3085

Date of Study: January 19, 1990

Sponsor: FMC

Testing Facility: FMC Toxicology Laboratory

Title of Report: Acute Dermal Toxicity Study in Rabbits

Author: Christene Freeman

Quality Assurance: Luann R. Seaman

Conclusion: This study does not satisfy the guideline data requirement (81-2) for an acceptable acute dermal toxicity study.

Classification of Data: Supplementary

Deficiency: The purity of the test material was not reported.

Toxicity Category: III, for dermal toxicity.

0007

Experimental Design

Animals - Five male and five female young adult New Zealand white rabbits weighing between 2.1 and 2.3 kg were used in this study.

Test material - The technical material (of unknown purity), a tan solid of batch No.31-89-0478, was applied to the intact skin of five male and five female rabbits at 2000 mg/kg.

Procedure - The undiluted test material was weighed onto a 4 x 4 inch gauze pad, moistened with water, secured to the dermal area with hypoallergenic tape and occluded with impervious plastic sheeting for a 24-hour exposure. Each animal was fitted with an Elizabethan collar and housed individually for the duration of the study. Following the 24-hour exposure the wrapping material was removed, the test sites were wiped with gauze moistened with methanol and then rinsed with tap water. All animals were observed for mortality and signs of toxicity at 0.5, 1, 2, 3, 4, and 6 hours on the day of dosing then twice daily for 13 days. Skin reactions were recorded on days 1, 3, 7, and 14 of the study. Body weights were recorded initially then on days 7 and 14. Gross necropsy was performed on all animals.

Results

LD_{50} > 2000 mg/kg (0/10) for a 24-hour exposure.

Signs of Toxicity - The animals appeared normal except for a mucoid anal discharge observed for 1/5 female rabbits on day four through day 13 of the study. A normal body weight gain was reported. No dermal irritation was observed.

Necropsy - No gross pathological findings were observed.

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DATA EVALUATION REPORT

Study Type: Primary Eye Irritation - Rabbit (81-4)

Project No.: 1-1765
MRID No.: 419116-08
Chem. No.: 129081

Test Material: Technical, of unknown purity

2-(2,4-dichloro-5-methylsulfonylamidophenyl)-4-diflurolmethyl-2,4-dihydro-5-methyl-3H-1,2,4-triazol-3-one

Classification: Herbicide

Synonym: FMC 97285 and F6285

Study No.: A89-3086

Date of Study: February 8, 1990

Sponsor: FMC

Testing Facility: FMC Toxicology Laboratory

Title of Report: Primary Eye Irritation Study in Rabbits

Author: Christene Freeman

Quality Assurance: Luann R. Seaman

Conclusion: This study does not satisfy the guideline data requirement (81-4) for a primary eye irritation study.

Classification of Data: Supplementary

Deficiency: The purity of the test material was not reported.

Toxicity Category: III, for eye irritation.

0099

Experimental Design

Animals - Nine young adult New Zealand white rabbits weighing between 2.3 and 3.8 kg were used in this study.

Test material - The technical material (of unknown purity), a tan solid of batch number 31-89-0478, was used in this study.

Procedure - The undiluted test material (100 mg) was placed in the conjunctional sac of the right eye of each of nine rabbits. Thirty seconds after application of the test material, the eyes of three rabbits were washed with 100 ml of tap water. The eyes of the remaining six rabbits were not washed. All eyes were examined for ocular irritation prior to treatment, then at 1, 24, 48, and 72 hours followed by observations on day four. Ocular irritation was graded according to the method of Draize. Tetracaine HCl was instilled into both eyes of each rabbit at 15 and 30 minutes prior to dosing to minimize pain. All eyes were subjected to fluorescein examination prior to treatment then at each observation interval (except at one hour) until a negative response was observed.

Results:

For Unwashed Eyes - Within one hour slight chemosis and discharge were observed. Corneal opacity (with iris clearly visible) in 4/6 eyes, slight iritis in 1/6 eyes and diffuse irritation in 6/6 eyes was observed within 24 hours clearing by day four of the study.

For Washed Eyes - Slight chemosis was observed within one hour clearing by the 24 hour observation.

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009263

DATA EVALUATION REPORT

Study Type: Primary Skin Irritation - Rabbit (81-5)

Project No.: 1-1765
MRID No.: 419116-09
Chem. No.: 129081

Test Material: Technical, of unknown purity

2-(2,4-dichloro-5-methylsulfonylamidophenyl)-4-diflurolmethyl-2,4-dihydro-5-methyl-3H-1,2,4-triazol-3-one

Classification: Herbicide

Synonym: FMC 97285 and F6285

Study No.: A89-3087

Date of Study: February 8, 1990

Sponsor: FMC

Testing Facility: FMC Toxicology Laboratory

Title of Report: Primary Skin Irritation Study in Rabbits

Author: Christene Freeman

Quality Assurance: William D. Barta

Conclusion: This study does not satisfy the guideline data requirement (81-5) for an acceptable dermal irritation study.

Classification of Data: Supplementary

Deficiency: The purity of the test material was not reported.

Toxicity Category: IV, for dermal irritation.

Experimental Design

Animals - Six young adult New Zealand white rabbits weighing between 2.9 and 3.4 kg were used in this study.

Test material - The technical material (of unknown purity), a tan solid of batch number 31-89-0478, was applied to the shaven intact skin of three male and three female rabbits.

Procedure - The undiluted test material (0.5 g) was weighed onto a 2 x 2 inch gauze pads, moistened with saline, applied to each side of the animal, secured with hypoallergenic tape and wrapped with a cheesecloth bandage for a four hour exposure. Each animal was fitted with an Elizabethan collar and housed individually for the duration of the study. Following the four hour exposure, the wrapping material was removed, the test sites were wiped with gauze moistened with methanol and then rinsed with tap water. Skin reactions were evaluated by the Draize method at 4, 24, 48, and 72 hours.

Results

No erythema or edema were observed from a 4-hour exposure to the technical material.

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DATA EVALUATION REPORT

Study Type: Sensitization - Guinea Pig (81-6)

Project No.: 1-1765
MRID No.: 419116-10
Chem. No.: 129081

Test Material: Technical, of unknown purity

2-(2,4-dichloro-5-methylsulfonylamidophenyl)-4-diflurolmethyl-2,4-dihydro-5-methyl-3H-1,2,4-triazol-3-one

Classification: Herbicide

Synonym: FMC 97285 and F6285

Study No.: A89-3088

Date of Study: February 14, 1990

Sponsor: FMC

Testing Facility: FMC Toxicology Laboratory

Title of Report: Skin Sensitization Study in Guinea Pigs

Author: Christene Freeman

Quality Assurance: William D. Barta

Conclusion: This study does not satisfy the guideline data requirement (81-6) for an acceptable dermal sensitization study.

Classification of Data: Supplementary

Deficiencies: 1. The purity of the test material was not reported.

2. A positive control was not included in this study.

Dermal application of FMC 97285 as a 25% (w/v) mixture in mineral oil once a week over a three week period did not induce a dermal sensitization response.

Experimental Design

Animals - Young adult Hartley guinea pigs weighing between 310 and 366 grams were used in this study.

Test material - The technical material (of unknown purity), a tan solid of batch number 31-89-0478, was prepared as a 25% (w/v) mixture in mineral oil.

Procedure - The test method follows that of Ritz, H.L. and Buehler, E.V.*. The test material (0.30 ml) was applied to the shaven left shoulder of 20 animals within a Hill Top Chamber® once a week for three weeks during the induction phase. The chamber was covered with a 4 x 4 inch gauze pad and secured with hypoallergenic tape. The animals were placed in a Newman restrainer for a six-hour exposure. Following a six-hour exposure, the wrapping and chamber were removed, the test sites were wiped with gauze moistened with methanol and then rinsed with tap water. Fourteen days after the third induction application, the animals were challenged on the right shoulder. In addition a challenge control group consisting of 10 guinea pigs received 0.30 ml of the test material applied to each animal in the same manner as for the induction phase. Skin reactions were evaluated at 24 and 48 hours after each application using the method of Draize. Body weights were recorded initially and at the termination of the study.

Results

Dermal application of FMC 97285 as a 25% (w/v) mixture in mineral oil once a week over a three week period did not induce a dermal sensitization response. A normal body weight gain was reported for the induction and challenge groups.

* "Planning, Conduct, and Interpretation of Guinea Pig Sensitization Patch Tests." Current Concepts in Cutaneous Toxicity. Academic Press 1980; pp. 25-40.

Reviewed By: Ray Landolt 2/5/92
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009263

DATA EVALUATION REPORT

Study Type: Acute Oral Toxicity Study - Rats (81-1)

Project No.: 1-1765
MRID No.: 419116-12
Chem. No.: 129081

Test Material: 39.6% Formulation

2-(2,4-dichloro-5-methylsulfonylamidophenyl)-4-difluromethyl-2,4-dihydro-5-methyl-3H-1,2,4-triazol-3-one

Classification: Herbicide

Synonym: FMC 97285 and F6285

Study No.: A91-3384

Date of Study: April 29, 1991

Sponsor: FMC

Testing Facility: FMC Toxicology Laboratory

Title of Report: Acute Oral Toxicity Study in Rats

Author: Christine Freeman

Quality Assurance: Luann R. Seaman

Conclusion: This study followed the EPA and OECD revised testing guidelines to utilize the most sensitive sex. Based the LD_{50} of 2084 mg/kg in female rats, this study is acceptable and supports Category III precautionary labeling for oral toxicity and the signal word Caution.

Classification of Data: Minimum

Deficiency: A single dose was administered to five male rats at 2500 mg/kg.

Experimental Design

Animals - Young adult Sprague-Dawley (Tac: N[SD]fBR) rats weighing between 211 to 263 grams were fasted overnight prior to dosing.

Test material - The formulated product (39.6%), a brown liquid with a density of 1.29 g/ml, was identified as PL90-372.

Procedure - Selection of dosage levels followed the EPA and OECD revised testing guidelines to utilize the most sensitive sex. The initial dosage level of 2500 mg/kg was administered to five male and five female rats with the subsequent levels administered to five female rats per dose level of 2000 and 1500 mg/kg. All animals were observed for mortality and signs of toxicity at 0.5, 1, 2, 3, 4, and 6 hours on the day of dosing then twice daily for 13 days. Body weights were recorded initially then on days 7 and 14 of the study. Gross necropsy was performed on all animals.

Results

LD_{50} female - 2084 (1713 to 2455) mg/kg with a slope of 16.3

Signs of Toxicity - Within one hour following the administration of the 2500 mg/kg level chronic convulsions, tremors, decreased locomotion, splayed hindlimbs, recumbency, bloody oral discharge, and abdominogential staining were observed persisting through the six hour observation period. The test material was more toxic to females at the 2500 mg/kg level with 3/5 deaths recorded between 2 and 6 hours on the day of dosing followed by 4/5 deaths within 24 hours of the initial dose. Deaths (2/5) were recorded for males between 3 and 6 hours on the day of dosing at the 2500 mg/kg level. Additional levels were not administered to male rats. In addition lacrimation, rales, and "abdominal gripping" were reported between 3 and 6 hours. No signs of toxicity were observed at the 24 hour interval. Survivors maintained a normal body weight gain over the 14-day observation period.

Necropsy - No gross pathological findings were observed.

Reviewed By: Ray Landolt 2/3/92
Section I, Toxicology Branch II - HFAS (H7509C)
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Section I, Toxicology Branch II - HFAS (H7509C)

009263

DATA EVALUATION REPORT

Study Type: Acute Dermal Toxicity Study - Rat (81-2)

Project No.: 1-1765
MRID No.: 419116-13
Chem. No.: 129081

Test Material: 39.6% Formulation

2-(2,4-dichloro-5-methylsulfonylamidophenyl)-4-difluromethyl 2,4-dihydro-5-methyl-3H-1,2,4-triazol-3-one

Classification: Herbicide

Synonym: FMC 97285 and F6285

Study No.: A91-3385

Date of Study: March 22, 1991

Sponsor: FMC

Testing Facility: FMC Toxicology Laboratory

Title of Report: Acute Dermal Toxicity Study in Rats

Author: Christine Freeman

Quality Assurance: Luann R. Seaman

Conclusion: This study is acceptable and satisfies the guideline requirement (81-2) for an acute dermal toxicity study.

Classification of Data: Guideline

This study supports Toxicity Category - III precautionary labeling for dermal toxicity and the signal word Caution.

0017

Experimental Design

Animals - Ten young adult Sprague-Dawley rats weighing between 243 and 289 were used in this study.

Test material - The formulated product (39.6%), a brown liquid with a density of 1.29 g/ml, was identified as PL90-372.

Procedure - The undiluted formulation was applied onto a 2 x 2 inch gauze pad, positioned on the shaven intact skin of five male and five female rats at a dosage level of 2000 mg/kg. The test site was occluded with an elastic plastic bandage for a 24-hour exposure. Following the 24-hour exposure, the wrapping material was removed, the test sites were wiped with gauze moistened with methanol and then rinsed with tap water. All animals were observed for mortality and signs of toxicity at 0.5, 1, 2, 3, 4, and 6 hours on the day of dosing then twice daily for 13 days. Skin reactions were recorded on days 1, 3, 7, and 14 of the study. Body weights were recorded initially then on days 7 and 14. Gross necropsy was performed on all animals at the termination of the study.

Results

LD_{50} > 2000 mg/kg (0/10) for a 24-hour exposure.

Signs of Toxicity - No deaths or signs of toxicity were reported from the topical application of 22 mg/cm^2 to the intact skin. A normal body weight gain was reported. No dermal irritation observed.

Necropsy - No gross pathological findings were observed.

Reviewed By: Ray Landolt 2/3/92
Section I, Toxicology Branch II - HFAS (H7509C)
Secondary Reviewer: Mike Ioannou 2/4/92
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009263

DATA EVALUATION REPORT

Study Type: Primary Eye Irritation - Rabbit (81-4)

Project No.: 1-1765
MRID No.: 419116-14
Chem. No.: 129081

Test Material: 39.6% Formulation

2-(2,4-dichloro-5-methylsulfonylamidophenyl)-4-diflurolmethyl-2,4-dihydro-5-methyl-3H-1,2,4-triazol-3-one

Classification: Herbicide

Synonym: FMC 97285 and F6285

Study No.: A91-3386

Date of Study: March 1, 1991

Sponsor: FMC

Testing Facility: FMC Toxicology Laboratory

Title of Report: Primary Eye Irritation Study in Rabbits

Author: Christine Freeman

Quality Assurance: Luann R. Seaman

Conclusion: This study is acceptable and satisfies the guideline data requirement (81-4) for a primary eye irritation study.

Classification of Data: Guideline

Toxicity Category IV: No precautionary labeling required.

Experimental Design

Animals - Six young adult New Zealand white rabbits weighing between 2.0 and 2.2 kg were used in this study.

Test material - The formulated product (39.6%), a brown liquid with a density of 1.29 g/ml, was identified as PL90-372.

Procedure - The undiluted formulation (0.1 ml) was placed in the conjunctival sac of the right eye of each of six female rabbits. All eyes were examined for ocular irritation prior to treatment then at 1, 24, 48, and 72 hours. Eyes were not washed. Ocular irritation was graded according to the Draize method. Tetracaine HCl was instilled into both eyes of each rabbit at 15 and 30 minutes prior to dosing to minimize pain. All eyes were subjected to fluorescein examination prior to treatment then at each observation interval (except at one hour) until a negative response was observed.

Results

No irritation was observed from the application of 0.1 ml of the 39.6% formulation to the right eye of six rabbits.

Reviewed By: Ray Landolt 2/3/92
Section I, Toxicology Branch II - HFAS (H7509C)
Secondary Reviewer: Mike Ioannou 2/4/92
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009263

DATA EVALUATION REPORT

Study Type: Primary Dermal Irritation - Rabbit (81-5)

Project No.: 1-1765
MRID No.: 419116-15
Chem. No.: 129081

Test Material: 39.6% Formulation

2-(2,4-dichloro-5-methylsulfonylamidophenyl)-4-diflurolmethyl-2,4-dihydro-5-methyl-3H-1,2,4-triazol-3-one

Classification: Herbicide

Synonym: FMC 97285 and F6285

Study No.: A91-3387

Date of Study: February 27, 1991

Sponsor: FMC

Testing Facility: FMC Toxicology Laboratory

Title of Report: Primary Skin Irritation Study in Rabbits

Author: Christine Freeman

Quality Assurance: Luann R. Seaman

Conclusion: This study is acceptable and satisfies the guideline data requirement (81-5) for a primary dermal irritation study.

Classification of Data: Guideline

Toxicity Category IV: No precautionary labeling is required.

0021

Experimental Design

Animals - Three male and three female young adult New Zealand white rabbits weighing between 2.0 and 2.5 kg were used in this study.

Test material - The formulated product (39.6%), a brown liquid with a density of 1.29 g/ml, was identified as PL90-372.

Procedure - The undiluted formulation was applied to the shaven intact skin under a 2 x 2 inch gauze pad positioned on each side of the animal at 0.5 ml per test site. The pads were secured with hypoallergenic tape and the area was wrapped with a semiocclusive cheesecloth bandage for a four hour exposure. Following the four hour exposure the wrapping material was removed, the test site was wiped with gauze moistened with methanol and rinsed with tap water. Skin reactions were evaluated by the Draize method at 4, 24, 48, and 72 hours.

Results

After the four hour exposure slight irritation was reported within 30 minutes of unwrapping of the test site on 3/6 rabbits, clearing within 24 hours.

Reviewed By: Ray Landolt 2/3/92
Section I, Toxicology Branch II - HFAS (H7509C)
Secondary Reviewer: Mike Ioannou 2/4/92
Section I, Toxicology Branch II - HFAS (H7509C)

009263

DATA EVALUATION REPORT

Study Type: Dermal Sensitization - Guinea Pig (81-6)

Project No.: 1-1765
MRID No.: 419116-16
Chem. No.: 129081

Test Material: 39.6% Formulation

2-(2,4-dichloro-5-methylsulfonylamidophenyl)-4-diflurolmethyl 2,4-dihydro-5-methyl-3H-1,2,4-triazol-3-one

Classification: Herbicide

Synonym: FMC 97285 and F6285

Study No.: A91-3383

Date of Study: April 29, 1991

Sponsor: FMC

Testing Facility: FMC Toxicology Laboratory

Title of Report: Skin Sensitization Study in Guinea Pigs

Author: Christène Freeman

Quality Assurance: William D. Barta

Conclusion: This study does not satisfy the guideline data requirement (81-6) for an acceptable dermal sensitization study.

Classification of Data: Supplementary

Deficiency: A positive control was not included in tnis study.

Dermal application of 39.6% formulation of FMC 97285 once a week over a three week period did not induce a dermal sensitization response.

0023

Experimental Design

Animals - Young adult Hartley guinea pigs weighing between 321 and 418 grams were used in this study.

Test material - The undiluted test material (39.6%), a brown liquid identified as PL90-372, was used in this study.

Procedure: The test method follows that of Ritz, H.L.and Buehler, E.V.*. The test material (0.30 ml) was applied to the shaven left shoulder of 20 animals within a Hill Top Chamber® once a week for three weeks during the induction phase. The chamber was secured with hypoallergenic tape and the animal was wrapped with an elastic, plastic-lined bandage for a six hour exposure. Following a six-hour exposure, the wrapping and chambers were removed, the test sites were wiped with gauze moistened with methanol and then rinsed with tap water. Fourteen days after the third induction application, the animals were challenged with 0.3 ml applied to the right shoulder. In addition a challenge control group consisting of ten guinea pigs, received 0.3 ml each of the test material applied in the same manner as for the induction phase. Skin reactions were evaluated at 24 and 48 hours after each application using the method of Draize. Body weights were recorded initially and at the termination of the study.

Results

Dermal application of the 39.6% formulation of FMC 97285 once a week over a three week period did not induce a dermal sensitization response. Animal body weight gain was reported for the induction and challenge groups.

* "Planning, Conduct, and Interpretation of Guinea Pig Sensitization Patch Tests." Current Concepts in Cutaneous Toxicity. Academic Press 1980; pp. 25-40.

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FINAL

DATA EVALUATION REPORT

FMC 97285 (F6285)

Study Type: Mutagenicity: Salmonella typhimurium/Mammalian Microsome Mutagenicity Assay

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
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Work Assignment Number: 1-38
Clement Number: 91-134
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GUIDELINE SERIES 84: MUTAGENICITY
SALMONELLA

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DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: Salmonella typhimurium/mammalian microsome mutagenicity assay

EPA IDENTIFICATION Numbers:

Tox Chem. Number:

MRID Number: 419116-11

TEST MATERIAL: FMC 97285 (F6285)

SYNONYMS: None listed.

SPONSOR: FMC Corporation, Philadelphia, Pennsylvania

STUDY NUMBER: A86-2033

TESTING FACILITY: FMC Corporation, Princeton, New Jersey

TITLE OF REPORT: Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)

AUTHORS: J. P. Wojciechowski and T. Cascieri

REPORT ISSUED: October 13, 1986

CONCLUSIONS--EXECUTIVE SUMMARY: Under the conditions of two independently performed Salmonella typhimurium/mammalian microsome plate incorporation assays, doses ranging from 0.100 to 10.00 mg/plate (100 to 10,000 µg/plate) FMC 97285 (F6285) did not induce a cytotoxic or mutagenic response in S. typhimurium strains TA1535, TA1537, TA1538, TA98, or TA100, either in the absence or the presence of microsomes derived from Aroclor 1254-induced rat livers (S9). Based on these findings, it was concluded that FMC 97285 (F6235) was tested over an appropriate range of concentrations with no evidence of a mutagenic effect. The study, therefore, satisfies Guideline requirements for genetic effects Category I, Gene Mutations.

STUDY CLASSIFICATION: The study is acceptable.

A. MATERIALS:

1. Test Material: FMC 97285 (F6285)

Description: Solid
Lot number: E4711:1518
Purity: 95.5%
Receipt date: March 18, 1986
Stability: Unstable if heated
Contaminants: None listed
Solvent used: Dimethyl sulfoxide (DMSO)
Other provided information: The test material was stored at room temperature (~20°C); test solutions were prepared immediately before use.

2. Control Materials:

Solvent/final concentration: DMSO/50 µL plate

Positive:

Nonactivation:

Sodium azide	5	µg/plate TA100, TA1535
2-Nitrofluorene	5	µg/plate TA98, TA1538
9-aminoacridine	75	µg/plate TA1537

Activation:

2-Aminoanthramine	4	µg/plate all strains

3. Activation: S9 derived from male Sprague-Dawley

x Aroclor 1254	x induced	x rat	x liver
_____ phenobarbital	_____ noninduced	_____ mouse	_____ lung
_____ none		_____ hamster	_____ other
_____ other		_____ other	

The rat liver S9 was purchased from an FMC-approved supplier.

S9 mix composition	Final concentration
Sodium phosphate buffer (pH 7.4)	100 mM
Glucose 6-phosphate	5 mM
NADP	4 mM
$MgCl_2$	8 mM
KCl	33 mM
S9	100 µL/mL

4. Test Organism Used: S. typhimurium strains

_____ TA97 x TA98 x TA100 _____ TA102 _____ TA104
x TA1535 x TA1537 x TA1538
list any others:

Test organisms were properly maintained: Yes. Fresh cultures were inoculated directly from stocks stored at -80°C or -196°C.
Checked for appropriate genetic markers (rfa mutation, R factor): Yes

5. Test Compound Concentrations Used:

(a) Preliminary cytotoxicity assay: Ten doses (10.0, 33.3, 66.7, 100, 333, 667, 1000, 3333, 6667, and 10,000 µg/plate) were evaluated with and without S9 activation in S. typhimurium strain TA100. Single plates were used per dose per condition.

(b) Mutation assay: Five doses (100, 333, 1000, 3333, and 10,000 µg/plate) were evaluated in the absence and presence of S9 activation; all tester strains were used.

B. TEST PERFORMANCE:

1. Type of Salmonella Assay:
__x__ Standard plate test
_____ Pre-incubation (_____) minutes
_____ "Prival" modification
_____ Spot test
_____ Other (describe)

2. Protocol:

(a) Preliminary cytotoxicity/mutation assays: Similar procedures were used for the preliminary cytotoxicity and the mutation assays.

Approximately 10^8 cells (0.1 mL of a 10^9 cells/mL overnight broth culture) of the appropriate tester strain were added to tubes containing 2.5 mL volumes of molten top agar, along with 50 µL of the appropriate test material dose, solvent, or positive control. For the S9-activated tests, 0.5 mL of the appropriate S9-cofactor mix was added to 2 mL of the top agar; tester strains, test doses, and control solutions were added as described. The contents of the tubes were mixed, poured over Vogel-Bonner minimal medium E, and incubated at 37°C for ≈48-72 hours. At the end of incubation, plates were either scored immediately for revertant colonies or were refrigerated and subsequently counted. Means and standard deviations for the mutation test were determined from the counts of triplicate plates per strain, per dose, per condition.

(b) Sterility controls: The sterility of the highest test dose, the S9 mix, the solvent, and the top agar were determined.

(c) Evaluation criteria: The test material was considered positive if it caused at least a doubling in the mean number of revertants per plate of at least one strain, and the increase was dose-related. If the increase observed with strains TA1537 or TA1538 was less than three-fold, it must be reproducible.

C. REPORTED RESULTS

1. Preliminary Cytotoxicity Assay: Ten doses of the test material ranging from 10 to 10,000 µg/plate were evaluated without and with S9 activation using strain TA100. No compound precipitation was apparent at any of the nonactivated or S9-activated doses. No decrease in the number of revertant colonies per plate or thinning of the background lawn of growth was seen at any dose. Based on these findings, the dose range selected for the nonactivated and S9-activated mutation assay was 100-10,000 µg/plate.

2. Mutation Assay: Representative results from the nonactivated and S9-activated mutation assays with FMC 97285 (F6285) are presented in Table 1. Evaluation of the background lawn of growth under nonactivated and S-9 activated conditions produced no evidence of compound-induced cytotoxicity. The slight variations in the number of revertant colonies per plate were not dose-related, and thus probably resulted from normal plating variability. FMC 97285 (F6285) did not induce a mutagenic effect in any tester strain in either the absence or presence of S9 activation. In contrast, all strains responded to the appropriate nonactivated and S9-activated positive controls. From the overall findings, the study author concluded that FMC 97285 (F6285) was not mutagenic in this test system.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: We assess that the study authors' interpretation of the data was correct. Both in the absence and presence of exogenous metabolic activation derived from rat liver microsomes, FMC 97285 (F6285) was assayed to 10,000 µg/plate but failed to induce a cytotoxic or mutagenic effect in a well-controlled study. In addition, the response of all tester strains to the appropriate direct-acting or promutagenic positive controls indicated that the assay had an adequate level of sensitivity to detect a mutagenic response. It was concluded, therefore, that FMC 97285 (F6285) was not mutagenic in this microbial test system.

E. QUALITY ASSURANCE MEASURES: Was the test performed under GLP? Yes. (A signed quality assurance statement, dated July 7, 1986, was present.)

F. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 5-10.

TABLE 1: Representative Results of the Salmonella typhimurium/Mammalian Microsome Mutation Assay with FMC 97285 (F6285)

Substance	Dose/Plate	S9 Activation	Revertants per Plate of Bacterial Tester Strain[a] TA1535	TA1537	TA1538	TA98	TA100
Solvent Control							
Dimethyl sulfoxide	50 µL	-	22±10	7±2	16±1	43±2	118±5
	50 µL	+	18±4	6±2	21±3	61±10	117±15
Positive Controls							
Sodium azide	5 µg	-	2001±198	--	--	--	2264±256
9-Aminoacridine	75 µg	-	--	1202±242	--	--	--
2-Nitrofluorene	5 µg	-	--	--	1461±293	1100±142	--
2-Aminoanthramine	4 µg	+	594±130	694±69	4988±310	5835±520	8173±760
Test Material							
FMC 97285 (F6285)	10,000 µg[b]	-	22±4	4±1	11±2	51±5	104±10
	10,000 µg[b]	+	15±2	7±5	24±5	66±6	146±10

[a]Means and standard deviations of the counts from triplicate plates.

[b]Results for lower doses (100, 333, 1000, and 3333 µg/plate) -/+ rat S9 did not suggest a mutagenic effect.