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THR-4296

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

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2/1/85

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DATE:

SUBJECT: Revised EUP Request For Use Of COMMAND 6EC On Soybeans.

TO: Robert Taylor, PM #25
Registration Division (TS-767)

FROM: Carolyn Gregorio, Toxicologist
Toxicology Branch/ HED (TS-769) CAG 1-31-85

THRU: Robert P. Zendzian, Ph.D.
Acting Section Head/ Section III
and
Theodore M. Farber, Ph.D. Chief,
Toxicology Branch/ HED (TS-769)

Chemical: COMMAND, FMC 57020

Caswell No.: 463D

Petitioner: FMC Chemical Corporation

Petition No.: 279-EUP-93

Accession No.: 072817

Action Requested: The Petitioner has requested the revision of their Experimental Use Permit request which "includes the use of a 6 lb. a.i. per gallon formulation, COMMAND 6EC.

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An EUP using this product was not proposed previously."

Background: A previous request for an EUP-Crop Destruct has been approved for use of COMMAND 4EC on soybeans (memo Holder to Taylor, dated January 3, 1984). In addition, the Petitioner's request for a establishment of a Temporary Tolerance (4G2987) for use of COMMAND on soybeans has been recommended for approval (memo, Gregorio to Taylor, dated January 2, 1985).

ACUTE TOXICITY DATA REVIEW

Study Type	Technical*	4EC*	6EC**
Oral LD50, rat	2077 mg/kg (M) 1369 mg/kg (F)	2343 mg/kg (M) 1406 mg/kg (F)	2388 mg/kg (M) 2235 mg/kg (F)
Dermal LD50, rabbit	greater than 2000 mg/kg	greater than 2000 mg/kg	greater than 2000 mg/kg
Inhalation LC50, rat	6.25 mg/L (M) 4.23 mg/L (F)	4.47 mg/L (M) 4.70 mg/L (F)	3.06 mg/L (M) 2.48 mg/L (F)
Eye Irritation, rabbit	Slight	Moderate to Severe	SEVERE
Dermal Irritation, rabbit	Slight	Moderate to Severe	Moderate to Severe
Skin Sensitization, guinea pigs	non-sensitizer	non-sensitizer	non-sensitizer

* Previously reviewed by James Holder (memo to Robert Taylor, dated January 3, 1983).

** The inerts for the 6EC Formulation have been cleared (see attached Inerts Ingredient clearance).

RECOMMENDATION: The toxicology data base is adequate to support the Petitioner's request for an Experimental Use Permit for use of COMMAND 6EC on pre-emergence soybeans.

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Command toxicology review

Page 3 is not included in this copy.

Pages _____ through _____ are not included in this copy.

The material not included contains the following type of information:

- ✓ Identity of product inert ingredients
- ___ Identity of product impurities
- ___ Description of the product manufacturing process
- ___ Description of product quality control procedures
- ___ Identity of the source of product ingredients
- ___ Sales or other commercial/financial information
- ___ A draft product label
- ___ The product confidential statement of formula
- ___ Information about a pending registration action
- ___ FIFRA registration data
- ___ The document is a duplicate of page(s) _____
- ___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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Chemical: Command; FMC 57020

Caswell No.: 463D

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Formulation: 6EC (64.3% Active Ingredient)

Citation: Acute Oral Toxicity Study of FMC 57020 6EC In Rats. Conducted and Submitted by FMC Toxicology Laboratory. Study No. A84-1176. Study Director John D. DeProspo, M.S. Dated July 2, 1984.

Petitioner: FMC Chemical Corporation

Accession No.: 072817

Reviewed By: Carolyn Gregorio, Toxicologist
Toxicology Branch/HED (TS-769) CG 1-8-85

Secondary Review: Robert P. Zendzian, Ph.D. 1/1/85
Acting Section Head
Toxicology Branch/HED (TS-769)

Material and Methods: Young adult Sprague-Dawley rats (10/sex/dose) were fasted overnight prior to dosing. The test compound was administered as a single dose of FMC 57020 (Command; purity 64.3%) as a 10% (weight/volume) solution in corn oil by oral intubation. The doses used are as follows:

a. Males: 2500, 2450, 2380, 2300, 2000, mg/kg
b. Females: 2450, 2300, 2100, 2000, 1800 mg/kg

"The animals were observed for mortality and clinical signs at 0.5, 1, 2, 3, 4 and 6 hours on the day of dosing and twice daily thereafter for 13 days; on day 14 they were observed once. Body weights were taken on days 0, 7 and 14 of the study." Gross necropsy was performed on all animals.

"LD_{50} calculations were performed using a TI-59 Logit Linear Regression Program written by Jim Gibbins, Texas Instruments Calculation Projects Division, and modified for an Appple II+ computer."

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Reported Results: "Decreased locomotion, ataxia, abdominal-genital staining, hematuria, and oral, ocular and nasal discharges" were observed "approximately 30 minutes after dosing and continued to be observed until day 3 of the study, at which time most surviving rats had returned to normal."

Animals surviving the 14-day observation period, displayed average body weight increases.

Gross necrospy of animals that died on study showed "red fluid in the intestines, and stomach." One male had a hemorragic stomach lining and one female had a hollow, fluid-filled kidney and grey fluid in the bladder. Gross necropsy of surviving animals revealed no apparent treatment related changes.

All deaths occurred within three days of dosing. Mortality data are presented below (Table 1):

Table 1. Morality Data For Rats given COMMAND 6EC

Males		Females	
Dose mg/kg	# Died/Dosed	Dose mg/kg	# Died/Dosed
2500	7/10	2450	8/10
2450	7/10	2300	4/10
2380	5/10	2100	5/10
2300	2/10	2000	2/10
2000	0/10	1800	0/10

Note: This table is reproduced from the Registrant's submission.

Conclusion: This study indicates that the following:

Acute Oral LD_{50} (males) = 2388 (2309-2468) mg/kg
Acute Oral LD_{50} (females) = 2235 (2090-2380) mg/kg

Toxicity Category: III

Core Classification: Guideline

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Chemical: Command; FMC 57020

Caswell No.: 463D

Formulation: 6EC (Lot No. PL84-28; 64.3% A.I.)

Citation: Acute Dermal Toxicity Study of FMC 57020 6EC In Rabbits. Conducted and Submitted by FMC Toxicology Laboratory. Study No. A84-1178. Study Director John D. DeProspo, M.S.; Dated June 11, 1984

Petitioner: FMC Chemical Corporation

Accession No.: 072817

Reviewed By: Carolyn Gregorio, Toxicologist
Toxicology Branch/HED (TS-769) CAG 1-31-85

Secondary Review: Robert P. Zendzian, Ph.D.
Acting Section Head
Toxicology Branch/HED (TS-769) 2/1/85

Material and Methods: Young adult New Zealand white rabbits (5/sex) were clipped free of dorsal hair from the scapular to pelvic region using an electric clipper. The test compound was applied (2000 mg/kg) under impervious plastic sheeting on a gauze pad and held in place for 24 hours. Animals were observed for body weight changes, clinical signs of toxicity, and mortality. Gross necropsy was performed on all animals.

Reported Results: No signs of clinical toxicity were observed except for one female animal which had "lacrimation from days 8 to 14 after dosing." Dermal irritation was observed on all rabbits "24 hours after dosing which resulted in eschar and fissuring on day 7 of the study. At termination, eschar and fissuring and desquamation were observed."

All animals lost weight during the study.

Gross necrospy revealed no treatment related pathology with the exception of one male which was observed to have "pitted kidneys."

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Conclusion:

Under the conditions of this study, COMMAND 6EC, the dermal LD_{50} is greater than 2000 mg/kg for males and females.

Toxicity Category: IV

Core Classification: Guideline

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Chemical: Command; FMC 57020

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Caswell No.: 463D

Formulation: 6EC (Lot No. PL84-28; 64.3% A.I.)

Citation: 4-Hour Acute Aerosol Inhalation Toxicity Study In Rats of FMC 57020 6EC. FMC Study No. A84-1179. Toxigenics Study 420-1517. Conducted by Toxigenics. Submitted by FMC Corporation. Dated July 6, 1984

Petitioner: FMC Chemical Corporation

Accession No.: 072817

Reviewed By: Carolyn Gregorio, Toxicologist CAG 1-3-85
Toxicology Branch/HED (TS-769)

Secondary Review: Robert P. Zendzian, Ph.D. 21,185
Acting Section Head
Toxicology Branch/HED (TS-769)

Material and Methods: Young adult albino rats (CRL:CD(SD) BR) Charles River Breeding Labs) were exposed to Command 6 EC for 4 continuous hours in stainless steel and glass inhalation chambers, followed by a 14-day observation period. "Each test aerosol atmosphere was generated by passing compressed outside air, which was filtered, conditioned, and dried, through a 1/4 J SS Air Atomizing Nozzle Assembly equipped with a 1650 SS Fluid Cap and a 64 SS Air Cap. The test article was pumped in Teflon tubing to the nozzle using an FMI Lab pump... Air flows were at least 10 turnovers per hour to insure sufficient oxygen supply during exposure... Particle size distribution was conducted for each exposure using a Delron Cascade Impactor, Model No. DCI-6. a sample was collected from the breathing zone of the test animals at approximately 1 and 3 hours into each exposure."

The rats (5/sex/dose) were exposed to the following concentrations of COMMAND 6EC (Table 1):

Table 1. Exposure Levels for 4-Hour Inhalation Rat Study

Test Group	Nominal Conc. (mg/L)	Gravimetric Conc.* (mg/L)	Analytical Conc.* (mg/L)
T-I	22.8	4.43	5.37
T-II	6.4	1.94	2.32
T-III	6.9	2.11	2.51
T-IV	11.1	2.64	2.98
T-V	6.4	2.61	2.97

* Time-weighted average concentration

Note: This table is abstracted from the Registrant's submission.

Animals were observed for body weight changes, clinical signs of toxicity and, mortality. Gross necropsy was performed on all animals.

Results:

Particle size analysis revealed 84.0% of the particles were less than or equal to 3.1064 microns; definitely within the respirable range for rats.

Clinical signs of toxicity noted during the study: "damp fur, irregular breathing, crusty muzzle, crusty eye, alopecia, gasping, prostration, salivation, crusty nose, red stained fur, ataxia, opacity of the eye, lacrimation, yellow/brown stained fur, and poor coat quality." Irregular breathing, gasping, opacity of the eye were noted for up to 8 days after exposure.

"At necropsy, no gross lesions were observed in 15 of the 50 rats. The remaining test rats exhibited abnormalities of the lungs, external surface, eyes, liver, stomach, nasal passages, intestines, and urinary bladder."

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All deaths occurred within 3 days of exposure. Mortality deaths are presented below (Table 2):

Table 2. Morality Data For Rats Exposed to 4-Hour Inhalation of 6EC

Test Group	Analytical Conc. (mg/L)	Mortality	
		Male	Female
T-I	5.37	4/5	5/5
T-II	2.32	2/5	2/5
T-III	2.51	2/5	2/5
T-IV	2.98	2/5	5/5
T-V	2.97	-	5/10

Note: This table is reproduced from the Registrant's submission.

Conclusion: Based on the conditions of this study, COMMAND 6EC, inhalation LC_{50} (Litchfield-Willcoxon) is as follows:

LD_{50} (males) = 3.06 mg/L (95% confidence limits: 1.96 - 4.79 mg/L)

LD_{50} (females) = 2.48 mg/L (95% confidence limits: 1.89 - 3.26 mg/L)

Toxicity Category: III

Core Classification: Guideline

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Chemical: Command; FMC 57020

Caswell No.: 463D

Formulation: 6EC (Lot No. PL84-28; 64.3% A.I.)

Citation: Primary Eye Irritation of FMC 57020 6EC In Rabbits. Conducted and Submitted by FMC Toxicology Laboratory. Study No. A84-1181. Study Director John D. DeProspo, M.S.; Dated June 20, 1984

Petitioner: FMC Chemical Corporation

Accession No.: 072817

Reviewed By: Carolyn Gregorio, Toxicogist CAG 1-31-85
Toxicology Branch/HED (TS-769)

Secondary Review: Robert P. Zendzian, Ph.D. 2/1/85
Acting Section Head
Toxicology Branch/HED (TS-769)

Material and Methods: Young adult New Zealand white rabbits (9 animals) were tested by introducing 0.1 ml of COMMAND 6EC into the conjunctival sac of the right eye by syringe; left eyes served as controls. After application, the eyelids were held closed for one second and released. The treated eyes of 6 animals remained unwashed; the treated eyes of 3 animals were rinsed with 100 ml of tap water approximately 30 seconds after treatment.

The eyes were scored for irritation potential using the Draize method at 1, 24, 48 and 72 hours on days 4, 7, 10, 13, 16, 19 and 22.

Results: The average Draize scores (total maximum scores: 110) for the unwashed and washed eyes are as follows (Table 1):

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Table 1: Average Draize Eye Irritation Scores.

Scoring Time	Unwashed	Washed
1 hr	37.0	32.0
24 hr	35.0	20.0
48 hr	27.8	17.3
72 hr	30.7	13.3
Day-4	24.7	7.3
Day-7	8.5	0
Day-19	7.0	0
Day-22	7.0	0

"One hour after dosing, all eyes had corneal opacities, iritis, and conjunctivitis. All of the washed eyes and most of the unwashed eyes returned to normal by day-7 of the study. At termination on day-22, one unwashed eye had an unresolved corneal opacity with pannus and vasculatization observed."

Conclusion: Based on the one animal with continued corneal opacity throughout the observation time (22 days), COMMAND 6EC is considered to have severe eye irritation potential.

Toxicity Category: I

Core Classification: Guideline

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Chemical: Command; FMC 57020

Caswell No.: 463D

Formulation: 6EC (Lot No. PL84-28; 64.3% A.I.)

Citation: Primary Dermal Irritation of FMC 57020 6EC In Rabbits. Conducted and Submitted by FMC Toxicology Laboratory. Study No. A84-1181. Study Director John D. DeProspo, M.S.; Dated June 20, 1984

Petitioner: FMC Chemical Corporation

Accession No.: 072817

Reviewed By: Carolyn Gregorio, Toxicologist CG 1-31-85
Toxicology Branch/HED (TS-769)

Secondary Review: Robert P. Zendzian, Ph.D.
Acting Section Head
Toxicology Branch/HED (TS-769) 2/11/85

Material and Methods: Young adult New Zealand white rabbits (3/sex) were shaved form the scapular to pelvic region. The site on the right is the spinal column was abraded and the left size remained unabranded. A gauze patch was taped to the shaved area and 0.5 of COMMAND 6EC was applied to the prepared skin. The gauze patch was removed 4 hours after application and the test sites were wiped with clean gauze.

The reaction of the skin was appraised 30 minutes after removal of the patch ("to allow for regression of pressure and hydration effects") and at 24, 48 and 72 hours and daily thereafter for 14 days.

Results: The average Draize scores (total maximum score = 8.0) for abraded and unbraded skin are as follows (Table 1):

Table 1. Average Draize Scores for Dermal Irritation

Scoring Time	Intact Score	Abraded Score
4 1/2 hrs	0	0
24 hrs	0	0
48 hrs	0	0
72 hrs	1.4	1.4
Day-7	0*	0*
Day-14	0*	0*

* Desquamation noted in 4/6 animals

Conclusion: Based on the 72-hour Primary Irritation Index, which was 1.4/8.0 for both abraded and unbraded skin, is indicative of well-defined erethema. Therefore, COMMAND 6EC is considered to have moderate to severe skin irritation potential.

Toxicity Category: II

Core Classification: Minimum

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Chemical: Command; FMC 57020

Caswell No.: 463D

Formulation: 6EC (Lot No. PL84-28; 64.3% Purity)

Citation: Skin Sensitization of FMC 57020 6EC In Guinea Pigs. Conducted and Submitted by FMC Chemical Corporation. Study No. A84-1177. Study Director John D. DeProspo, M.S.; Dated July 12, 1984

Petitioner: FMC Chemical Corporation

Accession No.: 072817

Reviewed By: Carolyn Gregorio, Toxicologist
Toxicology Branch/HED (TS-769) CG 10-31-85

Secondary Review: Robert P. Zendzian, Ph.D.
Acting Section Head
Toxicology Branch/HED (TS-769) 9/11/85

Material and Methods: The undiluted test material (0.4 ml) was applied topically to the preshaved skin of 20 male guinea pigs. The test material was allowed to remain in contact with the skin for approximately 6 hours during each induction treatment, one per week for 3 consecutive weeks. Dinitrichlorobenzene (DNCB), as a 0.15% (w/v) methanol solution, was applied to a concurrent positive control group of 10 animals. Fourteen days after the last induction application, the groups were challenged with 0.4 ml of the undiluted test material or DNCB as a 0.15% (w/v) solution in acetone. An additional group of 10 untreated animals was challenged with the test material and served as the challenge control group. Animals were observed for irritation 24 and 48 hours after each application.

Skin reactions were scored for irritation using the Draize method.

Results: The average Draize scores (total maximum score = 8.0) for skin sensitization are as follows (Table 1):

Table 1. Average Draize Scores for Skin Sensitization

Test Material	Draize Score
6EC *	
•24 hours	0/8
•48 hours	0/8
DNCB **	
•24 hours	2.5/8.0
•48 hours	2.5/8.0
Challenge Control**	
•24 hours	0/8.0
•48 hours	0/8.0

* 19 animals/group
** 10 animals/group

Note: This table is abstracted from Registrant's submission.

Conclusion: Under the conditions of this study, COMMAND 6EC is not a skin sensitizer in guinea pigs.

Core Classification: Guideline