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

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MEMORANDUM

JAN 3 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Robert Taylor
Product Manager 25
Registration Division (TS-767)

THRU: Christine F. Chaisson, Ph.D. C.F. Chaisson 12/15/82
Toxicology Section Chief IV
Hazard Evaluation Division (TS-769)

SUBJECT: EUP for Use of FMC 57020 Herbicide on Soybeans in Twenty-Nine States.

Identifying Number: 279-EUP-OG
Action Code : 700
Accession Numbers : 248473 and 248474
Record Number : 79949

Conclusions and Recommendations

1. All the present studies on FMC 57020 herbicide reviewed from FMC were classified as Core Guidelines except the inhalation studies which were classified Core Minimum. All studies reviewed here were conducted under Good Laboratory Practice (GLP).

2. Precautions expressed on the labeling should include a warning against the corrosiveness of FMC 57020 4EC (formulation) to the eye and to the skin. The proposed label is adequate to cover the EUP.

3. The toxicological studies submitted to Tox Branch support the present request for the EUP.

4. Tox recommends for the proposed EUP (1 year) on soybean application of FMC 57020 2,400 lbs. a.i. /800 acres in 29 States).

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Introduction

FMC is requesting an Experimental Use Permit (EUP) for the herbicide "FMC57020" in/on soybeans at a rate of 0.5 - 3.0 lbs/A in 10 gal. for ground spray or 1 gal. for aerial spray. The permit is requested for the herbicide use in the 1982/1983 growing season for soybeans (1 year) in the states of: AL, AR, DE, FL, GA, IL, IN, IA, KN, KY, LA, MD, ML, MN, MS, MO, NE, NJ, NY, NC, OH, OK, PA, SC, SD, TN, TX, VA, and WI (29 states). These applications, if made in all the listed states, encompass 99.7% of the U.S. soybean producing areas. The actual acreage to be treated (all states) is a total 800 acres, a total of 2,400 lbs. a.i. are to be applied.

The soybean crop treated with FMC 57020 is not to be used as a food or feed crop, but rather is to be destroyed (crop destruct) or is to be used for experimental purposes.

To assist in the review and future submissions on this new herbicide, physical and product chemistry was abstracted from Volume C, book 2, (EPA Acc. No. = 248474, reference 16) and appears as Attachment #1 to this memorandum. No animal metabolism or clearance studies were submitted with this EUP. Attachment #2 is the inert chemical composition of FMC 57020 (correspondence J. Dzuiben, R. D. to J. Holder, Tox., October, 1982). These inerts are cleared by EPA for use.

Studies submitted in support of the current EUP are:

Reviewed Studies herein on FMC57020 and FMC 57020 4EC

	Studies	FMC57020	FMC57020 4EC
A.	Acute Oral LD_{50}	+	+
B.	Acute Dermal LD_{50}	+	+
C.	Acute Dermal Irritation	+	+
C.	Dermal sensitization	+	+
D.	Eye Irritation	+	+
E.	Acute Inhalation	+	+
F.	Point Mutation	+	-

These studies are reviewed subsequently in Sections A thru G.

Review of Studies

A. Acute Oral Toxicity of FMC 57020

A series of graded doses of technical (88.8% a.i.) FMC 57020 was given orally to Sprague dawley rats and observations were made at 0.5, 1, 2, 3, 4, and 6 hours and subsequently every other day for thirteen days. The following incidence of lethality occurred due to FMC570-20 oral administration:

Oral Lethality of
Technical (88.8%) FMC 57020

Dose level (mg/kg)	No. Dead/No. Tested	
	Male	Female
2400	17/20	10/10
2167	4/10	-
1956	4/10	-
1766	3/10	-
1595	3/10	-
1300	2/10	8/10
1174	-	1/10
1064	-	2/10
864	-	0/10

A significant difference was noted between male LD_{50} = 2077 mg/kg (1976-2358 mg/kg, 95% conf. Limits) and female LD_{50} = 1369 mg/kg <1127-1611 mg/kg, 95% conf. limits). Clinical signs observed were decreased locomotion (peaking 3-4 hours post-treatment and decreasing thereafter) and recumbancy (6-24 hours), oral discharge (at one hr. and then disappearing thereafter), lacrimation, ataxia, chromodacryorrhea, and chromorhinorrhea. The signs occurred in all dose groups and were reversible.

The FMC 57020 4EC (formulation) was tested by oral administration also and the oral lethality results were:

Oral Lethality of Formulated(FMC57020 4EC (50% w/w of technical)

Dose level mg/kg	No. Dead/No. Tested	
	Male	Female
3228	10/10	-
2500	6/10	10/10
1936	2/10	9/10
1500	1/10	8/10
1162	-	2/10
899	-	0/10

The LD_{50} for males is 2343 mg/kg (2051-2635 mg/kg, 95% conf. limit) and LD_{50} females = 1406 mg/kg (1173-1639 mg/kg, 95% conf. limits). These values are not significantly different from the comparible LD_{50} values for the technical alone (see above) even though the emulsifiable concentrate formulation is 50% a.i. FMC 57020 and [redacted]

These values of LD_{50} (oral) place FMC57020 and FMC57020 4EC in Category III toxicity.

Study Classification: Core Guidelines

B. Acute Dermal Toxicity of FMC 57020

Ten New Zealand white rabbits were treated, after 24 hours pre-abrasion with a 22-23 ga. needle, beneath a gauze/plastic sheeting pad with approximately 4 mls of test material such that the resultant single dose for the 14 days was 2000 mg a.i./kg body weight. Observations were made for clinical signs at 0.5, 1, 2, 3, 4, 6 hrs and twice a day thereafter for a total of 14 days.

No rabbits died during the test. Weights and weight gains were normal and comparable to control rabbits for males and females. No gross external or internal lesions were observed from which it is concluded that FMC 57020 did not cause notable dermal toxicity under conditions of the test.

A similar protocol was carried out for formulated FMC57020. All treated rabbits survived. Clinical signs of lacrimation and nasal discharge were noted (approximately 8 hrs. after dermal application), but these signs are not considered compound-related. Gross observations indicated formulation-related damage to the skin at the application site. The damage was manifest in eschar and hair loss at the application site. These observations indicate corrosiveness of FMC 57020 4EC to skin which remains local to the site of application and which does not induce death at 2000 mg/kg.

These dermal toxicity studies place FMC 57020 and FMC57020 4EC in Category III.

Study Classification: Core Guidelines

C. Acute Dermal Irritation of FMC 57020

The backs of 2.5 kg. (approx) rabbits were clipped and divided to 4 quadrants - two abraded with a needle and two non-abraded. Each quadrant was approx. 5cm^2 and each received 0.5 ml technical or 4EC FMC57020. The test sites were occluded by by 8-ply gauze patches and whole body plastic wrap. Animals were restrained with Elizabethan collars. Scoring was done according to the Draize method of edema and erythema and eschar formation. GLP was followed in these tests.

Results of Primary Irritation Index (P.I.I.) from technical FMC 57020 was at 24 hrs 0.3/8.0 and at 72 hr 0/8.0 which averages to 0.2/8.0 (8.0 is possible maximum score) which relates qualitatively to a minimally irritating substance.

Contrary to the technical (above), the FMC 57020 4EC caused dermal irritation mostly with "well-defined" erythema and some "slight" edema. The combined 24 hr and 72 hr scores produce a P.I.I. = 2.1 out of a possible maximum score of 8.0. The edema had disappeared by 72 hrs with erythema and fissuring being manifest as clinical signs. Observations were continued eleven more days (14 days total). By day five the skin had thickened, was dry, and was also inelastic. Inelasticity and dryness likely promoted the bleeding observed at this time. This condition persisted and desquamation was noted which lead to sloughing of the top layers by day 9 and continued thru the 14th day.

A P.I.I. of 2.1 would normally be assigned to "mild irritation," but since FMC 570202 4EC promoted or caused fissuring, desqaumation, and finally sloughing of upper layers which was not reversible by 14 days, the qualitative rating was elevated to "Moderately to Severely Irritating." TOX agrees with this assignment.

It is suggested by these studies that the inerts or [redacted] in FMC 57020 4EC are causing the dermal irritation since the technical had a P.I.I. of only 0.2/8.0. Further studies with repeated applications, both occluded and non-occluded are suggested on the formulated product in support of future registration actions for permanent tolerance where repeated human dermal exposures might be anticipated.

Study Classification: Core Minimum

D. Dermal Sensitization to FMC 57020

Hartley guinea pigs (350-415 g.) were used to test 0.5 ml per application of FMC 57020 for skin sensitization to subsequent challenge. The first phase - sensitization - was performed by repeated 6 hrs patch occlusion. The potential for sensitization of skin was accomplished by 6 hr occlusion the first

day and the every other day for a total of ten exposures the last of which was on day 22 of the test period. Subsequent to the first phase, the second phase - challenge - was performed with 0.5 ml per shaved and depilitated virginal site after two weeks rest, i.e. on day 36 of the test. Skin reactions were scored according to the Draize method. A maximal dose producing minimal irritation in 24 hrs. was used which in this case was undiluted technical FMC57020. Observations were made and compared to control guinea pigs at 24 and 48 hours subsequent to challenge, i.e., on days 37 and 38 of the test.

Results showed the multiple (10 applications) patch occlusions were not irritating in the sensitization phase and further the challenge dose did not evoke anamestic response, i.e., FMC 57020 was not sensitizing. On the other hand, DNCB (dinitrochlorobenzene) at 0.05% was sensitizing in all 10 guinea pigs in the positive control group.

The formulated FMC 57020 4EC showed desquamation at day 5 of sensitization and some erythema at day 7. The results correlate with the irritations observed in the skin irritation tests on the formulated product. However, upon challenge FMC 57020 4EC did nct produce an anamnestic response.

These results for the a.i. and the formulated product show a lack of skin sensitization potential.

Study Classification: Core guidelines

E. Eye Irritation of FMC 57020

New Zealand rabbits (total of nine rabbits, three to be washed with water and six to be unwashed) were selected and treated with 0.1 ml of FMC 57020 or FMC 57020 in the right eye with the left untreated eye serving as an internal control. Observations were made according to the Draize System of Occular Lesions in the cornea (opacity and area), the iris, and the conjunctiva (redness, chemosis, and discharge). Observations were made at 1, 24, 48, and 72 hours after occular instillation of the test compound.

The test material technical FMC 57020 was found to be practically non-irritating. One hour following instillation a mild conjunctival redness was noted in 6 of 6 unwashed group and 1 of 3 of the washed group. However, by 24 hours all of symptoms subsided and remained normal throughout the test. Draize scores were: washed 0.7/110 and unwashed 2.0/110. These scores were not considered to be significantly different suggesting the test compound was cleared rapidly and/or was well tolerated by the rabbit occular tissue.

The formulation 4EC caused iritis in one washed and one unwashed eye while all eyes exhibited moderate to severe conjunctivitis after one hour. After 24 hours unwashed (6/6) and washed (2/3) manifest corneal opacity. At the end of the observation period 2/6 unwashed eyes remained opaque-thereby indicating a lack of reversibility of the effects. All other eyes were normal.

The a.i. is judged to be non-irritating and the 4EC is judged to be moderately to severely irritating.

These results agree with the skin irritation results in that the formulation ingredients show irritating and corrosive properties to epithelial tissue, viz. in the eye and in the skin.

Study Classification: Core Guidelines

F. Acute Inhalation of Aerosol FMC57020

Aerosol test groups were dosed with FMC57020 at 1.74, 3.67, 5.15, and 6.15 mg a.i./l. The average value for the size of the aersol droplet was mass median diameter = 2.2 um with a geometric standard deviation of ± 1.72 um. There were five males and five females in each test group, and in the air-treated control group. The weights of the albino rats (Crl: CD®, Charles River) were 231-293 grams (males) and 241-300 grams (females) on the exposure day. The rats were treated for 4 hours to aerosoled FMC 57020 (22 l/min, 500 l chamber volume, 2.6 exchanges /hr.) and then were observed for 14 days following GLP.

The lethality results were:

Dose (mg/l)	Males Deaths	Female Deaths
1.74	1/5 (1)	0/5 (none)
3.67	1/5 (1)	2/5 (1,3)
5.15	2/5 (1,1)	4/5 (1,1,2,2,)
6.15	3/5 (1,1,1)	3/5 (1,1,9)

The days after exposure for the deaths are indicated in parentheses.

All rats (except one female in high dose group) died shortly after or on the first day or by the second day with remaining animals surviving the fourteen day observation period.

The calculated male LC_{50} = 6.52 mg/l (95% conf. limits, 257-16.54 mg/l) with a slope of 1.77 probits/log dose. The female LC_{50} = 4.23 mg/l (95% conf. limits, 2.85-6.29 mg/l) with a slope of 417 probits/log dose. Both male and female LC_{50} fall into Category III inhalation toxicity.

Gross observations were damp and red stained fur, crustry noses and eyes, some alopecia, and excessive salvation with (in some cases) stronger reactions such as exophthalmus, ataxia, prostration, and labored treating. Animals either died early (1-2 days) or survived. Histopathogy showed abnormalities in the stomach of control groups with control rats showing abnormalities in spleen, lymph node, and testes. All groups showed abnormalities in lung, liver, and kidney with the severest responses in the treated groups.

The formulated product FMC57020 4EC was tested with GLC and followed the same protocol as with the a.i. studies (above) except for the following differences. The dosage concentration were 3.21, 4.23, 5.28, and 6.74 mg/l. The aerosol droplet average size was 2.09 um $\pm$ 1.73 um (geo.std. deviation). Weights were 230-299 (males) and 255-298 grams (females).

The flow rate was 20 l/min.

The lethality results were:

Dose (mg/l)	Males Deaths	Female Deaths
3.21	1/5 (3)	0/5 (none)
4.23	3/5 (1,2,2)	2/5 (2,3)
5.28	2/5 (1,1)	3/5 (1,2,3)
6.74	5/5 (1,1,1,1,2)	5/5 (1,1,1,2,2)

The days after exposure for deaths are indicated in parentheses.

Although all rats either died earlier or survived the 14 days, it is seen that these rats which did die, died somewhat later than those dying from the a.i. in the previously discussed experiment.

The calculated male LC_{50} = 4.47 mg/l (95% conf. limits, 3.34 - 5.97 mg/l) with a slope of 5.68 probits/log dose. The female LC_{50} = 4.70 mg/l (95% conf. limits, 3.79-5.84 mg/l, with a slope of 9.31 probits/log dose. Thus, the males and females did not respond differently from each other. These LC_{50} values placed the formulated product 4EC into Category III Inhalation Toxicity.

Study Classification: Core Minimum.

G. Assay for Point Mutation by FMC 57020

Five strains of Salmonela were tested in an Ames Type of Assay for point mutation: TA 98, TA 100, TA 1535, TA 1537, TA 1538. These strains were tested with FMC 57020 at plate concentrations of 6, 30, 150, 300, 600 ug/plate both with and without metabolic activation. This study followed GLP.

Positive controls showed good responsiveness to the strains tested:

Ames Test Results
Averaged Revertant Number for Strains TA-

chemical	ug/plate	98	100	1535	1537	1538
2-aminoanthracene	1.0	457	723			309
	4.0			158	278	
2-nitrofluorene	10	906				1669
1,3 propane sultone	.04		790	1214		
9-aminoacridine					730	

Note: numbers underlined were performed in the presency of S-9. Those not underlined had no S-9.

Negative and solvent controls produced very few revertants, 3-9 per plate. FMC 57020 produced 5-15 revertants randomly distributed in the dose range of 6 to 600 ug/plate. This finding of low reversion rates shows FMC 57020 does not produce point mutations in the five Salmonella test or strains.

Study Classification: Acceptable

J. W. Holder 11/22/82

James W. Holder, Ph.D.
Section IV
Toxicology Branch
Hazard Evaluation Division

G.Davis for J Holder:HOLDER II:HED/TOX: TS-769: CM#2,7-37a10

Attachment #1

copied from Registrant Submission (Caswell File)

FMC 57020 4 EC HERBICIDE

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I. Product Chemistry Information - FMC 57020 Technical

A. Product Identity - Technical Chemical

Chemical Name: 2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone

Chemical Abstracts Registry Number: None

Common Name: None

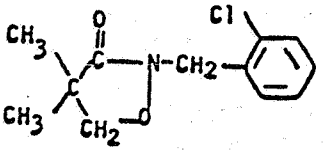
Trade Name: None

Company Code Number: FMC 57020

Molecular Formula: $C_{12}H_{14}ClNO_2$

Molecular Weight: 239.7

Structural Formula:



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Physical and Chemical Properties - FMC 57020 Technical Chemical

1. Color: light brown

2. Physical state: viscous liquid

3. Odor: light fatty acid

4. Melting point: not applicable

5. Boiling point: ~17.00 Pa at 100°C

6. Density: 1.192 at 20°C

7. Solubility: Completely soluble in:

Chloroform	Methanol	Methylene Chloride	Hexane
Heptane	Acetonitrile	Xylene	Toluene
Acetone	Dioxane		

8. Vapor Pressure: 1.92×10^{-2} Pa at 25°C

9. Octanol/Water Partition Coefficient: The octanol/water partition was measured by the technique described in the Federal Register, Volume 44 (No. 53), Pages 16254-16255, dated March 16, 1979 . The concentrations of FMC 57020 were determined by high pressure liquid chromatography (hplc). The partition coefficient for FMC 57020 = 27.5.

10. pH: not applicable

11. Storage stability: 96.6% technical chemical (MRW 267) - no loss at ambient temperature for one year; no loss at 50°C for three months.

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Physical and Chemical Properties - FMC 57020 4EC Formulations

1. Color: straw yellow
2. Physical State: liquid, at 20°C
3. Odor: characteristic of alkylated mononuclear aromatic hydrocarbons
4. Melting Point: not applicable
5. Boiling Point: not applicable
6. Density or Specific Gravity: density is 8.5-8.7 lb/gal, at 20°C; specific gravity is 1.02-1.04, at 20°C
7. Solubility: not applicable
8. Vapor Pressure: not applicable
9. Dissociation Constant: not applicable
10. Octanol/Water Partition Coefficient: not applicable
11. pH: 6.8-7.2, at 25°C
12. Stability: Not applicable.
13. Oxidizing or Reducing Action: The 4EC formulations contain inert ingredients which are recognized and accepted as not being oxidizing or reducing agents themselves, and as not being susceptible to oxidation or reduction reactions under typical use conditions. The active ingredient has not demonstrated potential for acting as an oxidizing or reducing agent under normal handling and use conditions, and by analogy to other known compounds is not expected to do so.
14. Flammability: flash point 104°-108°F, by Tag closed tester (ASTM D56-70)

15. Explodability: The 4EC formulations contain inert ingredients which are recognized and accepted as not being explosive ingredients themselves, and as not being explosive ingredients under typical use conditions. The active ingredient of this formulation has not demonstrated potential for acting as an explosive ingredient, and by analogy to other known compounds is not expected to do so.

16. Storage Stability:

    No loss at 25°C for one year;
    No loss at 50°C for three months.

17. Viscosity: 3.2-3.3 centipoise, at 20°C

18. Miscibility: Aqueous dilutions (emulsions) of the 4EC formulations at specified use rates have less than ten volume percent separation in water of 50 to 342 ppm hardness after standing undisturbed for one hour.

19. Corrosion Characteristics: The 4EC formulations are chemically and physically compatible with glass, aluminum, and double phenolic-lined mild steel containers.

20. Dielectric Voltage Breakdown: not applicable.

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Command toxicology review

Page _____ is not included in this copy.

Pages 16 through 17 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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