9-29-92

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 8340-UL
DAKOTA Herbicide

FROM: William S. Woodrow WSW 6-1-92
Precautionary Review Section
Registration Support Branch
Registration Division (H75-05C)
E 9/29/92

TO: J. Miller / E. Wilson (PM 23)
Fungicide - Herbicide Branch
Registration Division (H75-05C)

APPLICANT: HOECHST CELANESE

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
fenoxaprop-ethyl: (±)-ethyl 2-[4-[(6-chloro-2-benzoxazolyl)phenoxy] propanoate	3.01
MCPA, isooctylester: Isooctyl 2-methyl-4-chlorophenoxyacetate acid equivalent	50.06
Inert Ingredient(s):	46.93
Total	100.0%

BACKGROUND

Hoechst Celanese Corp. submitted acute oral, acute dermal, acute inhalation, primary eye and skin irritation and dermal sensitization studies to support registration of DAKOTA Herbicide (EPA Reg No. 8340-UL) MRID NOS used were 422409-13 through 422409-18.

RECOMMENDATION

1) The acute oral, dermal, eye and skin irritation and the acute inhalation studies, and the dermal sensitization studies are all acceptable; ~~[illegible]~~ E.

2) The acute oral and dermal sensitization studies were graded Core Minimum; a acute oral study - Unusual lack of mortality at higher male doses. It appears that once what appeared to be an approximate LD_{50} value for both males and females was tested, additional dosage increments did not increase mortality significantly as tested - A discussion of these findings would have been useful

b dermal sensitization - No mention was made of a positive control study. the tester should have used a Buehler scoring scale for the Buehler test employed, instead of the Draize irritation scoring scale.

3) Current acute toxicity profile for DAKOTA Herbicide (EPA 8340-UL):

study	Classification	Tox. Category
acute oral $LD_{50} > 2000$ mg/kg	Minimum	III
acute dermal $LD_{50} > 4000$ mg/kg	Guideline	III
acute inhalation $LC_{50} > 5.4$ mg/L	Guideline	IV
eye irritation Clearing in 8-21 days	Guideline	II
skin irritation P.I. Index = 0.88	Guideline	IV
dermal sensitization - not a sensitizer	Minimum	—

4) No additional acute toxicity data is required for DAKOTA Herbicide.

LABELLING

1) The WARNING signal word is appropriate

2) Change the Precautionary Statements as follows:

(precautionary statements Cont.)

"Causes substantial but temporary eye injury. Harmful if swallowed or absorbed through skin. Avoid contact with skin, eyes or clothing. Wear (goggles, face shield, or safety glasses). Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse."

3) Under Statements of Practical Treatment, the IF ON SKIN statement. Add "Get medical attention."

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

Product Manager: (23) 11-27-90
Reviewer: ~~M. Waller~~ Woodrow
MRID No.: 422409-13
Report Date: 5-28-92
Testing Facility: Pharma Res. Tox. + Path. Hoechst
Report No. 90.1413/90.0887
Author(s): G. Ehling, K.--
Species: Rat, Wistar
Age: 7-9 weeks
Observation Days (Post Exposure): ~~(14)~~; other (15)
Weight: M 177-202, F 164-200 g
Source: Hoechst AG breeding Colony
Test Material: DAKOTA Herbicide, liquid
Quality Assurance (40 CFR §160.12): yes (Q.A. + G.L.P.)

Conclusion: Higher male doses - significantly less mortality than much lower dose.

1. LD_{50} (mg/kg): Males = >2000 mg/kg; Females = ~~[illegible]~~; Combined = 3090 (2000-6250) ~~mg/kg~~
2. The estimated LD_{50} is >2000 mg/kg
3. Tox. Category: III. Classification: Core minimum

Procedure ~~(Deviations From §81-1)~~: Animals fasted about 16 hours pre-test, and were acclimated to lab conditions for 5 days. Test material emulsified in deionized water to produce dosing levels; doses were administered by gavage, at 10 ml/kg b.wt.

Results:

Reported Mortality

DOSAGE (mg/kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
1000 mg/kg	0/5	-	0/5
2000 "	5/10	0/5	5/10
2500 "	-	2/5	2/5
3150 "	-	4/5	4/5
4000 "	3/5	-	3/5
5000 "	1/5	5/5	6/10

Symptomology & Gross Necropsy Findings:

Clinical: ~~Irregular breathing~~, stilted gait, hunched posture, contracted pupils, ataxic gait, decreased activity, intoxication, reduced reflexes. Body wt. gains unpaired only in 4000 + 5000 dose levels.

Necropsies: Kidneys with dark spots at 1000 + 6000 mg/kg

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

Product Manager: (23) 10-23-90 Reviewer: ~~M. Walter~~ Woodrow
MRID No.: 422409-14 Report Date: 5-28-92
Testing Laboratory: Pharma Res. Tox. & Pathology Report No. 90.1311/90.0890
Author(s): G. Ehling, K-H. Leist
Species: Rat, Mal Wistar
Sex: M&F Wt.: 222-239(M), 211-248(F)
Test Material: DAKOTA Herbicide, liquid
Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.)

Summary:

1. LD_{50} (mg/kg): Males = ~~<~~; Females = ; Combined = ~~<~~;
2. The estimated LD_{50} is > 4000 mg/kg
3. Tox. Category: III. Classification: Guideline

~~1. Procedure (Deviations From §81-2):~~ Hair ~~removed by clipping~~ from dorsal areas of 5M&5F over 30 cm^2 area. Undiluted test material spread evenly over intact dorsal skin. Treated area covered with aluminum foil, held in place with plastic, elastic bandage. After 24 hours exposure)

Results:

Reported Mortality

DOSAGE (mg/kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
4000 mg/kg	0/5	0/5	0/10

~~Symptomology & Gross Necropsy Findings:~~

~~Wrapping removed and sites rinsed~~ & water. Animals weighed weekly, mortality & site recorded daily for 15 days. Animals subjected to autopsies.

Clinical: No clinical signs of intoxication

Necropsy: No gross abnormalities.

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

Product Manager: (23) 10-9-90 Reviewer: W. Woodrow
MRID No.: 422409-15 Report Date: 5-28-92
Testing Laboratory: Pharma Res. Tox. & Path. Report No. 90.1194
Author(s): T. Hoffmann, R. Jung study # 90.0891
Species: Rat, Wistar
Sex: 5M & 5F Weight: M 187-193, F 187-199 g
Source: Hoechst AG breeding colony
Test Material: DAKOTA Herbicide, liquid
Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.s)

Summary:

1. LC_{50} (mg/kg): Males ; Females = ; Combined =
2. The estimated LC_{50} is > 5.4 mg/L
3. Mean Concentration:
4. Tox. Category: IV. Classification: Guideline

Procedure (~~Deviations From §81-2~~): Animals acclimated to lab. conditions at least 5 days. 5M & 5F rats individually placed in cylindrical tubes and nose-only exposed for 4 hours to aerosol test material. 5 s/glass

Results:

Reported Mortality

Exposure Concentration (mg/L)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
5.4 mg/L	0/5	0/5	0/10

~~Symptomology & Gross Necropsy Findings~~:

exposure chamber with 60 L volume. Animals behavior during exposure was observed, and observation continued daily for 14 days. Body weights recorded days -1 & 14 post exposure. All animals subjected to gross necropsy examination.

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After passing through filters, air pumped at positive bar 4 to special nozzles and absolute filter special nozzles maintained at 900 l/m. Air supply at nozzle maintained. Test material injected at constant speed, the primary aerosol was formed in a separator. Difference in rate between introduction of air at 900 l/m through nozzle & its removal at 1100/l.

Granulitic analysis of aerosol concentration in animal breathing zones performed (5 min. interval - Samples collected through glass fiber filter and a membrane 2 pore width of 0.65 μ. Difference in filter weight ÷ l air sampled = mg/l air

Aerosol particle size determined (distribution) using an Anderson 7 stage cascade impactor (Model Mark III). Test atmosphere impacted at each stage onto steel discs, weighed before and after sampling. The MMAD, GSD and other distribution parameters were calculated.

Results - No mortality

1) Chamber concentration:

Average of 3 samples = 5.4 mg/l

2) Particle Size Distribution

1st measurement:

impactor cutoff stage	cumulative distribution
1.5–3.0 μ	100%

MMAD = 0.9 μ

GSD = 1.55

2nd measurement

1.5–3.0 μ	100%

MMAD = 1.09 μ

GSD = 1.46

Conclusion: Acceptable study

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

Product Manager: (23) 10-23-90 Reviewer: ~~M. Waller~~ (Woodrow)
MRID No.: 422409-16 Report Date: 5-28-92
Testing Laboratory: Pharma Res. Tox. + Path. Report No. 90.1191
Author(s): R. Hack, K.-H. Leist Study # 90.0889
Species: Rabbit, N.Z. white
Sex: 9 females Weight: 2.4-3.8 kg
Source: Hoechst, AG, laboratory breed
Dosage: 0.1 ml
Test Material: DAKOTA Herbicide
Quality Assurance (40 CFR §160.12): yes (Q.A. + G.L.P.)

Summary:

Tox. Category: II Classification: Guideline

Procedure (~~Deviation From §81-4~~): 24 hrs pre-test, eyes of 9 rabbits examined for defects under UV light, after 1 drop instillation of 0.01% sodium-fluorescein sol. 0.1 ml applied to conjunctival sac left eye of 6 rabbits (3 signs of irritation

~~Results~~: 72 hrs post treatment, test material applied to same area, left eye 3 other animals.

Observations (number "positive"/number tested)

	Hour	Days					
	1	1	2	3	4	7	14	21
Cornea Opacity	2/6	2/6	2/6	2/6		1/6	0/6	
Iris	2/6	3/6	1/6	1/6		1/6	0/6	
Conjunctivae Redness	0/6	1/6	2/6	2/6		0/6	0/6	
Chemosis	0/6	1/6	1/6	1/6		0/6	0/6	
Discharge	6/6	2/6	2/6	1/6		1/6	0/6	

~~Comments~~: Eyes examined and scored for irritation @ 1, 24, 48, 72 hrs post instillation (Draize)

" Clearing in 8-21 days [1]

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Product Manager: (23) 10-16-90
MRID No.: 422469-17
Testing Laboratory: Pharma Research & Path.
Author(s): R. Hack, K.-H. Leist
Species: Rabbit, N.Z. white
Age: 3-5 months
Sex: 6 females
Weight: 2.7-3.3 kg
Dosage: 0.5ml
Test Material: DAKOTA Herbicide, fluid
Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.)

Reviewer: ~~Ms Waller~~ Woodrow
Report Date: 6-28-92
Report No.: 90.1165
study # 90.0888

Summary:

The Primary Irritation Index = 0.88

Toxicity Category: IV

~~Classification~~: Guideline

Procedure ~~(Deviations From §81-5):~~ 24 hrs pre-test, dorsal region hair of body of 6 rabbits removed by clipper to expose area of about 25 cm^2. A 2.5x2.5 cm cellulose patch fitted to shaved area of each animal. 0.5ml undiluted test material applied under each patch. Area then covered with semi-occlusive bandage.

~~Results:~~ 4 hour skin exposure. Wrappings removed, test sites rinsed with water. Test sites examined and scored for irritation at 30-60 minutes, 24, 48, 72 hours, and at 7 days. Scoring according to the Draize system.

Time	SUM ER-ED scores	Average Irritancy index
30-60 m	0	0.0
1 day	6	1.0
2 days	7	1.2
3 days	8	1.3

Special Comments:

P.I. Index = 0.88

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

Product Manager: (23) 11-28-90 Reviewer: Woodrow ~~M. Waller~~
MRID No.: 422409-18 Report Date: 6-1-92
Testing Laboratory: Pharma Res. Tox. + Path Report No: A 44721
Author(s): R. Hack, K.-H. Leist study # 90.0892
Species: Guinea Pig, Pierbright
Sex: female Weight: F 227-289 g
Source: Hoechst, SPF breeding colony
Test Material: DAKOTA Herbicide, fluid
Positive Control Material: none
Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.)

Method: Buehler
no + control, used Draize scoring for Buehler test

Summary:
1. This product is / (is not a dermal sensitizer.)
2. Classification: ~~Core~~ Minimum

Procedure (~~Deviation From §81-6~~): 4 animals acclimated at least 5 days. study animal groups:

Test	20	animals
Control	10	"
~~Results~~: Prelim. Screen	6	" (det. concentration)

Preliminary screen for Concentration:
2 g.p./test Concentration: 1) undiluted 2) 50%, 3) 10%
Following hair removal, 2 g.p treated with 0.5ml applied and occluded for 6 hours. Sites examined 24 hrs & scored according to Draize. Undiluted test material selected for induction and challenge.

Induction - main study:
0.6ml undiluted test material applied to shaved areas (clipped area) on animal left flanks (20 animals), ~ 2x2 cm cellulose patch, which in Test was covered with occlusive polyethylene film and a bandage. The 10 control animals were

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Residuals treated with deionized water (0.5ml). Exposure for 6 hours. Wrappings removed, treated sites scored for irritation. This procedure repeated 3 x per week for total of 9 applications. Sites examined 24 hrs after patch removed.

Challenge: Animals rested for 15 days, following final induction application. Hair on exposed right flank removed using clippers. Challenge treatment performed using undiluted material (test). 0.5ml test material applied to cellulose patch, which was placed on skin and covered with an occlusive bandage. 6 hours exposure. Wrappings removed, sites rinsed. Sites examined and scored for irritation. " Test material considered a sensitizer if 15% or more of the treatment animals show a positive reaction and at the same time no irritant effects have emerged in the control group. Challenge sites scored 24 and 48 hours after patch removed.

Results:

1) Pilot study - no irritation c undiluted, except treated was rough, dry (slight).

Field study Continued:

Note: pilot study actually involved 3 applications: after 3rd treatment 1/2 g.p. treated = 50% test material showed 1.0 score, and similar scoring for 1/2 animals at 100%.

2) Induction:

a. Test animals: 5 animals showed 1.0 score - 1st induction; All animals responded @ 2nd induction: 6/20 - 2.0 score; 14/20 showed 1.0. 3rd application - 6/20 @ 1.0 score; 4th app.: 10/20 - 1.0 score, 5th app. - 7/20 - 2.0 score; (8/20 1.0 scoring, 6th - 2/20 - 2.0 score; 15/20 - 1.0 score. 7th app. 12/20 - 1.0 score. 8th app. - 13/20 - 1.0 score. 9th app. - 14/20 1.0 scoring.

b. Challenge - Induced test animals challenged at naive sites: NO scoring (0.0)

c. Control animals - NO scoring.

Conclusion: The test animals were treated with candidate test material, with obvious irritation, and the challenge naive sites were all negative. Also, control animals were negative. Test material did not sensitize guinea pigs.

Tox Chem. No. 128701

File Last Updated

Current date 6-1-92

Study/Species/Lab/Study# Date	Material	MRID No.	Results	Tox. Cat.	Core Grade
acute oral LD_{50}, Rat Pharma Res. Tox. & Path. # 90.1413/90.0877 11-27-90	DAKOTA Herbicide	422409 -13	LD_{50} > 2000 mg/kg	III	minimum
acute dermal LD_{50}, Rat Pharma Tox. & Path. #90.1311/90.0890 10-23-90	"	422409 -14	LD_{50} > 4000 mg/kg	III	Guideline
acute inhalation LC_{50}, Rat Pharma Tox. & Path. # 90.0891 10-9-90	"	422409 -15	LC_{50} > 5.4 mg/L	IV	Guideline
eye irritation, Rabbit Pharma Tox. & Path. # 90.0889 10-23-90	"	422409 -16	Eyes clearing in 8-21 days	II	Guideline
skin irritation, Rabbit Pharma Tox. & Path. # 90.0888 10.16-90	"	422409 -17	P.I. Index 0.88	IV	Guideline
dermal sensitization, guinea pigs Pharma Res. tox. ..... #90.082 1-28-90	"	422409 -18	not a sensitizer	—	minimum