

US EPA ARCHIVE DOCUMENT

9-29-72

MEMORANDUM

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

FROM: William S. Woodrow WSW 6-1-72  
Precautionary Review Section  
Registration Support Branch  
Registration Division (H75-05C)

E 9/29/72

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

APPLICANT: HOECHST CELANESE  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

FORMULATION FROM LABEL:

<u>Active Ingredient(s):</u>	<u>% by wt.</u>
<u>fenoxaprop-ethyl : (±) -ethyl 2-[4-[(6-chloro-2-benzoyl-2-ethyl (phenoxy) propanoate</u>	<u>3.01</u>
<u>MCPA, isooctyl ester : Isooctyl 2-methyl-4-chlorophenoxyacetate acid equivalent</u>	<u>50.06</u>
<u>Inert Ingredient(s):</u> . . . . .	<u>46.93</u>
	<u>Total 100.0%</u>

## 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; ~~with the exception of the acute oral study~~ 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<sub>50</sub> 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 8340-01):

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!"

5  
**DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§81-1)**

Product Manager: (23) 11-27-90 Reviewer: M. <sup>Woodrow</sup> Waller  
 MRID No.: 422409-13 Report Date: 5-28-92  
 Testing Facility: Pharma Res. Fox. & 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: M177-202, F164-200 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.

- LD50 (mg/kg): Males = > 2000 mg/kg; Females = ~~3090 (2000-6250) mg/kg~~
- The estimated LD50 is > 2000 mg/kg
- Tox. Category: III. Classification: Care 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

Results: dosing levels; doses were administered by gavage, at 10ml/kg b.wt. 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 impaired only in 4000 & 5000 dose levels.

Necropsies: kidneys with dark spots at 1000 & 5000 mg/kg

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

Product Manager: (23) 10-23-90 Reviewer: ~~H. 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, MAF 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. & Q.L.P.)

Summary:

- LD50 (mg/kg): Males = \_\_\_\_\_; Females = \_\_\_\_\_; Combined = \_\_\_\_\_;
- The estimated LD50 is > 4000 mg/kg
- Tox. Category: III Classification: Guideline

~~Procedure (Deviations From §81-2): Hair removed by clipping~~  
 from dorsal areas of 5 M & 5 F over 30 cm<sup>2</sup> area. Undiluted  
 test material spread evenly over intact dorsal skin. Treated  
 area covered with aluminum foil, held in place with

Results: plastic, elastic bandage. After 24 hours exposure,

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:

~~Woundings removed and sites rinsed E water. Animals weighed~~  
 weekly, mortality notes recorded daily to 15 days. Animals  
 subjected to autopsies.

Clinical: No clinical signs of intoxication

Necropsy: No gross abnormalities.

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (S81-3)

Product Manager: (23) 10-9-90 Reviewer: W. Woodrow  
 MRID No.: 422,409-15 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.)

Summary:

1. LC50 (mg/kg): Males \_\_\_\_\_; Females \_\_\_\_\_; Combined = \_\_\_\_\_
2. The estimated LC50 is 75.4 mg/L
3. Mean Concentration: \_\_\_\_\_
4. Tox. Category: IV. Classification: Guideline

Procedure (Deviations From S81-2): 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 of test material. 55/glass

Results:

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

Symptomology & Gross Necropsy Findings:

exposure chamber with 60L volume. Animals behavior during exposure was observed, and observation continued daily for 14 days. Body weights recorded days 7 & 14 post exposure. All animals subjected to gross necropsy examinations.



After passing through filters, air pumped at pressure bar 4 to special meter and absolute filter special nozzle maintained at 800 lpm. Air supply at nozzle maintained. Test material injected ~~nozzle~~ at constant speed, the primary aerosol was formed in a separator. Difference in rate between introduction of air at 800 lpm through nozzle & its removal at 1100/l.

Geometric analysis of aerosol concentration in animal breathing zones performed (5 min interval). Samples collected through glass fiber filter and a membrane  $\bar{c}$  pore width of 0.65  $\mu$ . Difference in filter weight  $\div$   $\bar{c}$  air sampled = mg/L air. Aerosol particle size determined (distribution) using an Anderson 7 stage cascade impactor (Model Mark IV). 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

cumulative

stage

distribution

1.5-3.0  $\mu$ 

100%

MMAD = 0.9  $\mu$ 

GSD = 1.55

2nd measurement

1.5-3.0  $\mu$ 

100%

MMAD = 1.09  $\mu$ 

GSD = 1.46

Conclusion: Acceptable study

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

Product Manager: (23) 10-23-90 Reviewer: Woodrow M. Waller  
 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 2 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~~): 2 hrs pre-test, eyes of 9 rabbits examined for defects under UV light, after instillation of 0.01% sodium-fluorescein sol. 0.1 ml applied to conjunctival sac left eye of 6 rabbits (if signs of irritation

Results: 72 hrs post treatment, test material applied to same area, left eye

Observations

	(number "positive"/number tested)							
	Hour	Days						
		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	

3 other animals.

Comments: Eyes examined and scored for irritation @ 1, 2, 4, 48, 72 hrs post instillation (Draize)

"Clearing in 8-21 days"

6-1

Woodward

Product Manager: (23) 10-16-90  
 MRID No.: 422469-17  
 Testing Laboratory: Pharma Res. Tex. & Path.  
 Author(s): R. Hack, K. H. Leist  
 Species: Rabbit, N 2 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 (O.A. & G.L.P.)

Reviewer: Mr. Waller  
 Report Date: 5-28-92  
 Report No.: 90-1165  
 Study # 90-0888

Summary:

The Primary Irritation Index = 0.88

Toxicity Category: 10

Classification: Guide 1ml

Procedure (~~Deviations from §81.57~~): 24 hrs pre-test, dorsal region hair of body of 6 rabbits removed by clippers to expose area of about 25 cm<sup>2</sup>. A 2.5x2.5 cm Cellulose patch fixed to shaved area of each animal. 0.5ml undiluted test material applied under each patch. Area then covered with semi-occlusive bandage.

Results: If raw skin appears. Wrapping 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.T. Index = 0.88

(1)

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

Product Manager: (23) 11-28-90  
 MRID No.: 422409-18  
 Testing Laboratory: Pharma Res. & Path  
 Author(s): R. Hack, K.-H. Leist  
 Species: Guinea Pig, Pierbright  
 Sex: female  
 Source: Hoechst, SPF breeding colony  
 Test Material: DAKOTA Herbicide, fluid  
 Positive Control Material: none  
 Quality Assurance (40 CFR §160.12): yes (O.A. & G.L.P.)

Reviewer: Woodrow M. Waller  
 Report Date: 6-1-92  
 Report No.: A44721  
 Study # 90-0892

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

- Summary:
- This product is / is not a dermal sensitizer.
  - Classification: Cover Minimum

Procedure (~~Deviation From §81-6~~): A 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 removed, 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:  
 0.5ml undiluted test material applied to shaved areas (clipped areas) on animal left flanks (20 animals), 2x2cm cellulose patches, which in test was covered with adhesive polyethylene film and a bandage. The 10 control animals were

Animals treated with deionized water (0.5ml).  
 Exposure for 6 hours. Wrappings removed, treated  
 sites scored for irritation. This procedure repeated  
 3x per week to total 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 - Wrapping  
 removed, sites rinsed. Sites examined and  
 scored for irritation. "Test material considered  
 a irritant if 15% or more of the treated  
 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 in undiluted,  
 except treated and rough, dry (skin).

Pilot 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 scores - 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, 18/20 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 sandelwood test material, with obvious irritations, and the challenge naive sites were all negative. Also, control animals were negative. Test material did not sensitise 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 LD50, Rat Pharma Res. Tox. & Path. # 90.1413/90.0877 11-27-90	DAKOTA Herbicide	422409 -13	LD50 > 2000 mg/kg	III	Mini- mum
acute dermal LD50, Rat Pharma Tox. & Path. # 90.1311/90.0890 10-23-90	"	422409 -14	LD50 > 4000 mg/kg	III	Guide- line
acute inhalation LC50, Rat Pharma Tox. & Path. # 90.0891 10-9-90	"	422409 -15	LC50 > 5-4 mg/L	IV	Guide- line
eye irritation, Rabbit Pharma Tox. & Path. # 90.0889 10-23-90	"	422409 -16	Eye irritation in 8-21 days	III	Guide- line
skin irritation, Rabbit Pharma Tox. & Path. # 90.0888 10-16-90	"	422409 -17	P.I. Index = 0.88	IV	Guide- line
dermal sensitization, guinea pigs Pharma Res. Tox. .... # 90.082 1-28-90	"	422409 -18	Not a sensitizer	-	mini- mum