Returned: 4/6/89 4-6-89
(PL Review)

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 8340-GI
Tiller Herbicide

FROM: William S. Woodrow WSW 4-5-89
Precautionary Review Section E 4/6/89
Registration Support Branch
Registration Division (H75-05C)

TO: Larry Schnaubelt, Acting (PM 23)
Fungicide-Herbicide Branch
Registration Division (TS-767C)

APPLICANT: Hoechst Celanese Corp.
Route 202-206
P.O. Box 2500
Somerville, NJ 08876-1258

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
(±)-ethyl 2-[4-[6-chloro-2-benzoxazolyl) oxy] phenoxy] propanoate	8.85
2-ethylhexyl-2,4-dichlorophenoxyacetate	10.17
isooctylester-2-methyl-4-chlorophenoxy acetate	32.85
Inert Ingredient(s):	48.03
Total	100.0%

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BACKGROUND:

The Hoechst Celanese Co. submitted Acute Oral, dermal, inhalation, Primary eye and dermal irritation studies, and a Dermal sensitization study to support Registration of Tiller Herbicide (Reg. NO. 8340-GI). MRID NOS. used included: 409357-03 through 409357-08.

RECOMMENDATION:

The Acute Oral, dermal, inhalation studies, the Primary eye and dermal irritation studies, and the Dermal sensitization study are acceptable to Registration Support Branch/PBPS.

LABELING:

1) Change the product hazard signal word from "DANGER" to read "WARNING".

2) Change "Precautionary Statements" as follows: at the beginning "Causes substantial but temporary eye injury. Do not get in eyes." "Avoid contact with skin eyes or clothing." (The remainder of the Precautionary Statements are acceptable as shown on label).

3) Change "Statements of Practical Treatment" as follows: "If on skin, wash with plenty of soap and water. Get medical attention." No other changes are necessary.

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

Product Manager: (23) Reviewer: ~~M. Waller~~
MRID No.: 409357-03 Report Date: 4-6-89
Testing Facility: Pharma Res. Tox. & Path. Gr. Report No. A39342
Author(s): K.H. Leist & V. Schollmeir
Species: Rat, Wistar
Age: ? young adults Observation Days (Post
Weight: see below Exposure): (14); other ( )
Source: Hoechst AG
Test Material: fenoxaprop ethyl + 2,4D + MCPA liquid
Quality Assurance (40 CFR §160.12): satisfactory

Conclusion:

1. LD_{50} (mg/kg): Males = 4-5 g/kg ; Females = LD_{50} = 1.25-2.0 g/kg ; Combined = —
2. The estimated LD_{50} is 3.06 grams/kg
3. Tox. Category: III. Classification: Guidelines

Procedure ~~(Deviations From §81-1)~~: Start b. wts.: M 181-209g, F 168-196g. 7-9 weeks old. By gavage. Observed 14 days: mortality, toxic signs. All (dead & termed) grossly examined.

Results:

Reported Mortality

DOSAGE (mg /kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
800 mg/kg	—	0/5	0/5
1250 "	—	0/5	0/5
2000 "	—	5/5	5/5
3150 "	0/5	4/5	4/10
4000 "	0/5	—	2/5
5000 "	4/5	5/5	9/10

Symptomology & Gross Necropsy Findings:

Clinical signs included: reduced activity, irregular breathing, piloerection, reduced breathing rate, miosis, lacrimation. No alteration of body int. spaces. Dead animals showed: GI tract w/ white fluid, darkened fluid, congested lungs, marked livers.

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

Product Manager: (23) Reviewer: W. Woodrow
MRID No.: 409357-05 Report Date: 4-5-89
Testing Laboratory: Pharma Research Tox. & Path. Report No. A39340
Author(s): T. Hofmann & R. Jung
Species: Wistar Rat
Sex: 15M & 15F Weight: M 175-212, F 172-202 g.
Source: HOECHST AG Germany
Test Material: fenoxyprop ethyl + 2,4D + MCPA Liquid
Quality Assurance (40 CFR §160.12): Satisfactory

Summary:

1. LC_{50} (mg/kg): Males = —; Females = —; Combined = —
2. The estimated LC_{50} is > 5.07 mg/L
3. Mean Concentration: —
4. Tox. Category: IV. Classification: Guidelines

Procedure (~~Deviations From §81-2~~): Nose exposure: 15M & 15F - Chamber 60L. Aerosol by special nozzle. Primary aerosol in 10L flask, smaller aerosol particles (seemingly aerosol) into rising tube - int. exposure chamber. Animals observed during exposure & daily to 4 hr exposure

Results:

Reported Mortality

Exposure Concentration (mg/L)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
(ml/hr 30) = 2.88 mg/L	0/5	0/5	0/10
(ml/hr 60) = 4.75 mg/L	0/5	0/5	0/10
(ml/hr 120) = 5.07 mg/L	1/5	0/5	1/10

~~Symptomology & Gross Necropsy~~ Findings:

14 day necropsy. Analytical measurement for mass (u.t.) Particle size Distribution, using APS 33 Aerodynamic Particle Sizer mfd. by TSI, St. Paul. Measured: 0.486 - >15.4 µ; @ 30 min. intervals. Air sampling by withdrawing air @ 3 l/60 min. three gas washing flasks

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

Product Manager: (23)
Reviewer: ~~M. Waller~~ Woodrow
MRID No.: 409357-04
Report Date: 4-5-89
Testing Laboratory: Pharma Res. Tox. & Path. GE
Report No. A39339
Author(s): K-H. Diehl & K-H. Leist
Species: Rat, Wistar
Sex: 5M+5F
Wt.: M 208-222, F 202-211g
Test Material: fenoxyprop ethyl + 2,4D + MCPA liquid
Quality Assurance (40 CFR §160.12): satisfactory

Summary:

1. LD_{50} (mg/kg): Males = —; Females = —; Combined = —;
2. The estimated LD_{50} is > 4.0 grams/kg.
3. Tox. Category: III. Classification: Guidelines

Procedure (~~Deviations From §81-2~~): Undiluted. 4.0g/kg applied to shaved backs of 5M+5F rats. Covered w aluminum foil, elastic plastic bandages + Elastoplast - 24 hr contact. Toxic signs + mortality observations daily to 14 day - necropsies.

Results:

Reported Mortality

DOSAGE (g /kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
4.0g/kg	0/5	0/5	0/10

Symptomology & Gross Necropsy Findings:

reduced activity, piloerection, irregular breathing, altered gait. No remarkable necropsy findings.

in saline, filled with methanol, in cold bath.

Results: Body wt. gains impaired at 2 higher dose levels. Clinical signs: decreased activity, altered gait, irregular breathing, piloerection, gasping, crackling & crackling rales. Autopsy findings, revealed dark red lung discoloring, red spots on lung. G.I. tract inflated.

Approximate particle size means:

		MMAD
Dose (mass)	2.88 mg/L	4.73
	4.75 mg/L	6.76
	5.07 mg/L	6.76

Particulate matter was respirable

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

Product Manager: (23) Reviewer: ~~M. Waller~~ Woodrow
MRID No.: 409357-06 Report Date: 4-5-89
Testing Laboratory: Pharma Res. Tox. & Path. Report No.: A39346
Author(s): K. H. Leist & V. Schollmeir
Species: Rabbit, NZ white
Sex: Not given Weight: 2.7–4.2 kg
Source: Hoechst AG
Dosage: 0.1 ml
Test Material: Fenoxyprop ethyl + 2,4-D + MCPA liquid
Quality Assurance (40 CFR §160.12): satisfactory

Summary:

Tox. Category: II Classification: Guidelines

Procedure ~~(Deviation from §81-4):~~ 9 animals received 0.1 ml (undiluted) by instillation into left eye. 1 min. after application, eyes of 3 animals washed for 1 min. Eyes examined at 1, 24, 48, 72 hrs, 7, 14 & 21 days. Scoring for irritation/damage.

Results:

	Observations (number "positive"/number tested)							
	Hour	Days						
	1	1	2	3	4	7	14	21
Cornea Opacity	0/9	0/9	0/9	0/9		1/9	1/9	1/9
Iris	9/9	8/9	5/9	2/9		1/9	1/9	1/9
Conjunctivae Redness	9/9	9/9	9/9	2/9		1/9	1/9	1/9
Chemosis	9/9	9/9	3/9	1/9		1/9	1/9	1/9
Discharge	6/9	5/9	1/9	2/9		2/9	1/9	1/9

Comments: ~~Washed eyes with tap water 20 min.~~

Corneal involvement - 1 animal beginning 7 days - thru 14 & 21 days
Iris inflammation, 2/9 at 3 days, 1/9 at 7, 14 & 21 days
Chemosis 1/9 at 3 days, 1/9 at 7, 14 & 21 days. Discharge 2/9 at 3 days. 2/9, 1/9, 1/9 at 7, 14 & 21 days, respectively.

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DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5)

Product Manager: (23)
MRID No.: 409357-07
Testing Laboratory: Pharma Res. Tox. & Path.
Author(s): H.K. Leist & V. Schollmeir
Species: Rabbit, NZ White
Age: 3-5 months
Sex: not given
Weight: 1.7-2.3 kg
Dosage: 0.5 ml
Test Material: fenoxaprop ethyl + 2,4D + MCPA liquid
Quality Assurance (40 CFR §160.12): satisfactory

Reviewer: ~~M. Waller~~ Woodrow
Report Date: 4-5-89
Report No. A39344

Summary:

The Primary Irritation Index = P.I. index = 1.08

Toxicity Category: III

Classification: Guidelines

Procedure ~~(Deviations from §81-5)~~: 0.5ml under 2.5cm² surgical plaster to shaved backs of 6 rabbits. Contact 4hrs. Examination 30-60min, 24, 48, 72hrs, 7days. Erythema/edema/eschar scoring according to Draize.

Results:

0.0-0.5 non-irrit.
0.6-3.0 slightly irrit.
3.1-5.0 moderately irrit.
5.1-8.0 severely irritating

3/6 score 1.0 at 30-60 min (erythema) 4/6 1/6, 1.0 x 2.0 at 24hrs (eschar) 3/6, 1/6 scored 1.0, or 2.0 at 48hrs, 2/6, 1/6 scored of 1.0, or 2.0 at 72hrs 0.0 erythema at 7 days.

4/6 (24hrs) 3/6 (48hrs) & 2/6 (72hrs) edema scored of 1.0

Scores show slightly irritating 72 hours

Special Comments:

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

Product Manager: (23)
MRID No.: 409357-08
Testing Laboratory: Pharma Res. Tox. & Path
Author(s): K.H. Leist & U. Schallmeir
Species: Pirbright guinea pig
Sex: female 10 weeks Weight: 210-285 g
Source: HOECHST AG
Test Material: Fenoxy prop ethyl + 2,4D + MCPA liquid
Positive Control Material:
Quality Assurance (40 CFR §160.12): Satisfactory

Reviewer: ~~M. Waller~~ W. Dykstra
Report Date: 4-5-89
Report No. A39348

Method: Buehler

Summary:
1. This product [is] / is not a dermal sensitizer.
2. Classification: Guidelines

Procedure ~~(Deviation From §81-6)~~: Used a 50% solution of the test material + saline. Preliminary testing to determine minimally irritating conc. at 5%, 20% & 50% test material. Used 0.5ml - 6 hr contact, scored according to Draize.

~~Results:~~ Induction: (Main test)
0.5ml of 50% sol of test material in isotonic saline applied to 2x2 cellulose patch, first to front part of left flank/each of 20 guinea pigs - Covered & occlusive polyethylene for 6 hrs. 3X/week to total 9 induction applications. Control animals similarly treated with 0.5ml isotonic saline.

Challenge: Two weeks after last induction, all animals challenged (20 test + 10 control) with 50% test material in isotonic saline; 0.5ml for 6 hrs contact (similar to induction) - All applications examined for erythema/edema at 24 & 48 hrs post treatment.

Results:

sensitization centered? 2.

Body wt. gains unaffected. No clinical signs.
During induction (sensitization phase), skin of treated test animals was dry & chapped & fine & coarse scales. - peeling of coarse scales.
Challenge: No dermal reactions in control animals.
1) Tester indicates no erythema & edema during induction treatments; only dry chapped & fine scaling condition. This observation both for 24 & 48 hour scoring points.

2) At the 24 hour challenge reading, 4 of 20 rabbits showed an erythema score of 1.0. (20%) of the animals were positive. These findings were reversed at the 48hr reading (0.0)

thus, the 50% Test material did prove to be a slight, or weak sensitizing agent in guinea pigs.

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Tox Chem No. 204 File Last Updated _____ Current Date 4-5-89

fenoxaprop ethyl
2,4-D
MCPA

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX. Cat.	CORE Grade/ Doc. No.
Acute oral LD_{50}, rat. Pharma Res. Tox. Path. #A39342 10-20-88	ethyl 2-[4-[6-chloro-2-benzoxazolyl)oxy] phenoxy] propanoate 8.55% + 2-ethylhexyl-2,4-dichlorophenoxyacetate 10.27% + isooctyl ester-2-methyl-4-chlorophenoxyacetate 32.85%	409-357-03	LD_{50} = 3.06g/kg	III	Guidelines
Acute dermal LD_{50}, rat. Pharma Res. Tox Path. A39339 9-30-88	"	409357-04	LD_{50} = >4.0g/kg	III	Guidelines
Acute Inhalation LC_{50}, Rat. Pharma Res. Tox. Path. #A39340 11-7-88	"	409357-05	LC_{50} = > 5.07 mg/L	IV	Guidelines
Primary eye irrit, Rabbit. Pharma Res. Tox. Path. #A39346 11-8-88	"	409357-06	Corneal involvement: 1 animal beginning day 7 thru day 21. 1 animal irritation thru 21 days	II	Guidelines
Primary dermal irrit; Rabbit. Pharma Res. Tox. & Path. #A39344 11-8-88	"	409357-07	Erythema: 4/6 24hrs, 2/6 (48hrs) 2/6 @ 72hrs	III	Guidelines
Dermal sensitization, guinea pig. Pharma Res. Tox. & Path. # A39348	"	409357-08	50% test material did cause as a weak sensitizer in guinea pigs.	—	Guidelines