Reviewed
6/25/92

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 55947-RUU
Barricade F Herbicide

FROM: William S. Woodrow WSW 5-28-92
Precautionary Review Section
Registration Support Branch
Registration Division (H75-05C)
E 6/23/92

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

APPLICANT: Sandoz Agro, Inc.
1300 E. Touhy Ave.
Des Plaines, IL 60018

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Prodiamine [N^3, N^3-Di-n-propyl-2,4 dinitro-6-(trifluoromethyl)-m-phenylene diamine]	2.0
Inert Ingredient(s):	98.0
Total	100.0%

BACKGROUND

The Sandoz Corp. submitted acute oral, acute dermal, an inhalation feasibility study, primary eye and skin irritation studies, and a dermal sensitization study to support registration of BARRICADE FLOWABLE HERBICIDE (EPA REG. NO. 55947-RUU). MRID NOS. used were 422088-12 through 422088-17).

RECOMMENDATION

1) The acute oral, acute dermal, eye and skin irritation studies are acceptable, and were graded Core Guideline Studies.

2) A request to grant a waiver for conducting an acute inhalation toxicity study is granted:

a. The test material exhibits low water solubility, therefore dissolving in water to permit liquid aerosol formation is not feasible.

b. test mat. powder milled as fine as possible and tested for aerosol characteristics by generation in a Wright Dust generator

produced ≤ 17.8% particles at 3.5μ; the next cumulative % value was 3.3% ≤ 1.55μ. The MMAD was 6.1μ (using a Marple cascade impactor).

Thus, aerosolization of finely milled test mat. would not produce sufficient particles in inhalable ranges, therefore the inhalation waiver should be granted.

3) The dermal sensitization study was not acceptable, and was graded Supplementary Data:

a. The induction treatments must elicit irritation - the subject study (422088-17) did not produce any irritation, therefore guinea pig immune systems were not adequately challenged.

b. induction treatments should elicit irritation responses, the challenge concentration should be of less concentration than used for induction.

4) the Registrant must submit a new, properly conducted dermal sensitization study: induction applications must elicit irritation responses, concentration of challenge material should be less

than the concentration used for induction.

LABELLING

1) The CAUTION signal word is appropriate.
2) Add the following to the Precautionary Statements: "Causes moderate eye injury (irritation)." and "Wash thoroughly with soap and water after handling."
3) Under Statements of Practical Treatment, add: "Get medical attention", to the If on Skin statement.

DMI Note: Upon receipt of the requested dermal sensitization study, Precautionary Labeling may need revising.

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

Product Manager: (23) 10-4-90 Reviewer: ~~M. Walter~~ Woodrow
MRID No.: 422058-12 Report Date: 5-28-92
Testing Facility: Huntingdon Res Centre, Ltd. Report No. 909990/SNC/107/AC
Author(s): P. Baldrick, G. Harling
Species: Rat, Sprague Dawley
Age: 6 weeks Observation Days (Post Exposure): ~~(14)~~; other ( )
Weight: 99-110g
Source: Charles River, Margate, Kent.
Test Material: SAN 745H 2 GR 40% (A.I. is Prodiamine) 2% powder
Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.)

Conclusion:

1. LD_{50} (mg/kg): Males = ~~—~~; Females = ; Combined = ~~—~~
2. The estimated LD_{50} is > 5.0 g/kg
3. Tox. Category: 4. Classification: Guideline

Procedure ~~(Deviations From §81-1)~~: Used as 50% W/V dilution in distilled water; at 10ml/kg body wt. 5M & 5F rats dosed by gavage with 5.0 g/kg b.wt. Animals observed frequently ~~Results:~~ post dosing first day, and twice/day to 14 days for toxic symptoms, mortality

Reported Mortality

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

~~Symptomology & Gross Necropsy Findings~~:

All animals subjected to gross necropsy examination.
Clinical: Piloerection soon after dosing.
Terminal autopsy: No gross abnormalities.
All rats gained weight throughout study.

Animals acclimated for 5 days prior to test.

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

Product Manager: (23) 10-24-90 Reviewer: ~~H. Haller~~ Woodrow
MRID No.: 422088-13 Report Date: 5-28-92
Testing Laboratory: Huntingdon Res. Centre Report No. 901005D/SHC 103/AC
Author(s): P. Baldwin, G. Harding
Species: Rat, CDLI (SD)
Sex: 5M+5F Wt.: 225-273g
Test Material: SAN 745H 2 GR 403 (Prodiamine A.I.) 2% Powder
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 > 2.0 g/kg
3. Tox. Category: III. Classification: Guideline

Procedure ~~(Deviations From §81-2):~~ Test material prepared at conc. of 106.66% W/V in distilled water; administered at 1.88 ml/kg. 5M+5F rats treated with 2.0 g/kg test material - one day prior to test, hair removed from dorso-lumbar region & ~~Results:~~ each rat using clippers to approx 10% of body

Reported Mortality

DOSAGE (2g/kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
2.0 g/kg	0/5	0/5	0/10

~~Symptomology & Gross Necropsy Findings:~~

Surface. Test material evenly spread - Treated area covered with gauze - bds in place with impermeable dressing around trunk. 24 hour exposure. Wrappings removed, sites washed. Animals observed for Toxic signs - mortality to 14 day post dosing.
Clinical: No clinical symptoms - All rats gained weight
Necropsy: No gross abnormalities.

7.

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

Product Manager: (23) 10-3-91 Reviewer: W. Woodrow
MRID No.: 422058-14 Report Date: 5-28-92
Testing Laboratory: Huntingdon Res. Centre Report No. SNC 106/2711-IT
Author(s): G.C. Jackson, C.J. Hardy
Species: _____
Sex: _____ Weight: _____
Source: _____
Test Material: _____
Quality Assurance (40 CFR §160.12): _____

Summary: Title: "Aerosolizability Trials"

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

Procedure (Deviations From §81-2): _____

Study Result: Request for an acute inhalation study should be waived.

Results:

Exposure Concentration (mg/L)	Reported Mortality (NUMBER KILLED/NUMBER TESTED) Males	Females	Combined

Symptomology & Gross Necropsy Findings:

Special study attempt. To form aerosols of test material specially prepared as powder. 1-Kg sample test material air-milled "to the extent technically possible by Micron Mills, Ltd. St. Paul's Cray, Kent.

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A Wright Dust Generator was used to assess the feasibility of aerosolizing milled test material. The test (aerosol) chamber used was made from acrylic sheet, and had volume of approx 120 liters. A sample of milled material was packed into the powder container of the Wright Dust Generator, using hydraulic bench press in stages, applying a 0.3 ton weight force force.
Dust generator connected to aerosol chamber by rigid plastic tube. Clean dried compressed air to generator - flow rate of 25 lpm - Powder container advanced manually until scraper blade in contact with packed material. Feed continued approximately 1 hour. Two samples taken from test atmosphere through weighed glass fibre filter and analysed gravimetrically to determine chamber concentration - Another sample was obtained using a Marple Cascade impactor (Model 298); material on stages weighed to determine particle distribution.

Results:

1) Measured concentrations of test material were 2.61 mg/l at 20 minutes, and 2.69 mg/l at 45 min.

2) The particle size analysis showed that only 3.3% of the particles were smaller than 1 μm in size.

-Quoted from tester's Report:

Size (μm)	Amount collected (mg) PSD1	PSD2	Total PSD 1-2 (mg)	% of total	Cumulative % size	Probit
9.8	0.34	-	0.34	16.4	83.5	5.9741
6.0	0.82	-	0.82	39.6	43.9	4.8465
3.5	0.54	-	0.54	26.1	17.8	4.0770
1.55	0.30	-	0.30	14.5	3.3	3.1616
0.93	0.00	-	0.00	0.0	3.3	3.1616
0.52	0.03	-	0.03	1.4	1.9	2.9251
0.0	0.04	-	0.04	1.9	-	-
Totals	2.07	-	2.07		-	-

MMAD = 6.1 μm σg = 2.71 . % less than 1 μm = 3.3

-Unquote-

Discussion: According to the Tester, the powdered pesticide products exhibits low water solubility, and therefore dissolving in water to facilitate a wet aerosolization for aerosols.

inhalation study would be questionable. The milled material generated into a dry aerosol using a Wright Dust generator produced 17.8% cumulative particles ≤ than 3.5 μm; the respt cumulative % was 3.3 at 1.55 μm (≤). The MMAD was 6.1 μ, in this feasibility study.

The above discussion of the study results indicates that a waiver for requirement of an acute inhalation study for BARRICADE F Herbicide (55947-RUU) should be granted.

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

Product Manager: (23) 11-2-90 Reviewer: Woodtow
MRID No.: 422088-15 Report Date: 5-28-92
Testing Laboratory: Huntingdon Res. Centre Report No. 901087D/SNC 110/SE
Author(s): M.P. Liggett, L.A. McRae
Species: Rabbit, N.Z. White
Sex: 5F & 1 male Weight: 2.9-3.5 kg
Source: A. Smith, Surrey & Foxfield Farms, Petersfield England
Dosage:
Test Material: SAN 745H 2GR 408; A.I. is Prodiamine, powder
Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.)

Summary:

Tox. Category: III Classification: Guideline

Procedure (~~Deviation from §81-4~~): All eyes of 6 rabbits examined pre-test to ensure freedom from injury, damage. 0.1 ml liquid placed into lower everted lid of one eye each animal (Approx 50mg vs to 0.1 ml). Eyelids held together ~~Results:~~ one second. All animals ~~treated~~ eyes examined and scored for irritation at 1 hr, and 1, 2, 3, 4 and 7 days

Observations

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

~~Comments~~: post instillation, using the Draize Method. All irritation (conjunctival irritation only) absent by Day 7.

VI

Product Manager: (23) 11-2-90 Reviewer: ~~M. Waller~~
MRID No.: 422088-16 Report Date: 5-28-92
Testing Laboratory: Huntingdon Res. Centre Report No.: 901086D/SNC 109/SE
Author(s): M.P. Liggett, L.A. McRae
Species: Rabbit, NZ white
Age: 12-14 weeks old
Sex: 3M + 3F
Weight: 2.8-3.4 kg
Dosage: 0.5g
Test Material: SAN 745H 2GR 408 (Prodiamine A.I.) powder
Quality Assurance (40 CFR §160.12): yes (Q.A. + G.L.P.)

Summary:

The Primary Irritation Index = 0.00

Toxicity Category: IV

Classification: Guideline

Procedure (~~Deviations From §81-5~~): Rabbits acclimated to lab. conditions pre-test. Approx. 24 hours prior to application of test material, hair was removed from the dorso-lumbar region of each rabbit, using clippers. 0.5g test material applied under a 2.5cm gauze pad, moistened with ~~Results~~: 0.6ml distilled water to one intact skin site. Each site occluded with Elastoplast elastic dressing for a 4 hour exposure period. Wrappings removed and sites washed. Treated sites examined and scored for irritation using The Draize Scale) at 30 min after patch removal and on days 2, 3 and day 4.

Results:

~~Special Comments~~: 1) Approximately 30 min after patch removal, 6/6 rabbits exhibited 1.0 scoring for Erythema, 4/6 rabbits showed 1.0 scoring for edema.

2) No other scoring for any of the rabbits was recorded, for any subsequent examination periods.

"Mild or slight irritation".

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

Product Manager: (23) 11-30-90 Reviewer: Woodrow ~~M. Walter~~
MRID No.: 422058-17 Report Date: 5-28-92
Testing Laboratory: Huntingdon Res. Centre Report No.: 901124D/SAC 111/55
Author(s): B.T. Pascall, S.M. Denton
Species: Guinea Pig, Dunkin/Hartley
Sex: females Weight:
Source: D. Hall, Newchurch, Staffordshire, England
Test Material: SAN 745H 2 GR 408 (A.I. is Prodiamine), powder
Positive Control Material:
Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.)

Method: modified Buehler

Summary:
1. This product is / is not a dermal sensitizer.
2. Classification: SUPPLEMENTARY

Procedure (~~Deviation From §81-6~~): "The sensitivity of the guinea pig strain used is checked periodically at HRC with formalin, a known sensitizer." The positive control data included in the report did show

~~Results~~: guinea pig sensitivity.

Guinea pigs acclimated for 20 days pre-test.
20 females used for main study:
10 control animals
10 test animals

Preliminary investigation to determine (a) a slightly irritant concentration, suitable for the induction phase of the main study and (b) a more irritant concentration for the challenge phase". Results: Induction - 60% W/V in Alembical D (Alembical is a product of coconut oil - fractionating the fatty acids of coconut oil and re-esterifying with glycerine, to produce a Medium Chain Triglyceride (MCT) oil. This oil is

stable, has a low viscosity and surface tension and is easily absorbed into skin.

Induction: Nine applications; 3/week.

Skin on left shoulder of guinea pigs clipped free of hair using clippers. 2x2cm gauze patches (3-layer) were saturated with approx 0.5ml test material in Alembical D. Patch placed on skin and covered with impermeable plastic tape. An elastic adhesive bandage was then wrapped around grp. torsos and secured with tape. Skin contact for 6 hours. Wrappings/patch removed, treated sites scored for irritation according to an "arbitrary" scale 1-4 ER, 1-4 ED.

Control animals treated in same fashion as test animals, except no test material was used. (9 induction applications, 3/week).

Challenge:

The test and control animals were challenged two weeks after the ninth induction application, using 60% test mat. W/W in Alembical D. Area removed by clipping from 5x5cm area on right flank each guinea pig. 2x2cm gauze patch saturated with approx. 0.5ml test material (as done for induction). Patches sealed approx. 6 hours.

Challenge sites were evaluated 24, 48 & 72 hours after patch removal.

Results:

i) Induction

a. Control animals – no irritation (0.0)

b. Induced test animals – no irritation (0.0)

c. Challenge results – no irritation (0.0).

The same concentration of test material (60% W/V in Alembical D) was used for induction and for challenge.

Conclusion:

i) This dermal sensitization study must be graded

Supplementary Data:

a. The induction application must elicit irritation (no irritation was shown by induction).

b. The induction concentration should elicit irritation, and the challenge concentration should not produce irritation (in non-induced animals)

c. Because induction did not produce any irritation, an assumption must be made that test animals immune systems were not adequately stressed, as shown by lack of any induction irritation.

BASELINE:

Tox Chem. No. | File Last Updated | Current date

1102.01 Prodiamine | 5-28-92

Study/Species/Lab/Study# Date	Material	MRID No.	Results	Tox. Cat.	Core Grade
acute oral LD50, Rat Huntingdon Res. Centre #901990D/SNC/107/AC 10-4-90	Battlcade F Herbicide	422088 -12	LD50> 5.0g/kg.	IV	Guideline
acute dermal LD50, Rat Huntingdon #901005D/SNC 108/AC 10-24-90	"	422088 -13	LD50> 2.0 g/Kg	III	Guideline
acute inhalation LC50 — request for waiver Huntingdon # SNC 106/2711-IT	"	422088 -14	Request for study waiver granted	—	—
eye irritation, Rabbit Huntingdon #901087D/SNC 110/SE 11-2-90	"	422088 -15	All irritation absent by day 7	III	Guideline
skin irritation, Rabbit Huntingdon Res. Centre #901086D/SNC 109/SE 11-2-90	"	422088 -16	P.I. Index: 0.0	IV	Guideline
dermal sensitization, guinea pig Huntingdon Res. Centre. #901124D/SNC 111/SS 11-30-90	"	422088 -17	no scoring: induction challenge	—	Supplementary