9-29-92

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MEMORANDUM:

Subject: EPA File Symbol 524-EUP-56, Harness Plus

From: Mark J. Perry, Biologist
Precautionary Review Section
Registration Support Branch
Registration Division (H7505C)

MJP 9-29-92

To: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (H7505C)

Thru: Thomas C. Ellwanger, Section Head
Precautionary Review Section
Registration Support Branch
Registration Division (H7505C)

9/29/92

Applicant: Monsanto Company
Suite 1100
700 14th St. N.W.
Washington, D.C. 20005

FORMULATION FROM LABEL:

	% by wt.
Active Ingredient(s): Acetochlor	75.3
Inert Ingredient(s):	24.7
Total:	100%

BACKGROUND

Monsanto Company submitted acute oral, acute dermal, acute inhalation, eye irritation and dermal irritation studies in support of an EUP. The product, Harness Plus, is an emulsifiable herbicide to be tested for weed control in corn. Harness Plus (75.3% acetochlor) was initially referred to as TopHand Herbicide, therefore both names are used in this data package. The studies were performed at Food & Drug Research Laboratories and Bio/dynamics, and the MRID numbers are 424263-01 through 424263-05.

RECOMMENDATION

1. The acute oral, acute dermal, eye irritation and dermal irritation studies are acceptable as core guideline data. The acute inhalation study is acceptable as core minimum data.

2. The acute inhalation study received a core minimum grade for the following reason:

- The group I males are not considered "young adult" animals. The use of young adult animals is required by the Pesticide Assessment Guidelines.

3. The Registrant must submit an acceptable dermal sensitization study performed with the subject product.

LABELING

1. The appropriate signal word is "DANGER."

2. The Statements of Practical Treatment should include the following:

IF IN EYES: Flush with plenty of water. Call a physician.

IF SWALLOWED: Drink promptly a large quantity of milk, egg whites, gelatin solution, or if these are not available, drink large quantities of water. Avoid alcohol. Do not induce vomiting. Do not give anything by mouth to an unconscious person. NOTE TO PHYSICIAN: Probable mucosal damage may contraindicate the use of gastric lavage.

IF ON SKIN: Wash with plenty of soap and water. Get medical attention.

IF INHALED: Remove victim to fresh air. If not breathing give artificial respiration, preferably mouth to mouth. Get medical attention.

3. The Precautionary Statements should include the following:

Corrosive. Causes irreversible eye damage. May be fatal if absorbed through skin. Due to corrosive nature, may be harmful or fatal if swallowed. Harmful if inhaled. Do not get in eyes, on skin or on clothing. Wear protective clothing, rubber gloves and goggles or face shield when handling. Avoid breathing vapor or spray mist. Wash thoroughly with soap and water after handling and before eating, drinking or using tobacco. Remove contaminated clothing and wash before reuse.

4. Additional label changes may be required following submission of requested acute data.

ACUTE TOXICITY PROFILE

Acute Oral	Category G/3
Acute Dermal	Category G/2
Acute Inhalation	Category M/3
Eye Irritation	Category G/1
Dermal Irritation	Category G/4

NOTE TO PM: Due to eye irritation, this product meets the criteria for restricted use classification. The PM should decide if the label contains sufficient alternative labeling language to offset the hazard and the need for this classification.

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

Product Manager:25
MRID No.:424263-01
Testing Facility: Food & Drug
Author(s):E. Reagan
Species:SD Rat
Age: Young adult
Weight:231-357 g
Source: Charles River Labs
Test Material: Harness Plus (Tophand)
Quality Assurance (40 CFR §160.12): Present

Reviewer:M. Perry
Report Date:1/31/89
Report No.:FD-88-362

Conclusion:

1. **LD_{50} (mg/kg):** **Males** = --
   Females = 1702 mg/kg
   Combined = 1772 mg/kg
2. **The estimated LD_{50} is** 1702 mg/kg
3. **Tox. Category:**III **Classification:** Guideline

Procedure: The fasted test animals were dosed by gavage at 1000, 1500 and 2000 mg/kg of the undiluted test material. The animals were observed for mortality and signs of toxicity at least twice daily during the observation period. Body weights were recorded prior to dosing and on days 1, 4, 8 and 15 or at death.

Results:

Dosage mg/kg	(Number Killed/Number Tested)		
	Males	Females	Combined
1000	0/5	0/5	0/10
1500	0/5	1/5	1/10
2000	4/5	4/5	8/10

Symptoms & Gross Necropsy Findings: Ataxia, corvulsions, diarrhea, decreased activity and salivation were observed in many animals prior to study day two. Gross necropsy revealed fluid in the stomach, rugae absent from the stomach mucosa, discolored areas on the mucosa, mottled liver and puffy/dark lungs.

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

Product Manager:25
MRID No.:424263-02
Testing Laboratory: Food & Drug
Author(s):E. Reagan
Species: Rabbit
Weight:2.12-2.89 kg
Source: Ace Animals
Test Material: Harness Plus (Tophand)
Quality Assurance (40 CFR §160.12): Present

Reviewer:M. Perry
Report Date:1/31/89
Report No.:FD-88-362

Summary:

1. **LC_{50} (mg/kg):** **Males** = 2229 mg/kg
   Females = 1916 mg/kg
   Combined = 2081 mg/kg

2. **The estimated LD_{50} is** 1916 mg/kg

3. **Tox. Category:**2 **Classification:**Guideline

Procedure: The test material was applied to the clipped exposure sites and occluded with gauze, plastic wrap and a stockinette sleeve for a period of 24 hours. After dressing removal the test sites were gently wiped to remove excess test material. The animals were observed twice daily for mortality and signs of toxicity during the 15 day observation period. Body weights were recorded prior to dosing and on days 1, 4, 8 and 15 or at death.

Results:

Reported Mortality

DOSAGE mg/kg	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
1000	0/5	0/5	0/10
2000	2/5	4/5	6/10
5000	5/5	5/5	10/10

Symptoms & Gross Necropsy Findings: Anorexia, ataxia, decreased activity, nasal discharge, respiratory irregularity and salivation were observed in some animals during the study period. Among the animals which died during the study, gross necropsy revealed clear gel-like substance in the intestines, distended cecum, discolored lungs and pale areas on liver. No abnormalities were noted for the animals sacrificed at termination.

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

Product Manager:25
MRID No.:424263-03
Testing Laboratory: Bio/dynamics
Author(s):G. Hoffman
Species: Rat
Weight:192-331 g
Source: Charles River Breeding
Test Material: Harness Plus (Tophand)
Quality Assurance (40 CFR §160.12): Present

Reviewer:M. Perry
Report Date:3/31/88
Report No.:BD-87-113

Summary:

1. LC_{50} (mg/kg): **Males** = 3.2 mg/L
   Females = 2.1 mg/L
   Combined = 2.4 mg/L

2. **The estimated LC_{50} is** 2.1 mg/L

3. **Mean Concentrations:** 1.9/ 2.7/ 4.0/ 4.6 mg/L

4. **Tox. Category:**3 **Classification:**Minimum

Procedure: The animals in each dose group were exposed to the test atmosphere for four hours within a 100 liter chamber. An air atomizer (JSS Spraying Systems) with an FMI fluid metering pump was used for atmosphere generation. Chamber concentration (gravimetric) and particle size distribution were measured once per hour during the study period. Particle size was determined with a Delron DCI-6 Cascade Impactor. The animals were observed for mortality and signs of toxicity daily during the study period. Body weights were recorded just prior to dosing and on days 2, 3, 5, 8, 15, 22 (1.9 mg/L group) and 23 (4.0 mg/L group).

Deviation From §81-3: See recommendations

Results:

Reported Mortality

Exposure Concentration mg/L	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
1.9	1/5	2/5	3/10
2.7	2/5	4/5	6/10
4.0	3/5	5/5	8/10
4.6	5/5	5/5	10/10

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Symptoms & Gross Necropsy Findings: Lacrimation, salivation, labored breathing, decreased activity, matted coat, nasal discharge, ano-genital staining and tremors were observed in animals in all four dose levels. Discolored lungs, skin and fur were commonly observed upon necropsy.

mg/l							
Nom Conc	Grav Conc	Analyt Conc	MMAD	GSD	Temp[C]	Hum%	Air Flow [l/m]
13	1.9	---	2.0	2.4	72	69	20
28	2.7	---	2.9	2.1	74	79	20
46	4.0	---	2.9	2.1	74	82	20
83	4.6	---	3.2	2.4	73	75	20

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

Product Manager:25
MRID No.:424263-04
Testing Laboratory: Food & Drug
Author(s):E. Reagan
Species: Rabbit
Sex:--
Weight:--
Source: Ace Animals
Dosage:0.1 ml
Test Material: Harness Plus (Tophand)
Quality Assurance (40 CFR §160.12): Present

Reviewer:M. Perry
Report Date:1/31/89
Report No.:FD-88-362

Summary:

1. **Toxicity Category:**1

2. **Classification:**Guideline

Procedure: A 0.1 ml dose of the test material (undiluted) was placed into the right conjunctival sac of each animal. The eyelids were then held together for one second. The eyes were examined at 1, 24, 48 and 72 hours and 7, 14 and 21 days after exposure.

Results:

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

* Discharge not considered "positive" response

Comments: Due to the presence of corneal opacity on study day 21, the test material has been placed in category one for eye irritation.

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

Product Manager:25
MRID No.:424263-05
Testing Laboratory: Food & Drug
Author(s):E. Reagan
Species: Rabbit
Age: Young adult
Sex: --
Weight: 2-3 kg
Dosage:0.5 ml
Test Material: Harness Plus (Tophand)
Quality Assurance (40 CFR §160.12): Present

Reviewer:M. Perry
Report Date:1/31/89
Report No.:FD-88-362

Summary:

1. **The Primary Irritation Index** = --
2. **Toxicity Category:**4
3. **Classification:**Guideline

Procedure: A dose of 0.5 ml of test material was applied to the clipped exposure sites and occluded for a period of four hours. After removal of the dressings the sites were wiped with gauze to remove excess test material. Dermal evaluations were performed at 1/2, 24, 48 and 72 hours and 4, 7 and 10 days after patch removal.

Results: Grade one (5/6) and grade two (1/6) erythema were present at 0.5 hours. At 72 hours grade one erythema was present in only one animal.