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

9-17-90

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 241-286
Arsenal® Herbicide Technical (Imazpyr)

FROM: Lucy D. Markarian 4/9/90 Ea/17/90
Precautionary Review Section
Registration Support Branch
Registration Division (H75-05C)

TO: Robert Taylor (PM 25)
Fungicide Herbicide
Registration Division (H75-05C)

APPLICANT: American Cyanamid Co.
Agricultural Research Division
P.O. Box 400
Princeton, N.J. 08540

FORMULATION FROM LABEL:

352 it	Active Ingredient(s):	% by wt.
	<u>2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-2-pyridine carboxylic acid</u>	<u>95.0</u>
	Inert Ingredient(s):	<u>5.0</u>
	Total	100.0%

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BACKGROUND: American Cyanamid Co. under Adverse Effects Reporting Policy has informed EPA that their product Arsenal Technical Herbicide registered under EPA symbol 241-226 was found to be more severely irritating to the eye than indicated by previous testing. (Submitted in 1983 accession number 251501). As a result they have submitted four new tests, including an eye irritation assay, to be reviewed and support the revision of the label they find necessary. They feel, however that the change in the toxicity of the technical product should not affect any of the end use products derived from it, because all end-use products use Technical Arsenal dissolved and diluted. An acute Inhalation Toxicity study was included in the data submitted under accession number 251502 and a sensitization study was submitted under Accession number 251503.

RECOMMENDATION:

The four new studies: oral and Dermal Toxicity and eye and skin irritation Tests are considered core guideline data and acceptable.

LABELING:

The signal word is "Danger" based on the placement of eye irritation in Toxic category I instead of "Caution".

The precautionary statement must be altered to include:

Corrosive, causes irreversible eye damage. Harmful if absorbed through skin. Do not get in eyes or in contact with skin or clothing. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.

The statement of practical treatment must include:

If in eyes hold eyes open and flush with a steady gentle stream of water for 15 minutes.

If swallowed drink promptly a large quantity of milk, egg white, gelatin solution, or if not available, large quantities of water. Do not dilute. If on skin wash with plenty of soap and water. Get medical attention.

Note to Physician - Probable mucosal damage may indicate the use of gastric lavage.

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

Product Manager: (25) Reviewer: L. Markarian
 MRID No.: 415510-02 Report Date: 9/4/90
 Testing Facility: Toxicology Dept. American Cyanamid Report No. T-0222
 Author(s): Joel G. Fischer
 Species: Rat, Sprague Dawley
 Age: Young Adult, approximately 8 wks Observation Days (Post
 Weight: ♂ 135-144, ♀ 160-168 g Exposure): (14); other ()
 Source: Charles River Laboratories, Inc. Wilmington Ma
 Test Material: AC 243, 997 Arsenal Technical Herbicide (T-metapyr)
 Quality Assurance (40 CFR §160.12): Included

Conclusion:

1. LD₅₀ (mg/kg): Males = _____; Females = _____; Combined = _____
2. The estimated LD₅₀ is Greater Than 5000 mg/kg
3. Tox. Category: IV. Classification: core products

Procedure (Deviations From §81-1): The test material was administered as a 20% w/v corn oil suspension by gavage. Observations were taken during the first day and daily thereafter. Body weights were recorded at initiation and on days 7 & 14. Necropsy was performed on all survivors.

Results:

DOSAGE (mg /kg)	Reported Mortality (NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
<u>5000</u>	<u>0/5</u>	<u>0/5</u>	<u>0/10</u>

Symptomology & Gross Necropsy Findings:

There was no mortality or signs of toxicity during the 14 day observation period. At necropsy there were no observable signs of gross pathology

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

Product Manager: (25) Reviewer: L. Markarian
 MPID No.: 415516-02 Report Date: 9/4/90
 Testing Laboratory: Toxicology Dept. American Cyanamid Report No. T-022C
 Author(s): Joel E. Fisher
 Species: Rabbit, New Zealand white (Skoppe Farms, Skoppe, Pa.)
 Sex: 5 ♂ & 5 ♀ Wt.: ♂ 2.26 kg - 2.55 kg ♀ 2.15 - 2.46 kg
 Test Material: AC 243,997 Arsenal Technical Herbicide (Imazaapyr)
 Quality Assurance (40 CFR §160.12): Included

Summary:

- LD₅₀ (mg/kg): Males = _____; Females = _____; Combined = _____;
- The estimated LD₅₀ is Greater Than 2000 mg/kg
- Tox. Category: III. Classification: Cor. Guad. 2

Procedure (Deviations From §81-2): The test material was administered as received by placing the dose on the plastic wrap to cover approximately 10% of the body surface, moistening it by top water and placing the test animal ventral side down on the plastic and then wrapping the plastic around the body snugly and ending with adhesive tape. The plastic wrap was covered with cloth bandage. At 24 hr the wrappings were removed the residue from the test material was wiped with cloth wrap. Observations were frequent during the day of application and daily thereafter. Body weights were taken at initiation and ending 7th. Necropsy was performed. Results: on all animals.

Reported Mortality

DOSAGE (mg /kg)	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
2000	0/5	0/5	0/10

Symptomology & Gross Necropsy Findings:

No mortality or systemic toxicity was observed. Dermal toxicity was slight in 2/5 males as mild erythema observed for 48 hrs.

Necropsy revealed no abnormalities.

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

Product Manager: (25) Reviewer: L. Markarian
 MFID No.: 415510-01 Report Date: 9/4/90
 Testing Laboratory: Toxicology Dept. American Cyanamid Report No. T-0229
 Author(s): Joel E. Fischer
 Species: Rabbit, New Zealand White
 Sex: 6 Males Weight: not indicated
 Source: Skipack Farms, Skipack Pa.
 Dosage: 0.1 g
 Test Material: AC 248 997 Arsenal Technical Herbicide (Imazapyr)
 Quality Assurance (40 CFR §160.12): included

Summary:

Tox. Category: 1 Classification: Core Guideline

Procedure (Deviation From §81-4): The test material was instilled in the conjunctival sac of animals. The eyes were examined also prior to instillation. The eyes were evaluated at 1 hr, 24, 48, 72 hrs and on days 1, 7, 10, 14, 17 & 21. At 24 hrs the presence or absence of corneal lesions was tested by fluorescein dye. All evaluations were made according to Draize.

Results:

	Observations (number "positive"/number tested)									
	Hour	Days								
	1	1	2	3	4	7	10	14	17	21
Cornea Opacity	0/6	6/6	6/6	5/6	5/6	3/6	3/6	2/6	2/6	2/6
Iris	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
Conjunctivae Redness	0/6	6/6	6/6	6/6	6/6	5/6	4/6	4/6	0/6	0/6
Chemosis	0/6	4/6	6/6	6/6	6/6	1/6	3/6	0/6	0/6	0/6
Discharge	6/6	0/6	6/6	4/6	3/6	0/6	0/6	0/6	0/6	0/6
Vascularization of Cornea	0/6	0/6	0/6	0/6	0/6	0/6	3/6	2/6	2/6	1/6

Comments: _____

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

Product Manager: (25) Reviewer: L. Markarian
 MRID No.: 415510-05 Report Date: 9/9/90
 Testing Laboratory: Toxicology Dept. American Cyanamid Report No. T-0229
 Author(s): Jack E. Fisher
 Species: Rabbit, New Zealand White (Skippack Farms, Skippack, PA)
 Age: 12-14 weeks old
 Sex: 6 Male
 Weight: not specified
 Dosage: 0.2 g
 Test Material: AC 243,987 Arsenal Technical Herbicide (Imazapyr)
 Quality Assurance (40 CFR §160.12): Included

Summary:

The Primary Irritation Index = 0.05
 Toxicity Category: III
 Classification: Case Guideline

Procedure (Deviations From §81-5): The test formulation was applied as received to intact site on 1 inch square gauze patches moistened with tap water. Patches were held in site with adhesive tape and the trunk of the animal was wrapped in plastic and fitted close. After 4 hrs the wrapping was removed and site cleaned with gauze sponge and tap water. The sites were evaluated at 1, 24, 48 & 72 hours. Scoring of irritation was according to Draize.

Results:

There were no signs of systemic toxicity. The only sign of dermal irritation was the observation of barely perceptible erythema in one male at 1 hr.

Special Comments:

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