2-15-78

UNITED STATES ENVIRONMENTAL PROTECTION AG...

Caswell #3

DATE: February 15, 1978

SUBJECT: Registration Number 100-473

002372

FROM: J. Doherty

TO: Product Manager #25 Robert Taylor

Registrant: Ciba Geigy Corporatonn
Post Office Box 11422
Greensboro, North Carolina

Product: Evik 80W Herbicide
Chemical: 2- ethylamino-4-isopropylamino-6-methylthio-s-triazine

Structure:

Synonyms: Ametyrne,

Previous petitions, 3F1299, 8F0638, 9G0796, and 8F0903
Review by R. Coberly January 23, 1973 and September 1, 1972 see also Woodrow memo of October 18, 1977 to R. Taylor on Ametyrne (100-579).

Action Type: Review of Toxicological data to update files on Evik 80W formulation (No statement of formulation presented)

Remarks:

1) Ametyrne is listed on the memo of Dr. M. Regiff October 6, 1977 (see also Lampt memo October 20, 1977) as a product containing nitrosamines. Actions on Registration of products containing nitrosamines should be suspended.

2) Several of the studies were done by Industrial Biotest (see review). At least one study did not have a study number, audit of this data would be complicated.

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3) Summary of Acute Data

		Lab	Results	Toxicity Category
1)	Oral LD_{50}	IBT	1766 (1350-2390) mg/kg	III
2)	Dermal LD_{50}	IBT	> 10,2 gm/kg	III
3)	Skin Irritation	IBT	3.1/8.0 (score)	
4)	Eye Irritation-1	IBT	Croneal Opacity	II
	Eye Irritation-2	IRDC	Corneal Opacity	II
5)	Inhalation LC_{50}-1	IBT	71.35 mg/Li	Not acceptable
	Inhalation LC_{50}-2	IBT	2.22 mg/Li	III
	Inhalation LC_{50}-3	CIBA	6.5 mg/Li	III

4) The eye irritation studies both reveal transient corneal opacity, criteria for category II.

The registrant has requested that labelling conform to category III. Toxicology Branch requires category II labelling and appropriate warning for a category II eye irritant.

5) The other acute studies are core minimal.

Review of Acute Toxicity Studies EVIK 80W

1) Acute Oral Toxicity Study

i) Industrial Biotest, 8530-10-31, August 24, 1977

ii) Four groups of 10 rats (five male and five female) were given doses of 900, 1350, 2025 and 3038 mg/kg Evik 80W (FL-770062) and observed for symptoms of toxicity, mortality and necropsied.

iii) An acute oral LD_{50} of 1766(1350-2390) mg/kg was calculated. No difference between males and females in reported. This reviewed observes that the formulation may be more toxic to females than to males. Of the 19 of 40 animals that died, 13 of 19 died on the 6th day, the others died on the first or second day. This indicates that the formulation is slow acting. Since no controls were run simultaneously, the effect on weight gain is not established, although these are some indications of lower weight gain in rats treated at higher doses.

Pharmacological reactions included hypoactivity, muscular weakness, at the lower 2 doses. At higher doses (2025 and 3038 mg/kg) labored breathing, ptosis and prostration.

Gross necrosy findings included 3 incidences of pale livers in the rats in the 1350 mg/kg group. 6 incidences in the 2025 mg/kg group and only 5 incidences in the 3038 mg/kg group

iv) CORE minimal a LD_{50} is determined to put their product into category III.

2) Primary Skin Irritation

i) Industrial Biotest, 8530, 10431, August 24, 1977

ii) 6 albino rabbits were shaved and test material Evik 80W (0.5 gm) applied to two sites. One site was shaved skin the other was shaved and abraded skin. 24 hours were allowed for the material to react with the skin before washing.

iii) An irritation sure of 3.1/8.0 was determined to indicate the material was mildly irritating. The abraded skin showed moderate irritation (case 3) for both erythema and edema at 24 hours. At 72 hours there was still moderate erythema (2) but edema had subsided.

The intact skin showed less moderate (2) erythema and edema in 24 hours which subsided at 72 hours to slight (1-2) erythema but no edema.

iv) CORE minimal. The chemical product may be classified as a category III toxicant with regard to skin irritation.

3) Acute Dermal Toxicity

i) Industrial Biotest, No test Number, September 14, 197-

ii) Dose levels of 3.0, 4.6, 6.8 and 10.2 gm/kg of Ametryne 80W were applied to the backs of 4 rabbits (2 male and 2 female). The test material remained in place for 24 hours. Behavior reactions were observed and recorded

iii) No deaths or untoward behavioral reactions were observed among animals receiving a single dose. No evidence of skin irritation was observed as a consequence of the dermal application at these dose levels.

iv) CORE minimal*. The LD_{50} is 10.2 gm/kg. This reviewer finds a contradiction in the statement that no signs of skin irritation were observed at these dose levels. The skin irritation study reported above shows both erythema (3) and edema (3). The doses for these experiments were much higher.

* NO TEST NUMBER is given and study was by INDUSTIRAL BIOTEST.

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4) Eye Irritation (two tests)

i) Industrial Biotest, NO TEST NUMBER, September 14, 1964

ii) Five albino rabbits were used to evaluate the eye irritating properties of Ametryne 80W. 50 mg of test material were applied (instilled) into the conjunctival sac of each animal. Special emphasis was placed on the corneal tissue as opposed to the conjunctival and irridial areas. No washing was done.

iii) Ametryne 80W was found to be mildly irritating to the occular tissue In each of the five rabbits corneal opacity was observed. Opacity persisted for 72 yhours in one rabbits and 48 hours in another. The other rabbits showed opacity for 24 hours. In addition both the conjunctivae and iris showe irritation that persisted for 72 hours.

iv) CORE minimal. The presence of corneal opacity in all 5 of the rabbits, even though it is reversed is cause for placing this formulation into category II.

4A. Eye Irritation

i) International Research and Development Corporation
No. 382-019, June 9, 1977

ii) 6 New Zealand White rabbits were instilled with 0.1 ml of test material Evik 80W, FL-770436) into their conjunctival sacs. Three rabbits did not receive a wash following instillation. 3 rabbits were washed by 300 ml of distilled water 30 seconds following instillation

iii) Results

a) Unwashed eyes: 1 rabbit showed very slight corneal opacity at 24 and 48 hours, another showed slight opacity at 24 and 48 hours, both of these showed a dull luster of the cornea at 72 hours but were normal on the 7th day. The third rabbit was normal thoughout the experiment.

Iridial and conjunctivae irritation was slight to moderate and all rabbits showed some discharge. These effects were not evident on the 7th day. 2 of the rabbits developed petite hemorrhage in the conjunctival.

b) Washed eyes. No corneal damage or opacity reported. No iridial damage reported. Only very slight to slight conjunctivae irritation.

iv) CORE minimal. The presence of corneal opacity in the unwashed rabbits requires the product to be classified as a category II. This is in agreement with the IBT test.

5) Acute Inhalation (three tests)

i) Industrial Biotest, No Study Number, September 14, 1964.

ii) A group of 10 rats (5 male and 5 female) were exposed to an aerosol concentration of 27 mg/L of air of a 0.5 per cent W/V aqueous suspension of Ametyrne 80W. This corresponds to only 1.35 mg/L of Ametyrne 80W. Duration of exposure was for four hours.

iii) No deatns or untoward behavioval reactions were observed.

iv) NOT ACCEPTABLE. No LC_{50} dose established. These data make form a category II product since highest dose tested in category II range.

5A. Acute Dust Inhaltion study with Evik 80W

i) Industrial Biotest, May 16, 197[illegible].

ii) Test animals were exposed in a specially constructed inhaltion chamber designed so that the animals could be introduced into the test atmosphere after the desired test concentration was established. Exposure was for 4 hr at a atmospheric concentration of 2220 mg/m^3.

iii) There were no deaths during the exposure or the 14 day observaton period. Weight gain for the test animals was normal.

iv) CORE Minimal a) LC_{50} of 2230 mg/m^3 is established. (or 2.22 mg/Li), this is category III criteria.

5B. Acute Inhalation Toxicity of G-34162 WP80

i) Ciba-Geigy Limited, PH 2.635, December 10, 1976

ii) 9 male and 9 female were exposed to a concentration of 6.767 mg/Li for four hours (this was the highest concentration possible). Only the snout and nostrils were exposed to the dust.

iii) No deaths or untoward reactions were noted, there the LC_{50} is 6.5 mg/Li

iv) CORE minimal. Category III

J. Doherty

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