DATE: February 15, 1978
SUBJECT: Registration Number 100-673
FROM: J. Doherty
TO: Product Manager #25 Robert Taylor

Registrant: Ciba Geigy Corporation
Post Office Box 1122
Greensboro, North Carolina

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

Structure:

Synonyms: Ametynne,

Previous petitions, SF1399, SF0635, SG0796, and JP0903
Review by R. Coberly January 23, 1973 and September 1, 1972 see disc
Mootz memo of October 15, 1977 to R. Taylor on Ametynne (100-729).

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

Remarks:

1) Ametynne is listed on the memo of Dr. H. Regoff October 6, 1977
(see also Mootz memo October 20, 1977) as a product containing nitrosamines. Actions on Registration of products containing nitrosamines should be sus- pended.

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

<table>
<thead>
<tr>
<th>Lab</th>
<th>Results</th>
<th>Toxicity Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOT</td>
<td>$1766 (1350-2390)$ mg/kg</td>
<td>III</td>
</tr>
<tr>
<td>IST</td>
<td>&gt; 10.2 g/kg</td>
<td>III</td>
</tr>
<tr>
<td>IST</td>
<td>11/8.0 (score)</td>
<td></td>
</tr>
<tr>
<td>IST</td>
<td>Corneal Opacity</td>
<td>II</td>
</tr>
<tr>
<td>INST</td>
<td>Corneal Opacity</td>
<td>II</td>
</tr>
<tr>
<td>IST</td>
<td>$71.35$ mg/Li</td>
<td>Not acceptable</td>
</tr>
<tr>
<td>IST</td>
<td>$2.24$ mg/Li</td>
<td>III</td>
</tr>
<tr>
<td>CGRA</td>
<td>$6.5$ mg/Li</td>
<td>III</td>
</tr>
</tbody>
</table>

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 EYX 80W

1) Acute Oral Toxicity Study

i) Industrial Biocert, 5363-10-31, August 24, 1977

ii) Four groups of 10 rats (five male and five female) were given doses of 900, 1350, 2025 and 3035 mg/kg Evix 50 (FL-770062) and observed for symptoms of toxicity, mortality and necropsies.

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 4th 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 there are some indications of lower weight gain in rats treated at higher doses.
Pharmacological reactions included inactivity, muscular weakness, at the lower 2 doses. At higher doses (2025 and 3030 mg/kg) labored breathing, ptosis and prostration.

Gross necropy findings included 3 incidences of pale livers in the 1350 mg/kg group. 6 incidences in the 2025 mg/kg group and only 1 incidence in the 3038 mg/kg group.

iv) CORE minimal a LD50 is determined to put their product into category III.

2) Primary Skin Irritation

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

ii) 6 albino rabbits were shaved and test material Evik 100 (6.5 µm) 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 score of 1.1/8.0 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 48 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.

?) Acute Dermal Toxicity

i) Industrial Biotech, No test number, September 14, 1977

ii) Dose levels of 3.0, 4.5, 6.0 and 10.2 gm/kg of Amethystine 50X were applied to the backs of 4 rabbits (2 male and 2 female). The test material remained in place for 24 hours. Behavioral reactions were observed and recorded.

iii) No deaths or untoward behavioral reactions were observed among animal 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 LD50 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 dosis for these experiments were much higher.

* NO TEST NUMBER is given and study was by INDUSTRIAL BIOTECH.
1) Eye Irritation (two tests).

1) Industrial Biotech, No. 1ST NUMBER, September 14, 1964

11) Five albino rabbits were used to evaluate the eye irritating properties of Ametryne 30W. 50 mg of test material were instilled (instilled) into the conjunctival sac of each animal. Special emphasis was placed on the corneal tissue as opposed to the conjunctival and iridial areas. No washing was done.

111) Ametryne 30W was found to be mildly irritating to the ocular tissue. In each of the five rabbits' corneal opacity was observed. Opacity persisted for 72 hours in one rabbit and 48 hours in another. The other rabbits showed opacity for 24 hours. In addition both the conjunctivae and iris showed irritation. It persisted for 72 hours.

1v) OCER 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

1) International Research and Development Corporation

No. 352-019, June 9, 1977

11) 4 New Zealand White rabbits were instilled with 0.1 ml of test material Ethyl 30W, FL-770430) 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.

111) Results

c) 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 throughout 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 pettie hemorrhage in the conjunctival.

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

iv) OCER 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 IDT test.
5. Acute Inhalation (three tests)

1. Industrial Dusttest, No. Study Number, Sep 1964.

ii) A group of 10 rats (5 males and 5 females) were exposed to an aerosol concentration of \(27\, \text{mg/L of air}\) of a 0.5 per cent \(W/V\) aqueous suspension of Ametynne 80W. This corresponds to only \(1.35\, \text{mg/L of Ametynne 80W}\). Duration of exposure was for four hours.

iii) No deaths or untoward behavioral 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 Inhalation study with Evik 80W


ii) Test animals were exposed in a specially constructed inhalation chamber designed so that the animals could be introduced into the test atmosphere after the desired test concentration was established. Exposure was for 4 h at a atmospheric concentration of \(0.20\, \text{mg/m}^3\).

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

iv) CORE Minimal a) \(LC_{50} = 2230\, \text{mg/m}^2\) is established (or 2.22 mg/Li), this is category III criteria.

5B. Acute Inhalation Toxicity of C-34162 WP


ii) 9 male and 5 female were exposed to a concentration of \(6.76\, \text{mg/Li}\) 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 \(6.5\, \text{mg/Li}\)

iv) CORE minimal. Category III

J. Doherty