SUBJECT: Thiabenazole - Submission of Two Acute studies Submitted June 17, 1986 by Herb Sharp and Urna.
Ern No.: 000101
Acc No.: 234,289
Tox. Br. Project No.: 9-0296
Tox. Chm. No.: 6494

To: G. Werdig
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The: William Burnel, Acting Director
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Action requested: Review two acute studies submitted on thiabenazole as a result of a DCL.

Conclusions: These studies have been reviewed and the data evaluation reports are attached.

1. Acute Oral Toxicity in Rats

LD50 = 5.07 mg/kg for male rats
= 4.73 mg/kg for female rats
Toxicity Category: III (based upon LD50 for females)
Core Classification: Minimum

2. Acute Dermal Toxicity

LD50 > 2000 mg/kg
Toxicity Category: III
Core Classification: Minimum
DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Toxicity Study in Rats 61-1  Rm. Code: No.: 6-91

SUB No.: 57893-03

TEST MATERIAL: Thiadeniazole

STUDY NUMBER: TE 81-2091

SPONSOR: Merck Sharp and Dome

TESTING FACILITY: Merck Sharp and Dome Research Laboratories
West Point, PA

TITLE REPORT: Thiadeniazole Veterinary (Lot ER-211): Acute Oral Toxicity Study in Rats

AUTHOR(S): George A. Lankas

REPORT ISSUED: April 6, 1981

CONCLUSION: The acute oral LD50 for female rats was calculated to be 470 mg/kg (range 337-654) and for males 5070 mg/kg (range 362-639). Signs of toxicity included decreased activity, bradypnea and ptosis within 30 minutes of dosing. Deaths occurred mostly within the first 24 hours after dosing.

Toxicity Category: I (based upon the LD50 for females)
Core Classification: Maximum due to reporting errors (see results section.

LD50 = 5.07 g/kg for males rats
LD50 = 4.73 g/kg for female rats

MATERIALS:

1. Test compound: Thiadeniazole Veterinary, Lot ER-211; Purity 98.5% by HPLC analysis.

2. Test animals: Species: rat; Strain: Crl:CD(SU) BR; Age: 6 to 7 weeks; Weight: 117-190 g; Source: Charles River Laboratories, Wilmington, MA.

METHODS:

Rats were administered the compound on day 0 by oral intubation. They were observed frequently on the day the compound was administered and daily thereafter. They were weighed at pretest and days 7 and 12. They were fasted for 24 hours prior to necropsy unless they died prior to day 14. Necropsy was performed on 7
H. & L. rats.

RESULTS:

Mortality was as shown in the following table.

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>deaths/dose</td>
<td>deaths/dose</td>
</tr>
<tr>
<td>2222</td>
<td>0/10</td>
<td>2/10</td>
</tr>
<tr>
<td>3333</td>
<td>2/10</td>
<td>3/10</td>
</tr>
<tr>
<td>5000</td>
<td>6/10</td>
<td>4/10</td>
</tr>
<tr>
<td>7500</td>
<td>8/10</td>
<td>8/10</td>
</tr>
<tr>
<td>11250</td>
<td>9/10</td>
<td>9/10</td>
</tr>
</tbody>
</table>

Body weight data appeared to be reported for males only. Apparently there was an error from page 14–16 in Table 2. From dose level 2222 mg/kg on page 14 to page 16, the data are probably for females not males. In addition, body weight data were not given for days 7 and 14 for the one male in the 11250 mg/kg group that survived to final necropsy. Body weight gain was apparent at dosage levels at and above 5000 mg/kg for both males and females.

Clinical signs of toxicity consisted of decreased activity, bradypnea, ptosis, loss of righting reflex and alopecia (two 3333 mg/kg females only).

Findings at gross necropsy consisted mostly of petechial hemorrhages of the thymus and pinpoint tan foci of the lung.

A signed statement was included that stated that this study does not fall under the requirements for 40CFR Part 160.
STUDY TYPE: Acute Dermal Toxicity Study in rabbits 1-2

RKL No.: 407886-04

TEST MATERIAL: Thiadeniazole

SYNONYMS:

STUDY NUMBER: 4004-80

SPONSOR: Merck Sharp and Dohme

TESTING FACILITY: Bio/cynetics, Inc.
East Millstone, NJ

TITLE REPORT: Thiadeniazole (Batch #DR M6 17): Acute Dermal Toxicity Study in Rabbits

AUTHOR(5): Donna L. blaszczak

REPORT ISSUED: December 8, 1986

CONCLUSION: The acute dermal LD₅₀ for thiadeniazole in the rabbit is >2000 mg/kg.

Toxicity Category: III
Core Classification: Minimum, purity of test material not given.

MATERIALS:

1. Test compound: Thiadeniazole; off-white powder; Product #47962; Batch =DR M6 17; purity not stated.

2. Test animals: Species: rabbit; Strain: New Zealand; Age: at least 8 weeks; Weight: 2.1 to 2.6 kg; Source: Hazleton-Dutchland, Inc., Lenner, Pennsylvania.

METHODS:

Five male and five female rabbits were used. One day prior to dosing the trunk of each animal was shaved to expose approximately 10% of the body surface area. The test chemical (dry powder) was placed on gauze and moistened with saline. The only dose level used was 2000 mg/kg, the limit dose for this test. The treated gauze was held in place with an impervious plastic sleeve and Elizabethan collars were placed on the animals. The animals were exposed to the test chemical for 24 hours, at which time the material was removed and the skin
was wiped free of the material.

Animals were checked twice daily for mortality, 1, 2 and 4 hours after dosing for clinical signs of toxicity and daily thereafter for 14 days. Animals were weighed pretest and on days 7 and 14. At termination gross necropsy was performed on all animals.

RESULTS:

There were no deaths. Most animals gained weight from day 7 to termination of the study. Three animals showed decreased food consumption on the second day after dosing. There were no clinical signs of toxicity nor lesions seen at necropsy that could be attributed to treatment.

A quality assurance statement which was signed and dated was included.