Memorandum

Date: 16 August 1983

Subject: EPA Reg. No. 11678-42 ENDOSULFAN (THONEX) 50W
       Caswell #420
       In 6-15-83; Record No. 99310

From: B. T. Backus
      IRB/TSS

To: Mr. George LaRocca
    Product Manager 15

Registrant: Makhteshim-Agan (America) Inc.
Two Park Avenue
New York, NY 10016

Active Ingredient:
Endosulfan (Hexachlorohexahydromethan-2,4,3-
benzodioxathiepin 3-oxide)........................................50%
Inert Ingredients:....................................................50%

Background:
The registrant has sent in acute oral LD₅₀, dermal LD₅₀, inhalation
LC₅₀, primary eye and dermal irritation studies on this formulation
for purposes of reregistration, along with proposed labeling with
revisions based on the results of these studies.

Comments and Recommendations:

1. The acute oral LD₅₀, inhalation LC₅₀, primary eye and dermal
irritation studies received 5-31-83 are acceptable. The product
is in toxicity category I on the basis of oral LD₅₀ in females.

2. The acute dermal LD₅₀ study has been classified as supplementary
data, since significant mortality (50%) occurred at the lowest
dosage level tested, and it is not possible from the results to
classify the material as category I or II on the basis of
potential dermal toxicity.

3. Since there is some question as to whether this formulation is in
toxicity category I or II with respect to dermal toxicity hazard,
comments regarding the proposed precautionary and first aid
labeling will be deferred at this time.

Review:
The following studies were conducted at Life Science Research Israel,
Ltd., P.O. Box 139, Ness Ziona 70 451, Israel. Studies were conducted
on Thionex 50WP. Studies were received at EPA 5-31-83, and are in
Acc. 250399.

Procedure: Following a finding study, groups of 5M, 5F CD strain rats orally received dosage levels of 25, 39, 61, 96 or 150 mg/kg of test material administered in a volume of 20 mls/kg water with subsequent 14-day observation.

<table>
<thead>
<tr>
<th>Dosage Level (mg/kg)</th>
<th>Mortalities/Animals Dosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>25</td>
<td>0/5</td>
</tr>
<tr>
<td>39</td>
<td>0/5</td>
</tr>
<tr>
<td>61</td>
<td>0/5</td>
</tr>
<tr>
<td>96</td>
<td>4/5</td>
</tr>
<tr>
<td>150</td>
<td>4/5</td>
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</tbody>
</table>

Oral LD$_{50}$ (M) = 87 (61-113) mg/kg  
Oral LD$_{50}$ (F) = 47 (31-64) mg/kg  
Oral LD$_{50}$ (combined) = 65 (52-79) mg/kg.

Symptoms: decreased motor activity, hunched posture, clonic and tonic convulsions, bradypnoea. Salivation noted in animals which died. Some animals which died also showed congested and ulcerated stomach mucosa and staining around muzzle. Most survivors were unremarkable on post-sacrifice necropsy.

Study Classification: Core Guidelines Data

Product Classification: Tox. Cat. I (on basis of female oral LD$_{50}$)


Procedure: Groups of 4M, 4F NZ white rabbits received 24-hr occluded dermal exposure to dosage levels of 200, 320, 512 or 819 mg/kg. Test material was moistened with physiological saline solution. Half the subjects had abraded skin; other half were intact. There was subsequent 16-day observation.

<table>
<thead>
<tr>
<th>Dosage Level (mg/kg)</th>
<th>Mortalities/Animals Dosed</th>
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</thead>
<tbody>
<tr>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>200</td>
<td>2/4</td>
</tr>
<tr>
<td>320</td>
<td>2/4</td>
</tr>
<tr>
<td>512</td>
<td>-0/4</td>
</tr>
<tr>
<td>819</td>
<td>2/4</td>
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</tbody>
</table>

Test material appeared to be more toxic to subjects with intact skin.

Dermal LD$_{50}$ (M - abraded skin only), reported as 1052 mg/kg  
Dermal LD$_{50}$ (F - abraded skin only), reported as 305 mg/kg  
Dermal LD$_{50}$ (combined - abraded skin only), reported as 595 (107-1082) mg/kg  
Dermal LD$_{50}$ (F - intact skin only), reported as 238 mg/kg.

Symptoms: tremors, tonic and clonic convulsions, respiratory disturbances, with hypersensitivity to stimuli persisting in some survivors to termination. Some animals which died showed hemorrhagic gastric contents associated with mucosal erosion or ulceration. Skin changes included darkening and hemorrhage.
Study Classification: Core Supplementary Data (unable to determine whether product is in toxicity category I or II on basis of this study).


Procedure: 50 mg was applied to one eye of each of 9 rabbits. Three eyes were washed out about 30 seconds later.

Results: "Minor conjunctival irritation in 6/6 unwashed, 0/3 washed eyes. All eyes clear by day 7."

Study Classification: Core Minimum Data

Product Classification: Tox. Cat. III


Procedure: A single 0.5 gm aliquot was applied to one skin site on each of 4 rabbits, with 4-hr occluded dermal exposure.

Results: No irritation at 1, 24, 48 or 72 hrs after patch removed.

Study Classification: Core Minimum Data

Product Classification: Tox. Cat. IV

The following study was conducted at Lite Science Research, Stock, Essex England CM4 9PE. Study was received at EPA 5-31-83, and is in Acc. 250399.


Procedure: Groups of 5M Wistar strain rats were exposed to nominal concentrations of 0.57, 1.08 or 1.85 mg/L. Groups of 5F were exposed to nominal concentrations of 0.16, 0.31 or 0.57 mg/L. Exposure was 4 hr only. Concentration was also determined gravimetrically. Particle size data indicated 55-70% by weight of material was under 5 μm equivalent aerodynamic diameter. There was subsequent 14-day observation.

Results:

<table>
<thead>
<tr>
<th>Exposure Level (mg/L)</th>
<th>Mortality/Animals Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nominal</td>
<td>Measured</td>
</tr>
<tr>
<td>0.16</td>
<td>0.027</td>
</tr>
<tr>
<td>0.31</td>
<td>0.052</td>
</tr>
<tr>
<td>0.57</td>
<td>0.124</td>
</tr>
<tr>
<td>1.08</td>
<td>0.262</td>
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<tr>
<td>1.85</td>
<td>0.393</td>
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</table>

LC50 (t) = 0.357 (0.288-0.684) mg/L

LC50 (F) = 0.087 (0.059-0.127) mg/L
Symptoms: Hyperactivity, "hyperpnea" (presumably same as hyperpnea) during exposure. Other symptoms included decreased motor activity, hunched posture, muscle spasticity, tremors, piloerection, staining around snouts, salivation, clonic convulsions. Recovery in survivors generally by day 3. Some animals which died showed congestion, incomplete collapse or consolidation of the lung, abnormal gastric contents. Animals which survived showed on post-sacrifice necropsy nothing which appeared to be from exposure or dose-related.

Study Classification: Core Minimum Data

Product Classification: Tox. Cat. II

Byron T. Backus
IRB/TSS