BB-447
TXR-8153

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Memorandum

Date: 16 August 1983

Subject: EPA Reg. No. 11678-42 ENDOSULFAN (THIONEX) 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 LD_{50}, dermal LD_{50}, inhalation LC_{50}, 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 LD_{50}, inhalation LC_{50}, primary eye and dermal irritation studies received 5-31-83 are acceptable. The product is in toxicity category I on the basis of oral LD_{50} in females.

2. The acute dermal LD_{50} 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.

1 of 4

1. Acute Oral LD_{50} - rat. LSRI Report No. MAK/024/TNX 50WP; dated 30 September 1982.

Procedure: Following a range 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.

Results:	Mortalities/Animals Dosed	
Dosage Level (mg/kg)	M	F
25	0/5	2/5
39	0/5	0/5
61	0/5	5/5
96	4/5	5/5
150	4/5	5/5

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, bradyphnoea. 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})

2. Acute Dermal LD_{50} - Rabbit. LSRI Report No. MAK/025/TNX 50 WP. Dated 30 December, 1982.

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.

Results:	Mortalities/Animals Dosed	
Dosage Level (mg/kg)	M	F
200	2/4	2/4
320	2/4	3/4
512	0/4	3/4
819	2/4	3/4

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.

2

Study Classification: Core Supplementary Data (unable to determine whether product is in toxicity category I or II on basis of this study).

3. Primary Eye Irritation - Rabbit. LSRI Report No. MAK/027/TNX 50 WP. Dated 15 October 1982.

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

4. Primary Dermal Irritation - Rabbit. LSRI Report No. MAK/026/TNX 50 WP; dated 30 November 1982.

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

5. Acute Inhalation LC_{50} - Rat. LSR Report No. 83/MAK048/037. 23 February 1983.

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 snout 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:

Exposure Level (mg/L)		Mortality/Animals Exposed	
Nominal	Measured	M	F
0.16	0.027	-	0/5
0.31	0.052	-	1/5
0.57	0.124	0/5	4/5
1.08	0.262	1/5	-
1.85	0.393	3/5	-

LC_{50} (M) = 0.357 (0.288-0.684) mg/L
LC_{50} (F) = 0.087 (0.059-0.127) mg/L

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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 3/16/83

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4