

8EHQ-0793-1222

**COMPANY SANITIZED**

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July 16, 1993

8EHQ-93-12228

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**Express Mail- Return Receipt Requested**

Document Processing Center (TS-790)  
Attention: 8(e)Coordinator  
Office of Pollution Prevention and Toxics  
U. S. Environmental Protection Agency  
401 M Street SW  
Washington, D.C. 20460

OTS CBIC

93 JUL 20 AM 10:00

Dear :

**1-methyl-3-propylimidazol-2-thione (PTI)**  
**CAS Registry No.: 135011-47-1**

This letter is to inform you of the results of a recently completed subchronic toxicity study in rats.

Groups of 22 rats/sex/level were dosed by gavage with solutions of the test material in canola oil equivalent to 0, 5, 10, 25, or 75 mg/kg/day for 90 days. Body weights, food consumption, and clinical signs of toxicity were measured weekly throughout the study. During the study, blood was collected at various time points for clinical pathologic evaluation and analysis of serum thyroid hormones (T<sub>4</sub> and T<sub>3</sub>) and thyroid-stimulating hormone (TSH). Additionally, at the interim and final sacrifices, cell proliferation indices were determined for the thyroid and liver, and hepatic glucuronyltransferase activity was determined. At the end of the dosing period, 10 rats/group were sacrificed and necropsied. Selected tissues were weighed and examined macroscopically and microscopically.

A dose-dependent increase in hypertrophy/hyperplasia of the follicular cells of the thyroid gland was observed in both male and female rats dosed with 25 and 75 mg/kg/day (7 of 10 and 9 of 10 male rats, respectively, and 6 of 10 and 10 of 10 female rats, respectively).

In male and female rats dosed with 5 and 10 mg/kg/day, there were decreases in serum T<sub>4</sub> and T<sub>3</sub> levels. However, the T<sub>4</sub> and T<sub>3</sub> levels in rats dosed with 5 and 10 mg/kg/day were within the range of normal variability at all of the tested time points. Therefore, despite the apparent dose-dependent reductions in T<sub>4</sub> levels and sporadic reductions in T<sub>3</sub> levels, these findings are not considered biologically significant or adverse at all of the tested time points, due to the absence of related adverse findings, such as thyroid hyperplasia/hypertrophy or elevated serum TSH levels.

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In male and female rats dosed with 25 and 75 mg/kg/day there were statistically and biologically significant reductions in  $T_4$  and  $T_3$  levels. These corresponded with elevations in serum TSH levels, as well as elevated hepatic UDP-glucuronyl-transferase activity. This indicates that the test compound enhances the excretion of  $T_4$  into the bile, and that this enhanced rate of excretion of  $T_4$  is in part responsible for the sustained elevation of TSH and the corresponding pathological effects of thyroid hypertrophy and hyperplasia.

Under the conditions of this study, the overall no-observable-adverse-effect level (NOAEL) for the subchronic effects of the test compound in male and female rats was 10 mg/kg/day. The NOAEL was based on the effects on the thyroid gland in male and female rats dosed with 25 and 75 mg/kg/day; the hepatic centrilobular fatty change and the chronic progressive nephropathy in the kidneys, observed in male rats at these dose levels; the decreases in circulating erythrocyte mass and increases in serum cholesterol concentration in male and female rats dosed with 75 mg/kg/day; and, the substantial decreases in mean body weights (17%) and mean body weight gains (31%) observed in male rats dosed with 75 mg/kg/day. The body weight effects indicate that the maximum tolerated dose was exceeded in male rats dosed with 75 mg/kg/day.

Under these experimental conditions, the effects described above would appear to be reportable based upon EPA guidance regarding TSCA Section 8(e) criteria.

Sincerely,

**TESTS DATA:**

Submission # BEHQ-0793-12228 (5) SEQ. A

TYPE (INT) SUPP FLWP

SUBMITTER NAME: Confidential

**INFORMATION REQUESTED: FLWP DATE:**

- 0501 NO INFO REQUESTED
- 0502 INFO REQUESTED (TECH)
- 0503 INFO REQUESTED (VOL ACTIONS)
- 0504 INFO REQUESTED (REPORTING RATIONALE)

**DISPOSITION:**

- (0639) REFER TO CHEMICAL SCREENING
- 0678 CAP NOTICE

**VOLUNTARY ACTIONS:**

- (0401) NO ACTION REPORTED
- 0402 STUDIES PLANNED/UNDERWAY
- 0403 NOTIFICATION OF WORKER/OTHERS
- 0404 LABEL/MSDS CHANGES
- 0405 PROCESS/HANDLING CHANGES
- 0406 APP. USE DISCONTINUED
- 0407 PRODUCTION DISCONTINUED
- 0408 CONFIDENTIAL

SUB. DATE: 07/16/93 OTS DATE: 07/20/93 CSRAD DATE: 09/22/93

**CHEMICAL NAME:**

1-methyl-3-propylimidazol-2-thione

**CASE**

135011-47-1

**INFORMATION TYPE:**

**P F C**

0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX (HUMAN)	01 02 04
0211	CHR. TOX (HUMAN)	01 02 04
0212	ACUTE TOX (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

**INFORMATION TYPE:**

**P F C**

0216	EPICLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECOAQUA TOX	01 02 04
0221	CNV. OCCUR/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0229	METAB/PHARMACO (ANIMAL)	01 02 04
0230	METAB/PHARMACO (HUMAN)	01 02 04

**INFORMATION TYPE:**

**P F C**

0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEMPHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PRODUCE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

**TRIAGE DATA:**

**NON-CM INVENTORY**

**ONGOING REVIEW**

**SPECIES**

**TOXICOLOGICAL CONCERN:**

**USE:**

**PRODUCTION:**

YES (CONTINUE)

YES (DROP/REFER.)

RAT

LOW

NO (DROP)

NO (CONTINUE)

(MED)

(DETERMINE)

REFER.

HIGH

**COMMENTS:**

Non-CAP Target organs: thyroid, liver, kidney, RBC  
 NOAEL - stated to be 10 mg/kg/day but decreased T3+T4 levels  
 at 5+10 mg/kg, since thyroid was not done for  
 dose-related decrease, not sure if stated NOAEL is  
 correct.