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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Thiabendazole: FIFRA Sec. 6 (a)(2) Submission of a Specialized Protocol.

EPA ID# 060101-
Case No. 818982

DP Barcode D196185
Chem. ID No. 060101

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John E. Whalan 2-8-94

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THRU: Roger L. Gardner, Section Head
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Roger L. Gardner 2/8/94

KB 2/22/94

Dr. Samuel F. Rickard of Merck & Co., Inc. has submitted a draft protocol for a 14-week dietary thyroxine clearance study in rats which will explore the mechanism behind adverse findings of benign thyroid adenomas in a chronic toxicity / carcinogenicity study in rats.

This study is designed to assess whether thiabendazole alters thyroxine clearance and affects TSH or thyroid hormone levels in rats treated over 14 weeks, and whether compound-induced thyroid follicular hyperplasia is reversible during a 14-week recovery period. The doses selected for this study are 0 (vehicle control), 10, 90, and 270 mg/kg/day. Only male rats will be used. Dosing will be in the feed. The low and mid-doses are those used in a chronic feeding / carcinogenicity study. The high-dose exceeds the MTD, but is expected to be tolerated.

Clinical pathology analyses of TSH, T_3, and T_4 will be performed during dosing weeks 4, 8, 13, and recovery weeks 6 and 13. A thyroxine clearance study, using ^{125}I-thyroxine I.V., will be performed on 5 rats/group during week 13. Gross and microscopic necropsy will be performed only for the liver and thyroid. Organ weights will be measured for the brain, liver, and thyroid.

Although the protocol appears to be well designed, TB-I cannot assure the success of this study. Other than the thyroid battery, no other clinical pathology measurements are included in this protocol. It would probably be prudent to include activity measurements for the following enzymes:

T_4 Uridine diphosphate glucuronosyl transferase (UDPGT)
Hepatic deiodinase
Cytochrome P-450
Ethoxycoumarin O-deethylase (ECOD)
Aryl hydrocarbon hydroxylase (AHH)

Along with the protocol, Merck supplied statistical analyses from the chronic feeding / carcinogenicity study (attached). The incidence of benign thyroid adenomas was increased in the mid and high-dose groups (30 and 90 mg/kg/day, respectively), but statistical significance ($p < 0.05$, by trend analysis) was only found in the high-dose males. Focal cystic follicular cell hyperplasia was also increased in the mid and high-dose groups, but it was not statistically significant ($p > 0.05$). There were no other statistically significant tumor incidences at any site, and no increase in thyroid carcinoma in any group.

Dr. George Lankas believes these data present a classic case of species specific induction of thyroid follicular cell hyperplasia and adenomas by an indirect effect on thyroid hormone homeostasis as a consequence of stimulated hepatic clearance of thyroxine.