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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) Report of Preliminary Positive Findings in a Carcinogenicity Study.

EPA ID# 060101-000618
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FROM: John E. Whalan, D.A.B.T., Toxicologist
Section 1, Toxicology Branch I
Health Effects Division (H7509C)

John E Whalan 6-23-93

TO: Barbara Briscoe (PM Team # 51)
Special Review and Reregistration Division (H7508W)

THRU: Roger L. Gardner, Section Head
Section 1, Toxicology Branch I
Health Effects Division (H7509C)

Roger Gardner 6/25/93 KB 7/2/93

In compliance with FIFRA Sec. 6 (a)(2), Samuel F. Rickard of Merck Research Laboratories has written a letter (dated February 2, 1993) which provides preliminary data demonstrating adverse findings in a Chronic Toxicity/Carcinogenicity Study in Rats (Study TT #90-9009). The adverse finding is benign adenomas in the thyroid glands. Appended to the letter was an internal memorandum from Dr. George R. Lankas (dated January 20, 1993) which described the findings and offered an interpretation. Both documents are attached. Shortly after receipt of the Sec. 6 (a)(2) submission, Merck requested a meeting to explain their position. A meeting was held on March 10, 1993.

The in-life phase was completed in August, 1992. The doses used were 0 (control I), 0 (control II), 10, 30, and 90 mg/kg/day. A final study report is scheduled for submission to the EPA in November, 1993. There was a dose-related decrease in body weight gain of about 20-27% in the mid and high-dose males and high-dose females. Slight decreases in food consumption of about 4% were seen in the high-dose males and females only. There were no significant gross lesions found at necropsy.

Merck reported an increased incidence of benign thyroid adenomas coupled with focal cystic follicular hyperplasia at the two highest doses (30 and 90 mg/kg/day). These lesions were not increased above control levels in the low-dose group (10 mg/kg/day). These histopathologic findings, which are tabulated on the following page, were ascribed to a, "... species specific mechanism in which thiabendazole affects the thyroid in the rat indirectly by altering thyroxine clearance via increased hepatic metabolism."

Thiabendazole is metabolized to 5-hydroxy thiabendazole, which is then conjugated by the glucuronidation pathway and excreted, mainly in the bile. At sufficient dosages, liver metabolism is induced, and thyroxin and thiabendazole are both metabolized (by UDP-glucuronyl transferases) and eliminated. Merck believes that this accelerated thyroxin elimination stimulates the pituitary gland to secrete TSP, which in turn induces follicular hyperplasia as a compensatory response. Adenomas are a continuum of the hyperplasia. Merck considers 10 mg/kg/day to be a NOEL for adenomas.

The results from the recently completed study are preliminary, no thyroid hormones were measured, and no other substantiating data (such as liver weights) are available. Using the conclusions from two 14-week rat studies, Merck offers the following reasons for believing that the small increase in ademonas was caused by an indirect effect on thyroid hormone homeostasis:

1. At doses ≥40 mg/kg/day, there were increases in relative liver weights of 10-78%.

2. These rats had centrilobular hypertrophy characteristic of P-450 mixed function oxidase enzyme induction.

3. At doses of 160 and 400 mg/kg/day, there were increases in thyroid weights (as much as 64%).

4. Thyroid follicular cell hypertrophy and hyperplasia were found found at the same doses that induced these changes in the chronic study.

At the March 10, 1993 meeting, Merck agreed to perform a special study. It would be a short study (2 weeks to 90 days) performed at high doses. Parameters that could be measured include T_3, reverse T_3, T_4, TSH, iodine uptake, and biliary excretion. There should be a recovery period in order to assess reversibility in these parameters. Review of the chronic/carcinogenicity study should be delayed until this special study is available in order to assure a complete picture when it is peer reviewed.

The human anthelmentic dosing regimen is 15 mg/kg/day for 3 consecutive days, rest 1 week, then repeat. Since a link has not been demonstrated in humans between thyroid hyperplasia/hypertrophy and tumor formation, there may not be a cancer risk in humans. A simultaneous review of the chronic/carcinogenicity study and the special study should provide a better understanding of the health risk.

Selected Thyroid Histopathology

	Control I		Control II		10 mg/kg/day		30 mg/kg/day		90 mg/kg/day	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Number examined	50	50	50	50	50	50	50	49	50	50
Diffuse follicular cell hypertrophy	0	0	o	0	0	0	1	0	4	2
Focal cystic follicular cell hyperplasia	0	2	4	1	2	0	1	3	3	6
Follicular cell adenoma	0	1	0	2	1	0	5	1	6	5
Follicular cell carcinoma	0	1	1	0	0	0	0	0	1	0

♂ - Male
♀ - Female