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UNITED STATES GOVERNMENT

Memorandum

002774

TO : Mr. Louis Buckley
Petition Review Branch

DATE: August 31, 1965

FROM : Dr. Mary L. Quaife M. L. Quaife 9/2/65
Division of Toxicological Evaluation

SUBJECT: Thiabendazole, FAP No. 5A-1701. Request for tolerance at maximum residue concentration of 140 ppm in non-standardized baked goods as a mold inhibitor.

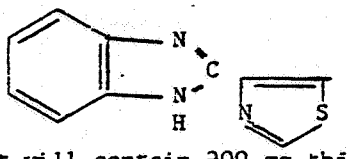
FOOD ADDITIVE PETITION NO. 5A-1701
(Final Evaluation)
4/5

Merck, Sharp, & Dohme Research Lab.
Division of Merck & Co., Inc.
Rahway, New Jersey
(AF 12-611)

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Introduction

Thiabendazole, $C_{10}H_7N_3S$, has a structural formula, as follows:



The commercial product will contain 900 mg thiabendazole (TBZ) per ounce [redacted]

According to FSA, memo of March 1, 1965, little or no TBZ is lost during baking of bread; so safety of its proposed usage should be judged on the assumption that it will actually occur at the maximum requested level.

Toxicity

Toxicological studies on TBZ are reviewed in detail by Drs. F. L. Earl and O. G. Fitzhugh in memo of 9/27/61. Their review is contained in the file on NDA 13-022. Findings given below are to supplement it, Cf., also, Robinson, et. al. (1).

The Robinson citation shows growth curves for (M and F?) rats fed TBZ in the diet at 0, 0.1, 0.2, 0.4, or 0.6% for 4 weeks. Growth was depressed

(1) Robinson, H. J., Stoerk, H. C., and Graessle, O. E., "Studies on the Toxicologic and Pharmacologic Properties of Thiabendazole." Toxicology and Applied Pharmacology 7, 53-73 (1965).

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proportionally to the level of TBZ in the diet; although the extent of depression in the 0.1% group is said to not be significant.

An additional item given in the Robinson citation concerning pharmacologic action is that ".....thiabendazole has no effect on the pressor response to epinephrine and norepinephrine or the depressor response to metacholine or histamine. These findings indicate that thiabendazole does not possess atropine-like, adrenergic-blocking or ganglionic blocking properties." Also, "topically applied TBZ appeared to be well tolerated by the skin and by the tissues of the eye."

Chronic dog study, Merck (finished after the 1961 memo).

Rather striking hemosiderosis was present throughout much of "the reticuloendothelial system" of (rats and) dogs, and these findings represented the only abnormal effect in dogs treated for a 2-year period with 100 and 200 mg of thiabendazole per kilogram. The hemosiderosis in these animals appeared to result from slight, prolonged degradation of erythrocytes but was not associated with measurable increases in serum bilirubin or increased urinary excretion of bilirubin (1).

Also, there was an apparent slight retardation in body weight gain in dogs on 200 mg/kg (FAP 5A-1701).

FAP 5A-1701 states that, "Some increases in liver, kidney, and adrenal weights were noted in the dogs given 100 or 200 mg/kg/day....(especially) ....when calculated on a body-weight basis."

However, the only organ weights which fell outside the range of "normal organ weights" for beagles, reported by Jackson and Cappiello (2), were the relative adrenal weights (to body weights) for male dogs on 200 mg/kg of thiabendazole. The difference is slight and, we conclude, not significant, toxicologically; since it is not dose-related, not found in females, and not confirmed by microscopic findings.

Chronic dog study, Woodard

No. of Animals. 3 M and 3 F per group.

Feeding Levels. 0, 20, 50, and 125 mg/kg body wt.

Duration. 2 yr

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(2) Jackson, B., and Cappiello, V. P., Toxicology and Applied Pharmacology 6 664-8 (1964).

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Mortality. 2 M at 125 mg/kg and 1 M at 20 mg/kg (latter due to intercurrent infection). Of former, one had markedly autolyzed tissues, the other, marked cirrhosis, seminal tubular degeneration, bone marrow atrophy, and degenerative renal change.

Body Wt. Changes from 0 to 2 yrs, averaged, for males, +1.9, +2.7, +0.6, and -1.1 kg and, for females, +2.6, +1.8, +1.7, and +0.8 kg (1 to r in order of increasing dose-level, starting with controls). All top-level males lost weight, and mean increase in males at 50 mg/kg was less than 1/3 that of controls.

Organ Wt. Mean kidney weight-body weight ratios increased with dose, for males, from 0.47 (controls), to 0.56, 0.62, and 0.94 and, for females, from 0.35 (controls), to 0.49, 0.49, and 0.59 g/100 g.

Clinical Lab. Tests. Blood urea N (I), serum alkaline phosphatase (II), S-GOT (III), blood glucose, prothrombin time, and coagulation time were determined. A dog at 125 mg/kg which died had elevated values for I, II, and III. A dog at 20 mg/kg had high values for I and III before death. There was more frequent occurrence of albumin in urine of high-level dogs; other results of urinalysis, normal. Reduced values for hemoglobin and packed cell volume in dogs at 125 mg/kg. Other hematological values and prothrombin unremarkable.

Neoplasms. None reported.

Histopathology. Moderate, chronic inflammatory liver changes, slight liver glycogen depletion, and inspissated material adhering to the gall bladder mucosa with no evidence of extraneous material in the bile ducts in dogs at 125 mg/kg and only slight liver glycogen depletion for three dogs each at 50 and 20 mg/kg.

No-effect Level. Except for possible growth retardation in males, 50 mg/kg. Certainly, 20 mg/kg.

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Chronic rat study, Woodard.

No. of Animals. 35 M and 35 F per group.

Feeding Levels. 0, 10, 40, and 160 mg/kg body wt.

Duration. 2 yrs.

Mortality. No significant differences in rats at any level from controls.

Body Wt. Mean values are tabulated for indicated time intervals.

Level (mg/kg)	Sex	Week 0	51	79	103
0	M	107	566	642	648
10	M	104	562	641	599
40	M	104	548	612	536
160	M	103	476	515	479
0	F	96	314	368	407
10	F	92	341	391	394
40	F	95	301	354	380
160	F	101	269	307	317

At the top feeding-level, both M and F rats grew very poorly. They weighed 16 and 14 % less than controls at 51 weeks and 26 and 22 % less at 103 weeks. From the 3rd to the 12th months, the mean wt. of M rats on 40 mg/kg thiabendazole was consistently about 20 g less than that of controls. During the 2nd year, the difference widened to 112 g. Male rats in all treatment groups declined in body wt. from 79 weeks on. Female rats in the 10- and 40-mg/kg groups showed little effect of thiabendazole on growth.

Organ Wts. Male rats at 10 mg/kg TBZ had heavier thyroids (mean wt = 43.0 mg) than did controls (mean = 28.2 mg) or rats at both higher dose-levels. Five of 8 M survivors at 10 mg had heavier thyroids than the heaviest ones in a M control.

Comment: Admittedly this increase in thyroid weight was not dose-related, but in view of petitioner's findings (cf. FAP 5A-1701, Sec. E, pp. A-7 and A-8) that, "In both species (rats and sheep) treatment with higher dose-levels of TBZ resulted in a diminution of colloid in the follicles of the thyroid.....(this) appeared somewhat reminiscent of thyroid stimulation. There was some

increase in the height of the lining of the follicles but no papillary infoldings as are seen in hyperthyroidism or after treatment with agents like thiouracil were evident," petitioner should have examined these heavier thyroids histologically. No such examination is reported for this rat study.

N.B. Thyroid effects in the other (Merck) rat study may be sex-related (affect males). (Cf. FAP 5A-1701, Sec. E, p. D-15, Table 12.).

Clinical Lab. Tests. Hematology values normal except for slightly reduced Hb and microhematocrits in rats at 160 mg/kg.

Histopathology. No changes attributed to thiabendazole.

Neoplasms. No significant difference in incidence of neoplasms between treated and control groups.

Reproduction. No effect in first and second litters of rats kept on 50 ppm of TBZ (from 4 weeks on) in fertility; gestation, lactation, or viability of young. No abnormalities in formation or bone structure in any newborn.

No-effect Level. Tentatively, none can be assigned because of possible growth-retarding effect in M rats on 40 mg/kg TBZ and because of (unevaluated) increased thyroid weights in M rats at 10 mg/kg.

Evaluation

A common effect for several animal species of TBZ at high dosage levels is retarded growth. Males are often more sensitive than females.

Whereas petitioner contends that animals tolerate TBZ at 40 to 50 mg/kg satisfactorily in chronic feeding tests (e.g., 2 yr), yet there was borderline weight depression, possibly, in M dogs on 50 mg/kg (Woodard, 2-yr study) and, certainly, in M rats at 40 mg/kg (Woodard, 2-yr study).

Further, M rats at 10 mg/kg (5/8) had heavier thyroids than did (heaviest thyroid of) M controls.

As to reproduction, the no-effect level in the five-generation mouse study is evidently 0.02% in the diet (= 200 ppm or 30 mg/kg); since 0.1% is an "effect" level in that weights of pups at weaning were reduced. Cf. below.

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No. of Generation	Weaning Wts of Mice in TBZ Study Group and Concentration (%) of TBZ in Diet A (0)	B (0.02)	C (0.1)	D (0.5)
1st	10.5	10.3	8.4	6.3
2nd	10.4	11.2	9.9	7.7
3rd	10.1	9.5	8.7	7.0
4th	10.5	10.4	9.4	7.3
5th	9.8	11.2	9.7	6.9
Mean	10.3	10.5	9.2	7.0

For a 100-fold safety factor to operate, maximum safe daily consumption of TBZ would be 0.30 mg/kg or 18 mg/day for a 60-kg man. This is based on the no-effect level of the reproduction study.

Based on average high consumption of bakery products of 3.1 to 3.77 lb/wk,* average intake of TBZ/day at 140 ppm would be 28 to 34.2 mg. Based on probable high average intake, as for example, by adolescent boys, of 0.5 kg bakery products/day, average daily intake of TBZ would be 70 mg per person. For a 60-kg man this latter is approximately 1.2 mg TBZ per kg body weight.

Therefore, the tolerance of 140 ppm requested for thiabendazole in FAP 5A-1701 is not safe.

Conclusion:

* Approximate ninth decile--from "High Consumption of Goods," p. 3, U.S.D.A., A.R.S., Household Economics Research Division, 11/17/60.

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