UNITED STATES ENVIRONMENTAL PROTECTION AGEN

Engler

DATE: April 19, 1977

SUBJECT: Tolerances for Thiabendazole; Re-assessment of ADI.

002773

FROM: Toxicology Branch

TO: Dr. E. Wilson
Product Manager
and
Chemistry Branch

Pesticide Petition: 6F1860 and 5F1646

The previous calculation of the ADI and thus the maximum permissible intake for man was based on a NEL of 40 mg/kg/day in a rat study. Discussions between the petitioner and officials of FDA however established that this level was in fact not a true NEL since some growth depression occured at this level. The NEL was thus set at the next lower feeding level, namely 10 mg/kg/day. This will reduce the ADI from 0.4 mg/kg/day to 0.1 mg/kg/day and the MPI from 24 mg/day to 6 mg/day. This change however, does not affect our previous conclusion about the safety of the proposed tolerances since this lowered ADI and MPI respectively is not exceeded by the existing and the proposed tolerances which result in a maximum theoretical exposure of roughly 1.0 mg/day.

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Toxicology Branch
Registration Division

EPA Form 1320-6 (Rev. 3-76)

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UNITED STATES GOVERNMENT

Memorandum

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION

TO : Petitions Control Branch (SC-13)

DATE: April 16, 1968

FROM : Dr. S. I. Shibko
Division of Toxicological Evaluation
Petitions Review Branch (SC-990)

SUBJECT: Thiabendazole in baked foods.

FOOD ADDITIVE PETITION NO. 5A-1701

Merck Sharp and Dohme
Division of Merck & Company, Inc.
Rahway, New Jersey 07065
(AF 4-715)

The petitioner has supplied the results of a three-generation rat study on Thiabendazole. Since the petition for use of thiabendazole in baked goods was withdrawan (August 1966), the petitioner has requested that this information be used as part of a master file.

Animals and Experimental Design:

Fo Animals - 48 male and 48 female (FDRL) mature albino rats, approximately 100 days of age assigned to one control group and three test groups containing 10 rats of each sex. At this time intragastric dosage of both sexes was commenced and the male and female rats were mated to produce the F_1 litters. Controls received 1 ml of a 0.5% CMC solution/kg body weight. Test groups received 20, 40 and 80 mg thisbendazole/kg body weight in sufficient 0.5% CMC so that each animal received it's respective dosage in 1 ml of solution. Drug dosage was administered to both sexes thru mating, and to females thru weaning of the second litter. The pups of litters of all generations did not receive thiabendazole directly until 28 days of age. Fifteen days after mating, the males were separated from the females, and the latter were allowed to cast litters naturally, and to nurse pups for the next 21 days. Pups were counted, weighed at birth 4 and 21 days, and results used to calculate fertility, gestation, viability and lactation indices. At 28 days all pups except 12 male and 12 female of the F_1, litter 1, generation were discarded.

Seven days after weaning their young, females of the F_o generation were remated with the males of the F_o generation. After 2 weeks the males were separated from the females who were allowed to cast their litters and nurse their pups to weaning.

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The dams were weighed at parturition, and at 4 and 21 days thereafter. Pups were counted and weighed at birth, 4 and 21 days. At 28 days they were sacrificed and examined grossly at autopsy.

The males and females of F_o generation were sacrificed and examined

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grossly at autopsy. Adrenals, pituitary, testes, seminal vesicles, prostate, vagina, ovaries and uteri were weighed. Adrenals, pituitary, gonads and adnexa and any abnormal tissue was examined microscopically.

F_1 and F_2 generations - 12 male and 12 female of F_1, litter 1, from each test group, and 14 male and 12 female rats of the control group and 10 male and 20 female of the 20 mg/kg dosage group, and 10 of each sex of the 40 mg/kg and 80 mg/kg dosage group of the F_2 litter were individually housed. The control group received basal diet, and the test groups, basal diet containing the thiabendazole at the appropriate level. Animals were examined daily for survival, behavior and appearance. Body weight and food consumption was recorded weekly for the first ten weeks, and thereafter, body weigh was recorded weekly.

Clinical chemical examinations were made prior to mating. At 100 days of age, animals were mated and reproduction studies carried out as described for the F_0 generation. Dietary administration of thiabendazole was discontinued and animals received thiabendazole by gastric intubation as described for F_0 animals.

F_3 generation - The first litter from F_2 mating was reared for one week after weaning. The second litter from the F_2 generation was sacrificed after weaning and submitted to clinical post-mortem examination.

Clinical examination of F_0, F_1, F_2 and F_3 generations - The following tests were performed on each animal. The F_0 group prior to drug administration, on the F_1 and F_2 generation prior to mating, and on the F_3 generation prior to sacrifice.

a. Blood - Hemoglobin, hematocrit, total and differential leucocyte counts, glucose, urea nitrogen and alkaline phosphatase.

b. Urine - Glucose, albumin, pH, specific gravity, occult blood and microscopic examination of the centrifuged sediment.

Results:

Body weight and food intake - At 28 days the body weight of the F_1 males at 20 and 40 mg/kg dosage levels were similar to control, but at the 80 mg/kg level there was a marked decrease in body weight. During the next ten weeks, at all levels, the body weights were less than control, although the rate of growth was similar. The decreased body weight was due to a decreased food intake, and not to

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a difference in efficiency of food utilization.

The female rats of the F_1 generation at the 80 mg/kg dosage level had a slightly lower weight than control. However, at the end of the subsequent ten week period, the body weight was equivalent to that of the control group, in spite of a slight decrease in food intake.

The weight changes observed in the F_2 generation males were similar to that observed for the F_1 generation. The mean body weight of the F_2 generation females were similar for all groups at 28 days, but during the subsequent period rats on the 80 mg/kg level showed some decrease in total weight gain over controls, although the rate of growth was similar. Food consumption was lower in the 40 mg and 80 mg/kg level groups than the control. The mean body weight at 28 days of the F_3 generation of male and female derived from treated groups showed slight depression compared to control.

Clinical Chemical Tests - Hematologic examination of the various groups showed no evidence of drug induced effects. Clinical chemical tests performed at the same time intervals showed no marked deviations from controls. Urine analysis showed no significant change had occurred in any of the test groups.

Organ weight data - F_0 groups showed no change in organ weight or organ/body weight ratio. For the F_2 generation, male rats on the test diets showed a decreased testes/body weight ratio, and also an absolute decrease in the prostate weight. The high dosage animals (80 mg/kg) also showed increased seminal vescile/body weight ratio and pituitary weight. Microscopic examination of adrenals and gonads of F_1, F_2 and F_3 generation showed no abnormalities related to ingestion of thiabendazole.

Reproduction performance

F_0 generation - The fertility index was slightly greater in treated animals than in controls. There was no adverse effect on gestation index. There was a decrease in the viability index in the high dosage groups. Lactation index was decreased in all test groups of rats, the most marked decrease occurring at the high level. However, the body weight of pups at 21 days was similar

for all groups. For litter 2 of the F_0 generation, fertility, viability and gestation indexes were the same in all groups. In contrast to litter 1, the lactation index of the treated groups was somewhat greater than that of the control.

F_1 generation - (litters 1 and 2) - There were no compound related effects for fertility, gestation and viability indexes. The viability index for the two high dose level groups was higher than that of control and the low dose level group. The lactation index was decreased for the mid level dose group, but increased for the high level group. For the second litter, the lactation index was greater in animals that were derived from treated dams, than those from controls.

F_2 generation - Indexes of fertility, gestation and viability revealed no marked adverse effects. For the first and second litters of this generation, there was a slight decrease in lactation index of rats maintained at the medium and high level dosage, compared with controls and low level dosage.

DISCUSSION:

The only treatment related findings were a decreased final body weight but not growth rate in the male rats at all dosage levels of the F_1 and F_2 generation. The decrease in body weight appeared to be due to a decrease in food consumption. There was a slight decrease in body weight and food consumption, but not growth rate, in female rats on the 80 mg/kg level. No compound related changes were detected in clinical chemistry and hematologic tests. At autopsy, observations on gross morphology and histological studies of the adrenals and gonads did not reveal any adverse compound related effect. The reproductive performance of the rats as indicated by the firtility, viability and gestation indexes was not changed (except for a decrease in the viability index of the first litter of the F_0 generation on the high level dosage). There was some slight changes in the lactation index in the F_0, F_1 and F_2 generation first litters, but this was normal for the second litters.

The petitioner, in a cover letter dated March 26, 1968, has requested conformation that the toxicity data will support a level of 6-8 mg of thiabendazole in the human diet. If we assume that a 60 kg individual would ingest products containing a total of 6 mg, the dosage level would be 0.1 mg/kg. Using the 100/1 safety factor that would be equivalent to a 10 mg/kg daily dose in rats. The reproduction study indicated that there is no adverse effect on the reproductive performance at this level. A previous memo by Dr. Quaife, dated October 1, 1965, indicated that the evidence obtained from a 2-year feeding study with rats supports a tolerance no higher than one based on the no-effect level of 10 mg/kg.

CONCLUSIONS:

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cc: SC-990
SC-510
FAP No. 5A-1701

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