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

004399

4/12/85

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Thiabendazole (TBZ)-PP #3F2882
Caswell No. 849A

TO: Henry Jacoby, PM No. 21
Fungicide-Herbicide Branch
Registration Division (TS -767C)

FROM: Carlos A. Rodriguez CAR 4/12/85
Section No. 6
Toxicology Branch/HED (TS-769)

THRU: Jane E. Harris, Ph.D., Section Head JEH 4/12/85
Section No. 6
Toxicology Branch/HED (TS-769)

Applicant: Merck Sharp & Dohme
P.O. Box 2000
Rahway, NJ 07065-0914

Action: Company responds to questions raised regarding historical control data in support of the TBZ mouse oncogenic study (EPA Letter of September 24, 1984).

Conclusions:

1. The information summarized by the applicant regarding the historical control data in support of the TBZ oncogenic mouse study (Applicant letter of October 30, 1984) is acceptable and resolves EPA concerns in the subject study.

2. The following information is extracted from Dr. Kasza's memo dated January 25, 1985.

   "From the submitted data, differences in oncogenicity and other pathological changes cannot be seen between control and test groups.

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> The only noteworthy difference in the experiment is the dose-related high mortality rate in test groups compared with controls. This may indicate a marked toxic effect of thiabendazole. In connection with the high mortality rate, other parameters such as weight loss and food consumption should be investigated also. It is advisable to investigate the date of death of individual animals. However, based on the available data in the livers, it is unlikely that any differences exist in incidences between the control and test groups."

Also, the following information is extracted from Dr. Squire's report dated December 4, 1984:

> There was no increase in the incidence or severity of neoplastic lesions which could be attributed to the test compound. A few hepatocellular adenomas were present, but these were scattered among several groups. No hepatocelluar carcinomas were present.

Based on Dr. Squire's report dated December 4, 1984, and the summarized results of Dr. Louis Kasza, Toxicology Branch Pathologist, it is the opinion of this reviewer that the compound thiabendazole is not oncogenic in female mouse livers.

MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
P.O. BOX 2000, RAHWAY, NEW JERSEY 07065-0914

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R. R. BUCK
ASSISTANT DIRECTOR
REGULATORY AFFAIRS

(201) 750-8657

October 30, 1984

Mr. Henry M. Jacoby
Fungicide-Herbicide Branch
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall #2, Room 229
Arlington, Virginia 22210

Dear Mr. Jacoby:

We are writing in reply to your letter of September 24, 1984 regarding an oncogenic study which is being reviewed with respect to pending petitions for thiabendazole.

Three questions were raised in the letter. The attached memorandum from Dr. G. R. Lankas to Mr. R. Buck responds to those questions.

We expect to have Dr. Squire's evaluation of the mice liver slides in the near future.

Very truly yours,

Robert R. Buck

RRB:daz
Attachment

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October 10, 1984

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MEMO

TO: Mr. R. Buck

FROM: Dr. G. R. Lankas

SUBJECT: Thiabendazole - Response to EPA's Questions Regarding Historical Control Data.

The EPA in its review of the thiabendazole mouse carcinogenicity study questioned the incidence of hepatocellular neoplasia in the high dosage group females. In response to this question Safety Assessment submitted historical control data for 6 mouse carcinogenicity studies conducted between 1976-1980 and also proposed that a consultant pathologist, Dr. Robert Squire, review liver slides from all female mice from the study in question.

Regarding the above response by Safety Assessment, the EPA has indicated that Dr. Squire is acceptable to them for the review of the liver sections from the female mice in the thiabendazole study. In addition, the EPA has raised a series of questions regarding the historical control data submitted to them in support of the TBZ mouse study. These questions and Safety Assessment's responses are indicated below.

1. Were the six studies submitted for the historical controls read by the same pathologist?

Response: No. The studies submitted represent all mouse carcinogenicity studies conducted in our laboratory between 1976 and 1980. Of these six studies three different pathologists each read two of the submitted studies.

2. Does the laboratory routinely run three control groups for each study?

Response: No. It is now our standard practice to include two control groups in all rodent carcinogenicity studies. However, this was not the case at the time these studies were conducted. As indicated in our earlier submission, the number of control groups in the studies submitted as historical control data ranged from 1 to 3 with 4 of the studies utilizing 2 control groups.

3. Were the livers from all 50 animals per group read for every group in every study?

Response: Yes. Livers were examined microscopically for all animals in all groups in every study with the exception of the study initiated in 1976. In this study livers were examined from all animals in both control groups and in the high dosage group. Liver sections from the low and mid dose level groups were examined only if gross lesions were evident. Since gross lesions were found in most of the livers from these animals, microscopic examination of liver sections was conducted for a majority of these animals.

G. R. Lankas

tmd

R. R. Buck

OCT 17 1984

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FEB 15 [illegible]

MEMORANDUM

February 13, 1985

TO: Mr. Henry Jacoby, PM #21
Registration Division (TS-767)

SUBJECT: Thiabendazole - Mouse Oncogenicity Issue
CAS # 849A EPA #618-75 Accession #255971

I am attaching Dr. Louis Kasza's review of the additional information sent in by the registrant of thiabendazole, (Merck). Basically Dr. Kasza agrees with the findings and opinions of Dr. Robert Squire.

Dr. Kasza's report, taken together with the fact that thiabendazole's current ADI is based on a NOEL of 10 mg/kg in a 2-year rat feeding study, indicate that there is no toxicological reason for holding up registration actions for this compound due to problems with the mouse oncogenicity issue. The mouse oncogenicity issue raised by the Batelle Report has been resolved.

William L. Burnam, Deputy Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

Attachment

cc:
TFarber
LKasza
CChaisson
CAS 849A

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D C. 20460

004399

January 25, 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Christine Chaisson, Ph.D. Section Head
EPA Toxicology Branch, TS-769

FROM: Louis Rasza, DVM, Ph.D., Pathologist
EPA Toxicology Branch, TS-769

SUBJECT: Evaluation of Dr. Squire's December 4, 1984, Report on Thiabendazone's Effect on Female Mouse

In the report, individual histopathologic data were reported separately of non-surviving and terminal sacrifice animals. In the same arrangement, Summary Tables were also prepared. There were 3 control groups (50 mice in each) and 3 test groups: 0.106%, 0.200% and 0.533%, respectively.

The number of livers which were examined in different groups were 48, 50, and 50 in the control groups, and 50, 50, and 50 in the test groups. Only 2 livers in the first control group were not examined.

The survival rate is rather low in test groups (17/50, 12/50, and 10/50) compared to the control groups (23/50, 22/50, and 26/50).

From the submitted data, differences in oncogenicity and other pathologic changes can not be seen between control and test groups. The only noteworthy difference in the experiment is the dose-related high mortality rate in test groups compared with controls. This may indicate a marked toxic effect of thiabendazole. In connection with the high mortality rate, other parameters, such as weight loss and food consumption, should be investigated also. It is advisable to investigate the date of death of individual animals. However, based on the available data in the livers, it is unlikely that any differences exist in incidences between the control and test groups.

cc. W. Burnam

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