

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH
SUMMARY OF TOXICOLOGY DATA

THIABENDAZOLE HYPOPHOSPHITE SALT

Chemical Code # 1952, Tolerance # 50807
SB 950 # 903

August 14, 1987
Revised 9/21/89, 12/11/89, 12/20/90

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	Data gap, inadequate studies, no adverse effect indicated
Oncogenicity, mouse:	No data gap, possible adverse effect [chronic effect, <u>not</u> oncogenicity]
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	Data gap, inadequate studies, possible adverse effect indicated
Teratology, rabbit:	No data gap, possible adverse effect
Gene mutation:	No data gap, no adverse effect

Chromosome effects: No data gap, no adverse effect
DNA damage: No data gap, no adverse effect
Neurotoxicity: Not required at this time

-----Toxicology one-
liners are attached.

All relevant record numbers through 090066 (Document #242-054) were examined in the 12/20/90 revision.

In the one-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: T901220

Revised by Aldous, 12/20/90.

The chemical grouping includes thiabendazole hypophosphite salt (chemical code # 1952, tolerance # 50807). See Thiabendazole (chemical code # 587, tolerance # 242) for reviews.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

CHRONIC TOXICITY, RAT

This reviewer (Aldous) concludes that there is **no need for additional rat chronic toxicity data**. None of the rat chronic studies (below) are individually acceptable, although useful data is provided. Considering the data based on the extensive testing and use in substantial dosages in man and domestic animals as an anthelmintic (see reviews in Vol. 242-012), there is no reason to expect new discoveries of untoward effects in the course of additional testing in the rat. **An acceptable rat oncogenicity study is required.** (Aldous, originally written between 8/12/87 and 12/11/89).

** 242-026 036977 (see also related chronic study 242-027 036978) "Safety evaluation by dietary feeding to rats for 104 weeks", Woodard Research Corp. 12/8/65. Thiabendazole, lot no. L-585216-0-40 (estimated purity 99.1%), was fed in the diet for 2 years to 35/sex/group at 0, 80 or 120 mg/kg. NOEL (considering information from both related chronic studies) = 40 mg/kg/day. **Acceptable only in fulfillment of chronic effects data requirement--a rat oncogenicity study is still required.** Insufficient numbers of animals subjected histopathology, several required tissues not examined, misc. other deficiencies preclude acceptance for oncogenicity data requirement. CDFA reviews by J. Remsen (Gee), 8-22-85 and 1-28-86 did not accept study for chronic or oncogenicity data requirements: re-examined by C. Aldous on 8/12/87 in light of new data and in consideration of the overall chronic effects data base, and accepted for chronic effects data requirement.

EPA one-liner: No core grade. Systemic NOEL < 80 mg/kg (LDT; growth depression, decreased adrenal weights and increased mortality) Oncogenic NOEL > 120 mg/kg (HDT)

242-012 033541 2-paragraph summary of 026 036977, above. (Review by J. Remsen (Gee), 8/22/85)

242-002 051499 Food consumption data for 026 036977.

242-027 036978 "Safety Evaluation by Oral Administration to Dogs and Rats for 104 Weeks." (Woodard Research Corp., 4-8-64) Thiabendazole, purity 99.1% [from Vol. 002, cover memo and Table 1], was administered in the diet to CD rats for 2 years to 35/sex/group at 0, 10, 40 or 160 mg/kg. Apparent NOEL = 40 mg/kg (decreased body weight) **Unacceptable as an individual study, but contributes to fulfillment of rat chronic effects data requirement (see one-liner for study 026 036977)**. As in study 026 036977, there were insufficient numbers of animals subjected histopathology, several required tissues not examined, misc. other deficiencies. CDFA reviews by J. Remsen (Gee), 8-22-85 and 1-29-86. Re-examination of data by C. Aldous, 8/12/87.

EPA one-liner: No core grade. Systemic NOEL = 10 mg/kg.

242-012 033540 2-paragraph summary of 026 036978, above. (Review by J. Remsen (Gee), 8/21/85)

242-003 051504 Contains no new rat chronic data. Sections D and E include data on a 6-month rat subchronic study. Section G is a duplicate of the entire contents of Vol. 027 (differs only in the placement of one page).

SUBCHRONIC RAT

242-056 087980 Kangas, L., "Thiabendazole: A Fourteen-Week Oral Toxicity Study in the Albino Rat". (Bio-Research Laboratories. Ltd., Laboratory Proj. I.D. 84114, Study No. TT#89-9014, 1/22/90). Thiabendazole, purity not given, administered by gavage at concentrations of 0 (0.5% aqueous methylcellulose), 25, 100, or 400 mg/kg/day to 20 albino rats/sex/group for 14 weeks. No CDFA toxicologist's review is required for this subchronic study, however it is noted that the investigators found marked body weight gain decrements in the high dose groups, suggesting that it may be necessary to select a dose level below 400 mg/kg/day for the high dose in subsequent lifetime feeding studies. No adverse effects were noted by investigators, who placed the NOEL at 25 mg/kg/day, based on changes in hematology (i.e., reduced RBC counts,

HCT, and Hgb), and on histological changes, such as lesions in stomach mucosa, thyroid follicular cell hyperplasia, and hepatocellular centrilobular hypertrophy. One-liner (without worksheet) by Kishiyama and Aldous, 12/19/90.

242-056 087981 Hill, R.N. et al., "Review: Thyroid follicular cell carcinogenesis", Fundam. Appl. Toxicol. 12:629-697 (1989). This review is a discussion of the relationship between thyroid-pituitary homeostasis and eventual development of thyroid follicular cell neoplasms. As of 12/19/90 there is no CDFA "review" of this review. Aldous, 12/19/90.

CHRONIC TOXICITY, DOG

Studies 242-027 036979 and 242-012 033542 are both 2-year dog studies, which should be considered together. Taken together, and considering additional information provided with 12/10/86 Merck & Co. rebuttal document, these studies fill the chronic dog data requirement. NOEL = 20 mg/kg/day (anorexia and weight loss, apparent anemia, and hemosiderosis of liver and bone marrow). **Note that in the 1/29/86 review of 027 036979 the reviewer indicated "possible adverse health effects" due to findings in liver and kidneys. Examination of the full dosage range employed in the subsequent study (012 033542) eliminates that concern (please see CDFA review of 8/6/87 by C. Aldous). These two dog studies are therefore acceptable, with no adverse effects indicated.** (Statement by Aldous, written on or before 12/11/89).

242-027 036979 "Safety Evaluation by Oral Administration to Dogs and Rats for 104 Weeks." (Woodard Research Corp., 4-8-64) Thiabendazole, tech., purity 99.1%, was administered to beagles, 3/sex/group, by capsule 5 days/week at 0, 20, 50 or 125 mg/kg. Apparent NOEL = 20 mg/kg/day ("mild lacrimation and scleral injection" noted at 50 mg/kg/day and above: salivation, rough hair coats, dry skin, reduced hemoglobin and hematocrit, seizures and some mortalities at 125 mg/kg/day (the latter two findings not necessarily direct treatment effects.) J. Remsen (Gee), 1/29/86; C. Aldous 8/6/87.
EPA one-liner: No core grade. Systemic NOEL = 50 mg/kg (decreased body weight).

242-012 033543 Very brief summary of 242-027 036979, initially reviewed by J. Remsen on 8/22/85.

242-002 051500 Individual body weights for 027 036979.

242-012 033542 "Two Year Chronic Oral Toxicity in Dogs." (Merck Sharp and Dohme Research Labs, 1-69) [Summary report]. Thiabendazole, tech. 99.1%, was given to beagles daily for 2 years at 0, 20, 100 or 200 mg/kg, 2/sex/group [doses were raised to above levels by degrees to prevent emesis of dose]. Interim sacrifices of one control and one 200 mg/kg/day male 5 months after 200 mg/kg/day treatment began. Apparent NOEL = 20 mg/kg/day (Hemosiderosis of liver and bone marrow at 100-200 mg/kg/day; reduced body weights, also reduced RBC counts, hematocrits, and hemoglobin at 200 mg/kg/day. Not an acceptable independent report, but useful data considering supplementary information, below. J. Remsen (Gee), 8-22-85; subsequent review with ancillary data by C. Aldous, 8/6/87.

242-003 051505 (Tab = "Section D", relevant pages are D-205 through D-297) provides data for study 012 033542. Data include individual food and water consumption, hematology, clinical chemistry, prothrombin time, urinary output, body weights, and organ weights. Body weights appear to be reduced in 200 mg/kg/day dogs, however there was no mortality. Males and females in the 200 mg/kg/day group appeared to have reduced RBC counts, hematocrits, and hemoglobin concentrations compared to all other groups. In tab marked "Section E" there were tables 15-19, indicating results of microscopic examination of dogs in the 1969 study, 012 033542. The only consistent apparent treatment effects were marked to moderate hemosiderosis in liver and bone marrow in 100 and 200 mg/kg/day groups (both sexes). Section G is a duplicate of the entire contents of Vol. 027 (differs only in the placement of one page). (Ancillary data only. See overall review of this study and of 027 036979, summarized above, worksheet by C. Aldous, 8/6/87).

SUBCHRONIC DOG

242-055 087979 Batham, P., "Thiabendazole. A Fourteen-Week Oral Toxicity Study in the Beagle Dog", (Bio-Research Laboratories. Ltd., Laboratory Proj. I.D. 84021, Study No. TT#89-9010, 1/22/90). Thiabendazole, purity 99.4%, administered orally via gelatin capsule at concentrations of 0 (placebo capsule), 35, 75, or 150 mg/kg/day to 4 beagle dogs/sex/group for

90 days. Incidence of emesis (NOEL = 35 mg/kg/day) and salivation increased; erythrocyte parameters (RBC, HGB, and HCT) decreased. It appears that the dosage range employed in this study would be appropriate for a subsequent chronic study, should such a study be undertaken. Note that studies 242-027 036979 and 242-012 033542 together have already fulfilled the chronic dog data requirement for CDFA. The information from this subchronic study is supplementary. (Kishiyama and Aldous, 12/19/90, one-liner without worksheet).

ONCOGENICITY, RAT

242-048 067761 "Chronic Toxicity of Thiabendazole (TBZ) in Rats," (Tokyo Metropolitan Research Laboratory of Public Health and Kogo Hirage, Department of Prophylaxis, Hichioju Insurance, Tokyo. Published in Ann. Rep. Tokyo Metr. Res. Lab. P.H., 36:377-389, 1985). Thiabendazole (lot no. BZA-539, purity = 98.5%) was administered to F344/DuCrj rats in diet at 0, 0.05, 0.1, 0.2 and 0.4% (30/sex/group) for 104 weeks. No adverse effect indicated. NOEL = 0.1% (in groups fed 0.4% TBZ there was significant decrease in weight gain; both sexes at 0.4% TBZ showed a significant decrease in RBC--anemia; both sexes at $\geq 0.2\%$ showed significant decreases in serum GOT & GPT; weight of urinary bladder increased in both sexes at 0.4% TBZ). This is a summary only. Information is supplementary. M. Silva, 9/9/88.

242-051; 074912; "Toxicity and carcinogenicity testing of thiabendazole in rats"; Tokyo Metropolitan Research Laboratory of Public Health; not dated; This was a manuscript of the pathology findings for doc. # 242-048, rec. # 067761. Dose-related effects were increases in hepatocellular foci and bile duct proliferation in females at 0.2 and 0.4 %; hepatic microgranuloma in both sexes at 0.05, 0.1, 0.2, and 0.4 %; urinary tract hyperplasia in both sexes at 0.1, 0.2, and 0.4 %; and adenomas of the preputial and clitoral glands at 0.4%. No adverse effect was indicated. The report is unacceptable because it is only a brief summary. A summary worksheet was done (Morris, 12/11/89).

242-051; 074911; "Enhancing effect of thiabendazole by urinary bladder carcinogenesis induced by sodium o-phenylphenate in F344 rats"; T. Fujii et al. (1986), Food and Chemical Toxicology,

24(3):207-211. This is paper from the open literature. No worksheet was done (Morris, 10/13/89).

ONCOGENICITY, MOUSE

**** 242-025 036966** "Lifetime Carcinogenic Study in Mice," (Merck, Sharp & Dohme, 1/2/80). Thiabendazole (purity = 99.3 - 99.8%) was administered to CD-1 mice (50/sex/group) in the diet at 0 (vehicle = 1% vegetable oil in the diet), 0.006, 0.066 and 0.20% (males) or 0.006, 0.200, and 0.533% (females) [low dose groups were initiated at higher levels, but adjusted to above levels at week 7]. Animals in a group were sacrificed when survival reached 20% (81-105 weeks). **Possible adverse effect indicated: (atrial thrombosis).** NOEL = 0.006% (i.e. 60 ppm or about 5.7 to 9.9 mg/kg/day (female) or 0.066% (660 ppm or about 63-121 mg/kg/day (male), based on increased mortality in both sexes dosed at $\geq 0.20\%$ in diet, due primarily to atrial thrombosis). Note: NOEL for males was incorrect in earlier review (see discussion in 9/21/88 review). **No oncogenic effect indicated.** This study was originally reviewed by J. Gee (1/30/86) as unacceptable but upgradeable, with a possible adverse effect (apparent increase in "Type B" hepatocellular tumors in 0.533% females). Study was re-examined by C. Aldous (8/11/87) and still considered to be unacceptable, but upgradeable upon receipt of additional information to clarify the statistical and toxicological meaning of the apparent increase in hepatic "Type B" neoplasms. The requested information (046:064610, which included "blind" re-evaluation of slides by R. A. Squire) removes the concern about possible hepatocellular tumors (no treatment effect seen on secondary review). Study is upgraded to **acceptable**. C. Aldous and M. Silva, 9/21/88.

EPA one-liner: Minimum. Oncogenic NOEL > 0.533% (HDT) systemic NOEL = 0.066% (lower weight gain).

242-046 064610 Additional information relating to study 025 036966. Definition of Type A and Type B hepatocellular tumors and interpretation of significance of data in the original report. Historical control data on such tumors. Report of "blind" secondary evaluation of

female liver slides by R. A. Squire, who found no evidence of treatment effect on tumors. One-page EPA memo, which indicated that EPA had determined that there was no oncogenic effect (following evaluation of Squire report and independent evaluation of slides by EPA). See CDFA review of 9/21/88 for details. C. Aldous, 9/21/88.

242-012 033544 Summary of 025 036966, above, reviewed by J. Remsen (Gee) 8/22/85.

342-002 051501 (Addendum to 025 036966) "Thiabendazole: Six-week pilot study in mice" [TT #77-004-0]. Merck Institute for Therapeutic Research, 8/24/77. Thiabendazole mixed in diet to provide daily doses of 0, 50, 150, 300, 600, and 900 mg/kg/day. Males had slight decrease in food consumption and body weight gain at 600 and 900 mg/kg/day. No changes in females. This study justifies the dose levels used in the primary study. D. Shimer/ C. Aldous, 7/11/87. [Note that C. Aldous requests additional information relating to the primary study.]

REPRODUCTION, RAT

** 242-028 036980 "Multigeneration Reproduction and Lactation Studies with Thiabendazole." (Food and Drug Research Labs, 12-26-67). Thiabendazole, purity approx. 98.8%, administered orally in diet (in very young rats) or by gavage (in older rats) from mating through weaning to FDRL rats at 0, 20, 40 or 80 mg/kg; 10/sex/group; NOEL > 80 mg/kg for reproduction; **no effect on reproduction parameters**. Originally classified as "unacceptable" in reviews of J. Remsen (Gee) [8/22/85 review of the summary of this report in 012 033547, and 1/29/86 review of final report in 028 036980]. Re-evaluated by D. Shimer/ C. Aldous on 8/10/87, and found **"Acceptable"**, on basis of additional data in 002 051502 (see below).

EPA one-liner: No core grade. Reproductive NOEL = 20 mg/kg (decreased viability index of F1A). [Note that CDFA does not agree with this determination, as there is no consistent treatment effect on viability or on other reproductive parameters].

242-012 033547 Brief summary of 242-028 036980 (see above).

242-002 051502 (Addendum to Document 028 036980, above). Explanation of dosing regime (part gavage, part dietary admixture), purity information (approx. 98.8% purity, process same as in current production), individual reproduction data, hematology, clinical chemistry, and organ weights for adults, reproduction and lactation data. These data allow upgrade of principal study to upgradeable status. D. Shimer/C. Aldous, 7/10/87,

242-030 036981 "Thiabendazole Evaluation of Teratogenic Potential in the Rat." [Study is actually a 1-generation reproduction study]. (Woodard Research Corporation, 4-8-64)
Thiabendazole, no purity stated, was given at 0 or 500 ppm in the diet for 70 days, 20/sex/group, 2 litters raised to weaning. NOEL > 500 ppm for 1 generation repro study. **No adverse effect** indicated. **Unacceptable**, inadequate protocol. J. Remsen (Gee), 1-29-86.
Re-examined after receipt of 002 051503 (see below) by D. Shimer/C. Aldous, 7/10/87.

242-012 033546 Brief summary of the 1-generation, 2-litter reproduction study, reported more fully in 030 036981, above. This summary reviewed by J. Remsen (Gee) on 8/22/85, and found unacceptable.

242-002 051503 (Addendum to 030 036981) New data are individual body weights of pups at birth and at 21 days. No changes in interpretation of study. Report is now complete, and study remains unacceptable. D. Shimer/C. Aldous 7/10/87.

REPRODUCTION, MOUSE

242-012 033545 "Reproduction and Teratogenic Studies: Multigeneration Reproduction Study in the Mouse." (Merck Sharp and Dohme Research Labs, 1-69) Brief summary of a 5 generation study in which thiabendazole was administered in the diet to 25/sex/group at 0, 0.02, 0.1 or 0.5 % of diet. Reproductive effects NOEL = 0.1% in diet (reduced numbers of mice born and weaned per litter, reduction of weanling weight). (**Note:** 8/22/85 review by J. Remsen (Gee) considered reproductive effects at 0.5% in diet to be a "possible adverse health effect". This dose was shown to be well into the toxic range in the mouse oncogenicity study (242-025 036966, which found increased mortality in males dosed with 0.066% and higher concentrations in diet and in females dosed 0.200% and above, also decreased body weight gain in both sexes at 0.200% and above). Reviewer (Aldous) therefore determines that **reproductive effects at this high and parentally-toxic level do not constitute a "possible adverse health effect"**. (Report remains **Unacceptable (no data provided)**). (Re-reviewed by C. Aldous, 8/14/87.)

EPA one-liner: No core grade. Reproduction NOEL = 150 mg/kg.

TERATOGENICITY, RAT

242-046 064612 "Report on Prenatal Toxicity Studies in Rats with Thiabendazole," (Institut für Pharmakologie, Toxikologie und Pharmazie, 8/14/85). Thiabendazole (analytical grade, no purity given; Ch. RMO 5878, Batch No. 18295 supplied by MSD) was administered in diet to mated Wistar SPF rats at 0 (vehicle = diet), 2, 15, 50 and 100 ppm during days 6-17 of gestation (presence of vaginal plug = day 0 of gestation). **Maternal NOEL** > 100 ppm (no significant effects were observed at any dose level). **Possible adverse effect indicated. Developmental NOEL** = 15 ppm (significantly lower body weights at 50 & 100 ppm; significant increase in major malformations in the skeletal system at 100 ppm). **Not acceptable** (no analysis of test chemical; no analysis of dosing material was included; individual maternal food and water consumption data and fetal visceral, skeletal, external effects and bodyweights were missing; no GLP or QA was included; an "annex" section was cited but missing from the report;

historical controls should have been included with the study). **Possibly upgradeable** (the above mentioned missing information must be submitted to CDFA). M. Silva, 9/7/88.

242-046 064611 "Thiabendazole - Review of Available Rat Teratology and Fetotoxicity Studies." In this report a number of studies are summarized, including 064611-12, 064615 and 064622. Other studies (Delatour et al.) were mentioned where one dose was tested on Sprague-Dawley rats and no developmental or maternal effects were noted at 80 mg/kg/day (gavage). Two studies performed at the Institute of Pharmacology and Toxicology in Hannover West Germany (Wistar Rats treated by gavage) were briefly described. Dose levels were: Study 1. 100, 200, 400 and 800 mg/kg/day and Study 2. 200 (15 mg/kg), 400 and 800 ppm. NOELs were not reached in the German studies and fetal effects (13% weight reduction) were observed at the lowest dose levels tested -100 mg/kg/day (maternal effects were not mentioned) in Study 1. **Both maternal and developmental effects were observed in Study 2 at 200 ppm (15 mg/kg/day)** but since a NOEL was not reached, indications of adverse effects cannot be determined. Based on the data presented in the summary, fetotoxic effects are secondary effects due to decreased weight gain in dams (maternal toxicity). It is not conclusive whether TBZ is teratogenic or selectively fetotoxic. **This information is supplementary.** M. Silva, 9/6/88.

242-046 064615 "Effect of Dietary Administration of Thiabendazole on Pregnant Rats and Fetal Development," (J. Food Hyg. Soc. Japan, Vol. 23, No. 6, pp. 468-473, 1982). Thiabendazole (> 98% pure) was given in diet to mated Wistar rats at 0 (vehicle = diet), 0.125 (92 mg/kg), 0.25 (154.5 mg/kg), 0.5 (223.7 mg/kg) and 1% (187.5 mg/kg, calculated to be less due to reduced food consumption in the 1% group) during days 7 to 17 of gestation (positive vaginal smear = day 0 of gestation). Maternal NOEL = 0.125% (maternal body weight gain and food consumption were significantly suppressed at $\geq 0.25\%$; clinical signs of toxicity, included piloerection, listlessness/general weakness were observed at $\geq 0.5\%$). Developmental NOEL = 0.125% (decreased body weight at $\geq 0.5\%$; increase in incidence of fetal death at 1%; increased skeletal variations at $\geq 0.5\%$; retardation of ossification at $\geq 0.25\%$). There was no evidence of fetal malformations attributable to thiabendazole ingested. Fetal changes were considered to be primarily induced by direct effects of thiabendazole on the fetuses as well as effects

due to maternal weight loss brought on by a marked decrease in food consumption. **No adverse effect** indicated. **This information is supplementary.** M. Silva, 9/7/88.

242-046 064622 "Teratologic Assessment of Maleic Hydrazide and Daminozide, and Formulations of Ethoxyquin, Thiabendazole and Naled in Rats," (J. Environ. Sci., Health, B14(6), pp. 563-577, 1979). Mated (positive vaginal smear = day 1 of gestation) Wistar rats were treated by gavage with 0 (vehicle = distilled water), 125, 250 or 500 mg/kg thiabendazole (formulation = 45% a.i. & 55% unknown ingredients) during day 6-15 of gestation. Maternal NOEL \geq 500 mg/kg (no effects were observed at any dose). **No adverse effect indicated.** Developmental NOEL = 500 mg/kg (although an increase in the total number of anomalous fetuses/number of fetuses examined in the 500 mg/kg group was observed ($P < 0.005$), no single anomaly was significantly increased in incidence). **This information is supplementary.** M. Silva, 9/7/88.

SUMMARY: All the reports demonstrated fetal effects, most of these effects appeared to be due to maternal toxicity and not teratogenicity of TBZ. The following is a dose comparison (apparently prepared by M. Silva, on or about 9/7/88). In the following summary, note that all animals were treated during approximately the same period of gestation.

Adverse Effect Indicated

Study 064612: 0.2, 1.5, 5.0, 10.0 mg/kg (Dev. NOEL = 1.5 mg/kg; Maternal NOEL = 5.0 mg/kg)
TBZ administered in diet, Wistar Rats

No Adverse Effect Indicated

Study 064611: In this report a number of studies are summarized, including 064611-12, 064615 and 064622. Other studies were mentioned with Sprague-Dawley Rats (Delatour et al.) where one dose was tested and no developmental or maternal effects were noted at 80 mg/kg/day (gavage). Two studies performed at the Institute of Pharmacology and Toxicology in Hannover West Germany (Wistar Rats treated by gavage). Dose levels were 100, 200, 400 and 800 mg/kg/day and 200 (15 mg/kg), 400 and 800 ppm. NOELs were not reached in these studies and fetal effects (13% weight reduction) were observed at the lowest dose levels tested -100 mg/kg/day (maternal effects were not mentioned) of one study. **Both maternal and developmental effects were**

observed in the other study at 200 ppm (15 mg/kg/day) but since a NOEL was not reached, indications of adverse effects cannot be determined.

Study 064615: 92, 154, 223, 187 mg/kg (Developmental and Maternal NOEL = 92 mg/kg) TBZ administered in diet, Wistar Rats

Study 064622: 125, 250, 500 mg/kg (Dev. NOEL = 500 mg/kg; Maternal NOEL \geq 500 mg/kg) TBZ administered by gavage, Wistar Rats. 45% Formulated material.

The definitive study 064612 is the only guideline type of study and most clearly demonstrated the possibility of an adverse effect. It was designed to administer low, non-toxic doses to rats in an effort to elucidate the individual fetal variations and establish a teratogenicity NOEL. Although previous studies may show a lack of adverse effects, the definitive guideline study, when complete will carry more weight in the final decision. Until 064612 is complete, TBZ will be considered to have a possible adverse effect for developmental toxicity. (Statement apparently prepared by M. Silva, on or about 9/7/88).

TERATOLOGY, RABBIT

****242-054 090065** Hoberman, A.M., "Thiabendazole: Oral Developmental Toxicity Study in Rabbits", (Argus Research Laboratories Inc., project No. 013-029; Merck & Co., Inc. study number: TT89-8005, October 27, 1989). Thiabendazole, purity 98.9%, administered by gavage at concentrations of 0 (0.5% methylcellulose), 24, 120, or 600 mg/kg/day to 18 artificially inseminated Hra: (New Zealand White) SPF rabbits/group on days 6 through 18 of gestation. Maternal toxicity NOEL = 120 mg/kg/day (marked body weight gain decrements, marked decrease in food consumption during treatment). Developmental toxicity NOEL = 24 mg/kg/day [4/18 litters with whole litter resorptions at 120 mg/kg/day: also hydrocephaly in 2 fetuses (2 litters) at 600 mg/kg/day and 1 fetus at 120 mg/kg/day]. The study technically indicates a **"possible adverse effect"**, based on embryo-fetal toxicity in the absence of definitive maternal toxicity. **Acceptable.** (Kishiyama and Aldous, 12/19/90).

242-054 090066 Rangefinding study for Record #090065, above. Dosage levels selected for the above primary study are justified. No CDFA worksheet for the pilot study, which is addressed in the review of the primary study. This 1-liner is by Aldous, 12/19/90.

242-030 036982 Entitled "Thiabendazole reproduction [sic] study in the rabbit" (actually a teratology study). Merck Institute for Therapeutic Research, June 29, 1966. Doses of 100, 200, 400, and 800 mg/kg/day by gavage in Methocel^R suspension. **No adverse effects indicated. Not complete, not acceptable, upgrade unlikely** (intercurrent disease, small group sizes, small numbers of fetuses subjected to skeletal examinations, etc.). Original review by J. Remsen (Gee), 1/29/86, [Not acceptable, possible upgrade indicated], subsequent review by C. Aldous considering additional information (below), 8/12/87, [Not acceptable, unlikely upgradeability].

242-002 (No record #, rebuttal on pp. 9-10 at front of volume). Addendum to study 030 036982. Identifies test article as purity of approx. 99.1%, comparable to currently manufactured product. Clarifies that data from 4 small studies conducted within 5 months were combined into one report. Indicates that individual data are available on request. No change in status of study indicated. Aldous (considered in 8/12/87 review, see above).

GENE MUTATION

** 242-029 036968 and 036969 "Mutagenicity Testing on Thiabendazole in Microbial Systems."
(The Institute of Environmental Toxicology, report no. 76-9814C, no date) Thiabendazole,
>98.6%, was tested with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, TA100 and
G46, E. coli strain WP2 hcr-, with and without rat liver activation at 0, 10, 100, 500, 1000
and 2500 ug/plate. **No increase in mutagenicity** was observed. **Acceptable.** (J. Gee, 1-28-86)
EPA one-liner: Acceptable. Negative, no increase in G46 revertants from mice exposed
to TB2.

242-029 036976 "Thiabendazole: Microbial Mutagenicity Studies (Ames Test) with Salmonella
typhimurium." (Merck, 1977, report no. 76-9813C) Several lot numbers of thiabendazole were
tested with S. typhimurium at 0 to 2000 ug/plate, with and without phenobarbital induced rat
liver enzymes. Data demonstrate that the low level mutagenic activity in TA98 was due to an
impurity in lot #F291764. **No adverse effect** indicated. **Unacceptable.** (J. Gee, 1-28-86)

EPA one-liner: Acceptable. Negative for induced revertants in all Ames strains except
TA98 + phenobarbital S-9.

242-012 033551 "Mutagenic Studies: Host Mediated Assay - Salmonella typhimurium in Male ICR
Mice." (Merck Sharp and Dohme Research Labs, 1-69, report no. 76-9814C) Summary report
states **no significant increase in mutation frequency** of Salmonella strain G46. **Unacceptable.**
(J. Gee, 8-22-85)

242-012 033662 "Mutagenic Studies: in vitro Bacterial Mutagen Tests - Reverse Mutation Tests
- E coli." (Merck Sharp and Dohme research Labs, 1-69) Single sentence states **no increase in
E. coli revertants.** **Unacceptable.** (J. Gee, 8-22-85)

242-012 033549 "Mutagenic Studies: in vitro Bacterial Mutagen Tests-Ames Tests." (Merck Sharp
and Dohme Research Labs, 1-69, report no. 76-9813C) Salmonella strains TA1535, TA1537,
TA1538, TA98 and TA100 with and without Aroclor-induced rat liver activation. Paragraph

states **no mutagenic activity found up to 2.5 and 5.0 mg/plate. Unacceptable.** (J. Gee, 8/22/85)

SUMMARY: There is no evidence for mutagenicity of thiabendazole in bacteria but there is a suggestion that an impurity in some lots may be weakly mutagenic in at least one strain of Salmonella - TA98 - for frameshift mutation. [CDFA reviewer name not stated: may have been J. Gee on or about 1/28/86].

CHROMOSOME EFFECTS

242-047 067213 "Selected Mutagenesis Studies on Thiabendazole," (SRI International, 3/77). Thiabendazole (purity and grade not specified) was used on human diploid fibroblast WI-38 cells in the log phase of growth at 0 (vehicle = 1% DMSO), 0.1, 1.0, 10.0, 100 and 1000 ug/ml without activation duplicate samples). **No increase in chromosomal aberrations** was observed at any dose level. Positive controls functioned as expected. **Unacceptable** (purity of test material was not provided nor was an analysis of dosing material; the test was not run with enzyme activation; only one time point was sampled; QA statement not included). **Not upgradeable.** (M. Silva, 9/9/88)

242-029 036970 "Cytogenetic Studies with Thiabendazole in Cultured Human Fibroblasts." (Institute of Environmental Toxicology, report no. 76-9815C, no date.) Thiabendazole, 98.6%, was tested with human embryo fibroblasts, strain #1162, for in vitro chromosomal aberrations; exposed to 0, 2, 10 or 50 ug/ml for 3 and 24 hours, no activation, **no increase in aberrations. Unacceptable.** An activation system must be used. (J. Gee, 1-28-86)
EPA one-liner: Acceptable. Negative - no increase in chromosome breakage in human embryonic fibroblast cultures.

242-012 033553 Summary of 029 036970.

242-012 033554 "Mutagenic Studies: Cytogenetic Studies - in vitro Studies with Human Diploid Fibroblasts." (Merck Sharp and Dohme Research Labs, 1-69) WI-38, 3 hour exposure. Summary

report states a depression in mitotic index but **no increase in aberrations. Unacceptable.**
(J. Gee, 8-22-85)

** 242-029, 047 036971, 067211-12 "Cytogenetic Studies With Thiabendazole in Rat Bone Marrow Cells," (Institute of Environmental Toxicology, Tokyo, Japan; report no. 76-9816C, no date). Thiabendazole (purity = 98.6%) was given by oral gavage as a single dose at 0, 100, 300 or 1000 mg/kg or 5 doses at 30, 100 or 300 mg/kg (5 males/group). Animals were sacrificed at 24 hours (single dose) and 3 hours (5 doses). **No increase in bone marrow chromosomal aberrations** are reported. The study was originally reviewed as unacceptable (J. Gee, 11/28/86) but upgradeable with justification of use of males only instead of both sexes as required. The requested information was received at CDFA (047 067211) and based on the fairly complete data base which indicated no sex differences in any of the tests, the study has been upgraded to **acceptable.** (M. Silva, 9/9/88)

EPA One-liner: Acceptable. Negative for chromosome damage in rat bone marrow cells.

242-049 067759 Exact duplicate of 047:067212.

242-012 033555 Summary of 029 036971.

242-029, 047, 049 036972, 067211, 067760 "Dominant Lethal Studies With Thiabendazole in Mice," (Institute of Environmental Toxicology, 76-9817C, no date). Thiabendazole (purity = 98.6%) was administered by gavage to C3H/HeCr mice (15 males/group) at 0, 200 or 600 mg/kg for 5 consecutive days. **No adverse effect indicated.** NOEL > 600 mg/kg for dominant lethal effect. Originally reviewed as unacceptable by J. Gee, 1/28/86 (no individual data; no analysis of dosing material; no justification of dose and dosing schedule). Justification for dose selection (range-finding study: 049 067760) was submitted to CDFA, however, results of the preliminary study do not justify the final dose selection. **The study remains unacceptable and not upgradeable.** (M. Silva, 9/9/88)

EPA one-liner: Not acceptable. Negative for dominant lethals in treated C3H/HeCR mice.

242-029 036974 "Thiabendazole: Mutagenicity Study in the Mouse Using the Micronucleus Test." (Merck, 6-3-77, report no. 76-8-83). Thiabendazole, lot no. F291764 (no purity stated), was administered by oral gavage to 8 (or 14 for control)/sex/group CD-1 mice at 0, 125, 250 or 500 mg/kg/day, 2 doses; sacrificed at 6 hrs; NOEL > 500 mg/kg; **no effect on micronucleus in PCE's or PCE/NCE** reported. **Unacceptable.** Doses are not justified, protocol is unacceptable, no purity stated. (J. Gee, 1-28-86)

EPA one-liner: Not Acceptable. Negative (up to 500 mg/kg) in CD-1 mice.

242-012 033552 Summary of 029 036974.

242-029 036975 "Thiabendazole: Mutagenic (Subacute Dominant Lethal) Study in the Mouse." (Merck, 1977, report no. 76-7030) Thiabendazole, lot no. F291764 (no purity stated), given by oral gavage to 10 CF₁S males per test group (20 for negative control), at 0, 125, 250 or 500 mg/kg/day in 5 daily¹ doses; NOEL for dominant lethal > 500 mg/kg; mated over 8 weeks, 1:1, **no adverse effect** reported. **Unacceptable.** No justification of doses, no concurrent positive control or appropriate historical data, not enough females per time point. (J. Gee, 1-28-86)

EPA one-liner: Not acceptable. Negative (up to 500 mg/kg) in CF₁S mice.

242-012 033557 Summary of 029 036975.

242-012 033556 "Mutagenic Studies: Dominant-Lethal Studies - C3H/HECR Mice." (Merck Sharp and Dohme Research Labs, 1-69) Summary report, 200 and 600 mg/kg given in 5 doses, **no effects noted over 6 weeks of mating.** No data. **Unacceptable.** (J. Gee, 8-22-85)

SUMMARY: Several chromosomal aberration studies have been performed, in vitro or in vivo, and all of these as of 12/20/90 are negative. Study # 036971, has been accepted by CDFA, so that the data requirement is filled. Aldous, 12/20/90.

DNA DAMAGE

242-029 036967 "Mutagenicity Testing on Thiabendazole in Microbial Systems." (The Institute of Environmental Toxicology, 76-9813C, no date.) Thiabendazole, >98.6%, was tested with Bacillus subtilis strains H17 and M45 at 0, 2, 10, 20, 50, 100, 200, 500 and 1000 ug/disc, no metabolic activation, **no adverse effect indicated. Unacceptable, not upgradeable.** Metabolic activation must be used. (J. Gee, 1-28-86)

EPA one-liner: Negative. No differential toxicity between B. subtilis strains H17 and M45.

242-012 033550 Summary of 029 036967.

** 50807-006 074699, "Thiabendazole, In Vitro Alkaline Elution/Rat Hepatocyte Assay", (Merck Institute for Therapeutic Research, West Point, PA., Study # 89-8312, 5/19/89), Thiabendazole, MK-0360, 98.9% purity. Primary rat hepatocytes, isolated from Charles River Cr1:CD*(SD) BR Sprague-Dawley rats, were exposed to 0, 0.3, 0.7, 1.0, or 1.3 mM (in 1% DMSO) for 3 hours and analyzed for DNA strand breaks by the alkaline elution method. Viability was ≥ 93 % of controls. Elution rates were less than 3X controls indicating no adverse effect. The study is acceptable (H. Green, S. Morris, 10/13/89).

NEUROTOXICITY

Not required at this time.