

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

THIOPHANATE METHYL

SB 950 # 121, Tolerance # 371
Chemical Code #1696

October 31, 1986

Revised 3/27/89, 12/31/92, 1/21/94, 10/10/95, and 2/21/96

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology rabbit:	No data gap, no 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. In these one-liners:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T960221

All data indexed under study type categories required by SB-950 through Record No. 136069 in Document No. 371-084 have been examined. This includes all such records indexed as of 1/16/96. (Aldous, 2/21/96).

Note: these pages contain summaries only. Individual worksheets may identify additional effects.

See also "Guidance for the Reregistration of Pesticide Products Containing as the Active Ingredient Thiophanate Methyl", EPA, May, 1986.

Note: Thiophanate methyl is related to benomyl and MBC (a "C" carcinogen). Gee, 3/89.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED RAT

****371-069 125651** Takaori, H., "Thiophanate-methyl - Combined chronic toxicity/oncogenicity study in rats", Toxicology Institute, Environmental Toxicology Laboratory, Nippon Soda Co.,

Ltd., Aug. 6, 1993. Project No. 0566. Study was flagged under 40 CFR 158.34 for elevated incidence and earlier onset of thyroid follicular tumors in high dose males. Thiophanate-methyl, 96.55%, was administered in diet to F-344 rats, 60/sex/group for up to 104 weeks (10/sex/group were allocated to 1-yr interim sacrifice). Dose levels were 0, 75, 200, 1200, or 6000 ppm. NOEL = 200 ppm (estimated mean exposure of 8.8 mg/kg/day for males, 10.2 mg/kg/day for females), based on decreased body weights (both sexes, especially in latter part of study); increased weights of thyroids, liver, and kidneys (both sexes); histopathology effects in liver (hypertrophy and lipofuscin pigmentation in both sexes), kidney (lipofuscin pigmentation and increased degree of age-related nephropathy in females), thyroid (hypertrophy and hyperplasia, both sexes), testes (increase in degree of atrophy); blood chemistry changes, particularly in aging males (decreased thyroxin, increased TSH; increases in BUN, creatinine, and cholesterol; decreases in albumin); and elevated urinary protein. These signs were often accentuated at 6000 ppm, along with other changes suggesting that an MTD had been exceeded. Findings primarily limited to 6000 ppm included hematology changes (minor decrements in RBC count, HCT, and Hb), bone resorption (males), calcium deposition in various tissues (both sexes), and parathyroid gland hypertrophy and hyperplasia (males). Thyroid follicular cell tumors (mainly adenomas) were clearly increased in high dose males, and slightly elevated in 1200 ppm males. The thyroid hypertrophy and hyperplasia, with the associated tumors constitute the primary **"possible adverse effects"**. Thyroid data are consistent with hormonal mediation. **Acceptable.** Aldous, 1/21/94.

371-069 125651 (same record # as combined study in this volume) Nishibe, T. and Takaroi, H., "Summary of mechanistic investigation of the effect of Thiophanate-methyl on thyroid and liver", Toxicology Institute, Environmental Toxicology Laboratory, Nippon Soda Co., Ltd., no "completion" date [initiation date was 11/27/90: this appears to be a preliminary (unaudited) report]. Thiophanate-methyl (TM) was fed to young F344 rats at 8000 ppm for 2 or 8 days. By day 8, thyroid weights were elevated, and TSH levels were markedly elevated in TM rats, and in propylthiouracil (PTU) positive controls. Levels of thyroid hormones (T_3 and T_4) were reduced by both TM and PTU. Total cholesterol was elevated by TM, and by controls PTU and phenobarbital (PB) by day 8. Liver weights were elevated by TM and PB by day 8. Thyroid weights returned to normal after 8 days treatment with TM or PB followed by 8 days recovery.

Co-administration of T_4 blocked the effects of TM on thyroid weight and on TSH levels, but not the elevation of liver weights or cholesterol. Rat liver microsomal fractions had increases in P-450, cytochrome b5, protein (mg/g liver), and UDP-glucuronosyltransferase activity in response to TM or PB. Porcine thyroid peroxidase was inhibited by TM and PTU (the latter being about 30X more potent). When male ICR mice or male F344 rats were administered TM or PB for 2 or 8 days, numbers of liver cells positive for proliferating cell nuclear antigen (PCNA) were elevated at day 2 only. Investigators concluded that "inhibition of [T_4] hormone synthesis could be the main cause of T_4 depression in rats". The conclusion is justifiable.

Aldous, 1/21/94.

CHRONIC RAT

005 981743, "The Chronic Oral Toxicity Studies of Thiophanate-Methyl, Dimethyl 4,4'-0-Phenylenebis (3-Thioallophanate), in Rats of Sprague Dawley Strain for 24 Months", (Nisso Institute for Life Sciences, 9/72). Thiophanate methyl technical, 94%, fed to Sprague-Dawley rats for 24 months at 0, 10, 40, 160 or 640 ppm, 50/sex in control group, 35/sex/treatment group; initially evaluated as insufficient information for assessment but reexamination indicates **a possible adverse effects to the thyroid and spermatogenesis -- note that an effect on the thyroid was also noted in dogs 005 981744**, UNACCEPTABLE (no description of test article, no justification of dose selection, no analysis of diet, poor presentation of data, inadequate number of animals at risk, no ophthalmology.) Apparent NOEL = 160 ppm (decreased body weight, thyroid hypertrophy of follicular epithelium and decrease in colloidal substance - 1/50 in control and 6/35 in males of high dose group, decrease in spermatogenesis in testes - 1/50 in control and 6/35 in high dose group.) No oncogenicity effect reported. (Christopher, 4/19/85, Gee, 10/30/86 and 3/89).

EPA 1-liner: Minimum. Oncogenic NOEL > 640 ppm, Systemic NOEL = 160 ppm (growth retardation, decreased spermatogenesis, histological evidence of thyroid effects.)

- 011 038835, summary of 981743.
- 014 981745, summary of 981743.
- 036 048655, duplicate of 981743.
- 040 Rebuttal for 981743.

011 981694, "Broad Spectrum Fungicide-Cercobin WP 50%: Chronic Oral Toxicity - Rats", (Pennwalt Corp., 69). Summary of chronic study in rats given 0, 8, 40, 200 or 1000 ppm [in the diet] with no data and insufficient information for evaluation. (Christopher, 4/22/85).

CHRONIC DOG

****371-059 113012** "A Chronic (1-Year) Oral Toxicity Study in The Dog Via Capsule Administration with Thiophanate-Methyl", (C.S. Auletta, Biodynamics, Inc., Project No. 89-3526, 2/18/92). Thiophanate-Methyl, purity 96.55%, was administered daily for 1 year at 0 (empty gelatin capsules), 8, 40 or 200 mg/kg/day to 4 beagles/sex/group. NOEL = 8 mg/kg/day [reduced serum thyroxine (T4), calcium, albumin, cholesterol, and inorganic phosphorus in males; also increased globulin levels in males: females also had slightly reduced inorganic phosphorus levels. Thyroid/parathyroid weights were increased in both sexes at 40 mg/kg/day and above (statistically significant only in females). Hypertrophy of the thyroid gland follicular epithelium was observed in 2/4 of the 40 mg/kg/day females, and in almost all high dose males and females. Thyroid findings are considered a "**possible adverse effect**". Small, but significant increases in weights of testes plus epididymides were observed at 40 and 200 mg/kg/day.] Common observations at 200 mg/kg/day included diminished weight gain (both sexes) and diminished food intake (especially in males), tremors (usually slight to moderate) in both sexes during first 3 weeks of the study, reductions in RBC parameters in males, elevated alkaline phosphatase in both sexes, elevated liver weights in both sexes, and comparable or increased degrees of the serum chemistry parameters noted above at 40 mg/kg/day. **Acceptable.** (Kishiyama and Aldous, 12/31/92).

005 981744, "The Long-Term Oral Toxicity Studies of Thiophanate-Methyl, Dimethyl 4,4'-0-Phenylenebis (3-Thioallophanate), in Beagle Dogs for 24 Months", (Nisso Institute for Life Science, Japan, 9/72). Thiophanate methyl, no purity stated, given by capsule to Beagle dogs daily for 24 months, 5/sex/group, at 0, 2, 10, 50 or 250 mg/kg (4/sex at high dose), sacrifice of 1/sex/group at 12 months; initial review by Christopher indicated insufficient information for evaluation but reconsideration by Gee notes **a possible adverse effect to the thyroid -- note that a similar finding was reported in rats (005 981743)**; UNACCEPTABLE (no justification for dose, no description of test article) but possibly upgradeable. Apparent NOEL = 50 mg/kg. Decreased colloidal substance in thyroid, 4/6 at 250 mg/kg, 3/8 in control group and increased weight in thyroids. (Christopher, 4/19/85, Gee, 10/30/86).

EPA 1-liner: Minimum. Systemic NOEL = 10 mg/kg (elevated thyroid weights, growth retardation.) Initial NOEL of EPA in 1985 was 50 mg/kg.

011 038837, interim summary of 981744.

036 048652, partial duplicate of 981744 (includes extra page (96), but does not affect the status of study.

014 981746, summary of 981744.

040 Rebuttal for 981744.

ONCOGENICITY, RAT

See comment under chronic rat above.

ONCOGENICITY, MOUSE

****371-064 119192** Lambing, C.A., "18-Month dietary oncogenicity study in mice with Topsin M", WIL Research Laboratories, Inc. [Study No. WIL-75024], Nov. 13, 1992. Thiophanate-methyl, Lot TIF-1016, was received in 2 shipments, with respective purity analyses of 96.55% and 95.93%. Sixty mice (Cr1:CD-1*(ICR)BR) per sex were assigned to dose levels of 0, 150, 640, 3000, or

7000 ppm in diet. Of those, 10/sex/group were killed at wk 39 interim sacrifice. A NOEL of 150 ppm for non-neoplasia effects in females is based upon centrilobular hepatocellular hypertrophy at 640 ppm (which was common in both sexes at 3000 to 7000 ppm). A plausibly treatment-related incidence of hepatocellular adenomas in females at 640 ppm further supports this NOEL. The NOEL for males is 640 ppm. Large numbers of hepatocellular adenomas in both sexes at 3000 to 7000 ppm constitute a **"possible adverse effect"**. Other treatment effects observed at higher doses included amyloidosis as the diagnosed cause of death in 3000 to 7000 ppm females and in 7000 ppm males. This single cause of death appeared to be the basis for reduced overall survival in the same groups. Thyroid effects were found chiefly at the time of the 39 wk interim sacrifice, and included increased thyroid gland weights (both sexes, 3000 to 7000 ppm); decreased thyroxin (T4) levels (7000 ppm females); and increased TSH (3000 to 7000 ppm males). Incidence of atrial thrombosis was elevated in 7000 ppm males and in 3000 to 7000 ppm females. Study is **acceptable**. Aldous, 12/31/92.

005 981755, "Carcinogenesis Studies of Thiophanate-Methyl, 4-4'-0-Phenylenebis (3-Thioallophanate), In Mice of ICR-SLC Strain for 24 Months", (Nisso Institute for Life Sciences, Japan, 7/73). Thiophanate methyl, 94%, fed to ICR mice at 0, 10, 40, 160 or 640 ppm for 24 months, 50/sex/group; NOEL \geq 640 ppm, no toxicity reported; UNACCEPTABLE (no analysis of diet, no justification of the high dose, age of mice at start not reported, problems with pneumonia and dermatitis during study, others.) (Christopher, 4/22/85).

EPA 1-liner: Initially graded as Minimum. Oncogenic NOEL > 640 ppm. Systemic NOEL = 640 ppm. Down-graded to supplementary in 1989 with a data gap created.

036 048653, duplicate information in 981755.

011 038841, interim summary of 981755.

014 981756, brief summary of 981755.

040 Rebuttal for 981755.

REPRODUCTION, RAT

371-070 125737 Müller, W., "Topsin-M: Two generation oral (dietary administration) reproduction toxicity study in the rat (with one litter in the P and two litters in the F1 generation)", Hazleton Deutschland GmbH, 8/20/93, HD Report No. 996-683-004. Thiophanate-methyl, 95.93%, was administered in diet to Crl; CD (SD)BR rats, 25/sex/group, at doses of 0, 200, 630, and 2000 ppm. Treatment was continuous over two generations. There were 3 mating trials, producing F1, F2a and F2b litters. In addition to routine reproduction study endpoints, thyroid hormones were assayed, also functional and morphological pup development was evaluated. Apparent parental NOEL = 200 ppm (slight thyroxin reduction, slight TSH increase). Hepatocyte hypertrophy and thyroid hyperplasia (often with hypertrophy) were common at 2000 ppm. Reproductive effects NOEL = 200 ppm (slight decrements in weanling pup weights, dose-related and significant for F2b weanling females). **No adverse effects. **Acceptable** (classified unacceptable in the 1994 review due to lack of histopathology examinations of intermediate group adults: this information was later provided in Record # 136069, below). Aldous, 1/21/94 and 10/3/95.

371-084 136069 Müller, W. and A. Singer, "Final addendum histopathology report and peer review pathology report to MRID 42899101". Addendum to Document No. 371-070, Record No. 125737. The addendum includes information from the study histopathologist (Prof. Dr. Klaus-Dieter Richter) of Hazleton Europe and a peer review examination by Dr. Allen W. Singer of Battelle (Columbus, OH). Date of addendum: 3/29/95. Liver and thyroid slides of all dose groups were evaluated by both pathologists (the peer review examination was performed "blind" to treatment group). Data from both analyses support a NOEL of 200 ppm in females, based on hepatocellular hypertrophy and thyroid follicular cell hyperplasia. There is no NOEL in this study for males, due to both of these findings being present in 200 ppm males. The findings **do not** warrant classifying the study as indicative of "possible adverse effects", since changes decreased from one generation to the next, and the degrees of lesions were clearly dose-related and of minor consequence at 200 ppm. Record No. 125737 is re-classified to **Acceptable** status. Aldous, 10/03/95.

005 981773, "Effect of Thiophanate-Methyl on Reproductive Function of Multiple Generations in the Rat", (Huntingdon Research, 5/30/72). Thiophanate methyl, no purity stated, fed in the

diet to 10 males and 20 females per group at 0, 40, 160 or 640 ppm for 60 days before mating, three generations, two litter each; UNACCEPTABLE (no analysis of diet, no histopathology on breeders, no characterization of test article.) Reproductive NOEL = 160 ppm (decreased litter size and weight at birth to weaning), systemic NOEL = 40 ppm (decreased body weight in adult males at 160 and 640 ppm). (Christopher, 4/19/85).

EPA 1-liner: Minimum. Reproductive NOEL = 160 ppm (reduced litter weights.)

011 038838, interim summary of 981773.

036 048654, duplicate of 981773.

014 981767, supplement (does not change status of study) and summary to 981773.

040 Rebuttal for 981773.

TERATOLOGY, RAT

371-035 048644, "Dietary Teratology Study of Topsin M Fungicide in Albino Rats", (WIL Research Labs, Ashland, Ohio, 4/9/1985). Thiophanate technical, 95.3%; fed in the diet to 25 per group, days 6 - 19, at 0, 250, 1200 or 2500 ppm (nominal); developmental NOEL \geq 2500 ppm; maternal effects consisted of significantly decreased food intake at the high dose and marginal decrease at the mid dose; the only clinical sign reported was an increase in the incidence of alopecia in high dose females; the decreased food intake could have been attributed to taste making it possible that oral gavage might have been a better route to reach a level of maternal toxicity. On the basis of food intake, the maternal NOEL could be considered as 250 ppm (nominal). There were no effects on fetal development. The report referred to a range-finding study (WIL 75001) for dose selection. This study had been requested to justify the dosage range used in the primary study (Gee, 10/30/86 and 3/24/89). This information was provided in Record No. 121149, below, and the study is now **Acceptable. Aldous, 1/21/94.

EPA 1-liner: Initially graded as Minimum. NOEL's as above. Down-graded to "Core Supplementary" with a data gap created.

039 063381 is a partial duplicate of 048644.

371-065 121149 [Relates to Document No. 371-035, Record No. 048644], "A range-finding teratology study in rats using Topsin*M Fungicide administered in the diet", WIL Research

Laboratories, Inc., 2/20/85. Charles River CD* rats, 6/dose, were administered 0, 100, 500, 1000, 5000, or 10000 ppm thiophanate-methyl in the diet from days 6 through 19 of gestation. Fetal data were recorded, including gross external observations of the fetuses. Marked, consistent b.w. decrements were limited to 5000 and 10000 ppm dams; weights were most seriously reduced on post-treatment day 1. A corresponding food consumption decrement was limited to the same groups, suggesting that palatability was not a serious problem at doses as high as 1000 ppm. There was no evident developmental effect aside from a small decrement in fetal weights at 10000 ppm. There were no grossly evident treatment effects on fetuses at any dose tested. The primary study is re-classified as **acceptable**, based on this confirmation that higher dietary doses would have sharply decreased maternal food consumption and thus maternal nutritional status. It should be noted that the limited evaluations of fetuses of the very high dose groups did not suggest any characteristic responses. Aldous, 1/21/94.

371-051 091267 protocol of 371-065 121149, above.

IRDC, 1981 study, referenced in the EPA reregistration standard is not on file at CDFA.

TERATOLOGY, MOUSE

005 981761, "Toxicological Evaluation on Thiophanate-Methyl (IV): Studies on the Teratogenic Effect of Thiophanate-Methyl upon the Fetus of ICR Strain of Mice", (Nisso Institute for Life Sciences, 8/70). Thiophanate methyl, no purity stated, given to ICR mice by oral gavage at 0, 40, 200, 500 or 1000 mg/kg, days 1-15, 20 per group; insufficient information for independent assessment; UNACCEPTABLE (early and late resorptions are not distinguished, no description of test article, no necropsy of dams reported, dose selection not justified with no maternal toxicity reported.) Systemic maternal NOEL \geq 1000 mg/kg/day. Decreased number of live fetuses / dam at 1000 mg/kg/day not significantly lower than control. (Christopher, 4/19/85).

EPA 1-liner: Supplementary. Incomplete description of protocol, fetal examinations did not appear to include soft tissue examinations. The 1000 mg/kg dose caused decreased number of implantations....

011 038836, brief summary of 987161.

014 981762, supplement (procedure, does not affect status of study) to 981761.

040 Rebuttal for 987161.

TERATOLOGY, RABBIT

** 039 063384, "Thiophanate Methyl: Teratology Study in the Rabbit", (Life Science Research, Suffolk, England, LSR report No: 86/NIS010/111, 5/20/86). Thiophanate methyl, Batch TM-948, purity 96.2%, administered by gavage at 0 (1% methylcellulose), 2, 6, and 20 mg/kg/day from day 6 to day 19 of gestation to 15 New Zealand White rabbits/group. Maternal NOEL = 2 mg/kg/day. (Thiophanate methyl administered to rabbits was associated with marginal maternal bodyweight effects and abortion/resorption at 20 mg/kg/day); developmental NOEL = 2 mg/kg/day - anomalies

of skeletal development, which were obvious at 20 mg/kg/day, marginal at 6 mg/kg/day and not apparent at 2 mg/kg/day. Although the anomalies were within historical control range at all doses, there was a suggestion of a trend with increasing dose. However, no evidence of any major structural toxicity of Thiophanate methyl in the rabbit at any dose. No major toxicity in the does but dose selection was based on a range-finding study. ACCEPTABLE. (Gee, 3/27/89).

EPA 1-liner: Supplementary. Maternal NOEL > 20 mg/kg/day. Another study is needed to confirm results before a conclusion can be made.

039 063383, "Thiophanate Methyl: Effects of Oral Administration upon Pregnancy in The Rabbit - Dosage Range-Finding Study", for 063384. (Gee 12/29/88). Included in above worksheet.

GENE MUTATION

**371-052 095962, "Thiophanate-Methyl : Reverse Mutation Study on Bacteria", (T. Nishibe, Toxicology Institute, Nippon Soda Co., Ltd., Japan, Report No. 0301, 8/25/90). Thiophanate-Methyl, purity 96.55%, at concentrations of 39.1, 78.1, 156.3, 312.5, 625, 1250, 2500, and 5000 µg/plate were tested in two trials using Σαλμονελλα τυπιμωριου (TA100, TA1535, TA98 and TA1537) and Εσχεριχια χολι (WP2 uvrA) without and with metabolic activation (Sprague-Dawley adult male rat liver induced by phenobarbital and 5,6-benzoflavone). Exposure time was 20 minutes preincubation, followed by 65 hours. The number of revertants did not significantly increase at any test article dose level, with or without metabolic activation. Test article precipitation was observed at 625 µg/plate and higher; and growth inhibition at higher than 312.5 µg/plate (TA98 and TA1537) and 625 µg/plate (TA100, TA1535) without metabolic activation. ACCEPTABLE. (Kishiyama and Gee, 11/10/92)

** 041 063491, "Gene Mutation in Chinese Hamster V79 Cells - Thiophanate-Methyl Technical", (Life Science Research, Rome, Lab. Report No. 063013-M-

05184, 9/28/84). Thiophanate-Methyl, purity 96.36%, at concentrations 0 (DMSO), 6.25, 12.5, 25.0, 50.0 and 100 µg/ml with and without S9 (rat liver, Phenobarbitone and Betanaphthoflavone induced) metabolic activation. No significant increases in mutation frequency were reported. The highest concentration (100 µg/ml) of Thiophanate-methyl in the absence of S9 metabolism reduced survival to 50% and was not toxic in the presence of S9 metabolism. ACCEPTABLE. (Gee 12/28/88).

EPA 1-liner: Acceptable.

015 039122, "Mutagenicity Testing on Thiophanate-Methyl in Microbial Systems (Host-Mediated Assay)(*Salmonella typhimurium*)", (Institute of Environmental Toxicology, Japan, 1976.). Host-mediated assay with Salmonella in male ICR mice given thiophanate methyl, 97.3%, at 500 or 1500 mg/kg, twice, then injected with G46 strain and cells harvested after 3 hours and assayed for his+ reversion, 6 mice per group with vehicle and DMN control. No increase in reversion rate. Reviewed as acceptable on 4/22/85 but reconsideration finds it UNACCEPTABLE (strain used, lack of evidence that bacteria were exposed to test article.) (Christopher, 4/22/85; Gee, 10/30/86)

EPA 1-liner: No grade. Negative.

035 048651, duplicate information in 039122.

015 981778, "Mutagenicity Testing of Thiophanate-Methyl in Microbial Systems (Reverse Mutation Tests, Typhimurium)", (Institute of Environmental Toxicology, Japan, 1976). Salmonella exposed to thiophanate methyl, 97.3%, strains TA1535, TA1537, TA1538, TA98 and TA100 at 0, 10, 50, 100, 500 or 1000 ug/plate with rat liver activation, 0, 10, 50, 100, 500, 1000 or 3000 ug/plate without activation, two plates per concentration, single trial, adequate positive controls for both activation and nonactivation. UNACCEPTABLE (single trial with duplicate plates, no reason given for not going to 5000 ug/plate.) Study includes E. coli as well. (Christopher, 4/22/85 and Gee, 3/23/89).

EPA 1-liner: No grade. Negative.

035 048650, duplicate information in 981778.

035 048648, "Evaluation of the Mutagenic Potential of Methyl-2-Benzimidazole Carbamate, 99 + % (MBC, 99 + %) in combination with Methyl Thiophanate (Topsin M Technical, 99 + %) toward Salmonella Typhimurium and Escherichia Coli", (Cannon, 3/18/78). Salmonella tested with thiophanate methyl, 99%, plus methyl-2-benzimidazole carbamate, 99%, mixed in a fixed ratio of 0.18 mg plus 0.1 mg, respectively, strains G 46 and TA1530 with and without rat liver activation; UNACCEPTABLE (no individual plate counts and no standard deviation, no explanation for use of the mixture, use of these two strains in 1978 is not acceptable.) Three trials were conducted but in trial (1) there was a high level of spontaneous revertants, in trial (2) the positive controls were inactive. The report contains data from trial (3) in which the +S9 controls (2AA, 2AF and 2AP) were also essentially inactive. (Gee, 10/29/86).

EPA 1-liner: Minimum. Negative.

005 981774, "Toward Salmonella Typhimurium Tester Strains In Vitro", (Cannon, 3/18/78). Thiophanate methyl, 99%, tested with Salmonella strains G46 and TA1530 at 0.18 mg/plate with and without rat liver activation; UNACCEPTABLE (no individual plate counts - no standard deviation, no justification of single concentration, no indication of cytotoxicity, no explanation for using these two strains, positive controls with activation were inactive.) See 48648 for explanation of three trials; same controls for 48648, 981774, -75 and -76. (Christopher, 4/22/85).

EPA 1-liner: Unacceptable. Incomplete report.

035 048645, duplicate information in 981774.

014 981777, brief summary of 981774.

005 981775, ""Evaluation of the Mutagenic Potential of Methyl-2-Benzimidazole Carbamate, 99 + % (MBC, 99 + %) toward Salmonella Typhimurium Strains In Vitro (Metabolite of Thiophanate Methyl)", (Cannon, 3/18/78). Methyl-2-benzimidazole carbamate (metabolite of thiophanate methyl), 99%, tested with Salmonella strains G46 and TA1530 with and without rat liver activation tested at 0.1 mg/plate only; UNACCEPTABLE (no justification for use of a single concentration, strain selection, positive controls inactive with activation.) See 048648 for discussion of three trials. (Christopher, 4/22/85).

EPA 1-liner: Unacceptable. Incomplete report.

035 048646, duplicate information in 981775.

005 981791, duplicate of 981775.

005 981776, "Evaluation of the Mutagenic Potential of 5-Hydroxy-Methyl-2-Benzimidazole Carbamate, 99+% (5-OH-MBC, 99+%) toward Salmonella Typhimurium Tester Strain In Vitro", (Cannon, 3/18/78). 5-Hydroxy-methyl-2-benzimidazole carbamate (metabolite), 99%, tested with Salmonella strains G46 and TA1530 at 0.11 mg/plate with and without rat liver activation; UNACCEPTABLE (no justification for single concentration, strain selection, positive controls inactive, no individual plate counts and no indication of number of replicates.) See 48648 for discussion of three trials.

EPA 1-liner: Unacceptable. Incomplete report. (Christopher, 4/22/85).

035 048647, duplicate information in 981776.

MUTAGENICITY, CHROMOSOME

371-051 091268, "Mutagenicity Test on Topsin M Technical in an In Vitro Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells", (H. Murli, Hazleton Laboratories America, Inc., Kensington, MD., Report # 10345-0-437, 12/7/88). Topsin M Technical (thiophanate-methyl), 95% purity, was tested in the in vitro cytogenetic assay in duplicate cultures with CHO-WBL Chinese Hamster ovary cells in the presence (2 hr) and absence (17.5 hr) of activation (Aroclor 1254 induced male Sprague-Dawley rat liver fraction) at untreated, 0 (DMSO), 100, 200, 250, 300, 400, 500, 750, or 1000 ug/ml (tested to the limit of solubility). Scored 100 cells per culture. **No increase in chromosomal aberration frequency. **Acceptable.** (H. Green and J. Gee, 11/10/92).

014 981789, "S/Mutagenicity Studies: Chromosomal Aberrations Dominant Lethal Mutation Study in Mice - Technical Thiophanate-Methyl", (Pennwalt Corp., no date). Dominant lethal in mice, no data presented but summary states no adverse effect. Insufficient information for evaluation. (Christopher, 4/22/85).

014 049447, "Mutagenicity Studies, Chromosomal Aberrations: Rats - Technical Thiophanate-Methyl - Cytogenic Analysis of Chromosomes of Bone Marrow and Meiotic Germ cells", (Pennwalt Corp., no date). Summary with no data stating no aberrations noted due to test article. (Christopher, 4/22/85).

011 038840, duplicate information in 049447.

MUTAGENICITY, DNA/OTHER

371-041 063286, "Evaluation of Pure Thiophanate-Methyl in the Primary Rat Hepatocyte Unscheduled DNA Synthesis Assay", (Litton Bionetics, Inc., Laboratory project ID 21191, October, 1981). Thiophanate-Methyl, lot CP 10B purity 99.8%, was evaluated at concentrations of 0 (1% DMSO), 0 (2-AAF), 5, 10, 25, 50 100, 250. 500 and 1000 µg/ml, 18 hours. Crystalline precipitate formed at 500 and 1000 µg/ml. Cell survival was 38.0% at 1000 µg/ml and 81.6% and 93.5% at 500 and 250 µg/ml, respectively, slightly less than 96.9% for the positive control. Scored 150 cells per concentration with 0.51% of cells cycling. Data indicate the test material did induce UDS in the test system. Initially classified unacceptable but upgradeable (needing a justification for not using technical grade, Gee, 12/28/88): a cover letter of 1/17/91 preceding record No. 095962 in Document No. 371-052 noted that the purity of analytical material and the higher purity lots of technical grade are comparatively close. The study is upgraded to **acceptable status. (Gee, 11/10/92)
EPA 1-liner: Acceptable.

371-052 [No Record # (letter precedes Record No. 95962)]. Additional information relating to 041 063286, "Evaluation of Pure Thiophanate-Methyl in the Primary Rat Hepatocyte

Unscheduled DNA Synthesis Assay", (Litton Bionetics, Inc., Laboratory project ID 21191, October, 1981). Letter notes that the purity of technical Thiophanate-methyl used in various mutagenicity studies has varied from 93 to 99%, without any difference in outcome (i.e., all studies are negative). It is reasonable to infer that the expected difference in outcome between the purer technical vs. analytical material would be small. Response is an acceptable justification for an upgrade of the study. This change is reflected in the Summary of Toxicology Data. Gee, 11/10/92.

015 981790, "Mutagenicity Testing on Thiophanate-Methyl in Microbial Systems (Rec-Assay/DNA Damaging) Technical Thiophanate-Methyl", (Institute of Environmental Toxicology, Japan, 1976). Bacillus subtilis H17/M45 strains exposed to thiophanate methyl, 97.3%, at 0, 20, 100, 200, 500, 1000 or 2000 ug/plate applied to a 10 mm disk in 20 ul; kanamycin and mitomycin C as positive controls; no activation, single plate per concentration; no difference in growth recorded and no significant cytotoxicity, therefore a "no test"; UNACCEPTABLE (no activation included, no rationale for highest concentration used.) (Christopher, 4/22/85).

EPA 1-liner: No grade. Negative.

035 048649, duplicate information in 981790.

014 981792, brief summary of 981790.

NEUROTOXICITY

Not required at this time.

005 981728, "Acute Delayed Neurotoxicity of Topsin M Technical 94% (N/B #77-126-3) in Chickens", (Cannon Labs, 2/15/78) Thiophanate methyl, 94%, given by oral gavage in corn oil to 10 hens per group at 0 or 10 g/kg with TOCP as positive control; single oral dose. No adverse effects indicated. UNACCEPTABLE, NOT UPGRADEABLE (no redosing, inadequate presentation of pathology regarding nerve tissues.) Christopher, 4/22/85.

014 981727, summary of 981728.

Note: The EPA reregistration standard, May, 1986, also discusses studies with carbendazim or MBC, a metabolite of thiophanate-methyl and a registered active ingredient itself. See SB 554, tolerance number 50664. Gee, 3/27/89.

OTHER STUDY TYPES (NOT SB-950)

371-076 129846 Naas, D.J., "21-Day dermal study in rabbits with thiophanate-methyl technical", WIL Research Laboratories, Inc., 11/15/91. Laboratory Study No. WIL-75030. Five NZW rabbits/sex/group were dosed on dorsal skin with 0, 100, 300, or 1000 mg/kg/day thiophanate-methyl 5 times weekly for 3 weeks. There was no NOEL identified for local effects, based on hyperkeratosis of treated skin (1 female affected per treated group). The NOEL for systemic effects was 100 mg/kg/day, based on slight decrements in food consumption in 300 mg/kg/day females. More consistent food consumption decrements were noted in both sexes at 1000 mg/kg/day. No adverse effects are indicated. Study is **acceptable. Aldous, 2/21/96.

371-074 129844 [Reviewed with the supplementary report: Document No. 371-075, Record No. 129845] Tanoue, T., "Thiophanate-methyl - Metabolism in rats", Nippon Soda Co., Ltd., 8/17/92 (main study): 12/3/92 (supplementary report). Laboratory Project ID Nos. EC-338 (main study), and NISSO EC-395 (supplementary study). Thiophanate-methyl was efficiently absorbed, and rapidly excreted. There was evidently some saturability of uptake processes and lengthening of elimination half-life at high dose levels or following sustained low dose exposures. Blood levels diminished quickly, and tissue levels were very low by day 4 in all cases. Primary metabolic changes included hydrolysis of side chain extremities, closure of remaining side chain portions, and oxidation of the phenyl moiety, producing a methyl hydroxybenzimidazolyl carbamate. The primary urinary metabolite was conjugated with sulfate. Fecal residues were largely thiophanate-methyl and a phenyl ring hydroxylated product. The study is **acceptable. Aldous, 1/24/96.