

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Thiram

Chemical Code # 00589, Tolerance # 00132
SB 950 # 108

8 December 1986

Revised 11/6/87; 8/17/90; 1/18/91; 12/24/93; 10/17/94; 3/25/96; 10/27/03

I. DATA GAP STATUS

Combined, rat:	No data gap, possible adverse effect.
Chronic toxicity, dog:	No data gap, no adverse effect.
Oncogenicity, mouse:	No data gap, no oncogenic adverse effect ¹ .
Reproduction, rat:	No data gap, no reproduction adverse effect ² .
Teratology, rat:	No data gap, possible 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, inadequate study, possible adverse effect indicated.

¹A systemic adverse effect was observed in this study.

²A developmental, not reproductive effect was observed in pups.

Toxicology one-liners are attached.

All record numbers through 181857 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T031027

Initial Summary by W. Choy - 12/8/86; revised by J. Gee - 11/87; M. Silva - 8/17/90 and 1/18/91;
Kishiyama & Silva - 12/24/93; M. Silva - 10/17/94, 3/25/96, 10/27/03

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

Definitive Study:

**** 052 111059**, "104-Week Combined Chronic Toxicity and Carcinogenicity Study with Thiram in Rats", (D.F. Kehoe, Hazleton Laboratories America, Inc., HLA 6111-113, 10/16/91). Thiram (purity = 97.5%) was administered in diet to Sprague-Dawley rats (50/sex/group) at 0, 30, 150, or 300 ppm for 104 weeks. Chronic (Actual) NOEL = 16.3 ppm or 54% of nominal (Based on clinical observations at 300 ppm in both sexes and decreased body weight and food consumption at \geq 150 ppm (nominal) in both sexes. There was a decrease in several hematological parameters (females) at \geq 150 ppm. Weights were significantly decreased in ovaries at 300 ppm. Histopathology was observed in pancreas (steatosis/fatty infiltration, multifocal acinar atrophy) at \geq 150 ppm, extramedullary hematopoiesis in males at \geq 150 ppm and females at 300 ppm and in spleen of females at \geq 150 ppm.) Oncogenicity NOEL = 16.3 ppm or 54% of nominal (There was an increased incidence in hepatocellular and thyroid C-cell adenomas and hyperplasia in both sexes at \geq 150 ppm.) **Possible adverse effect** (There was an increase in hepatocellular and thyroid C-cell adenomas and hyperplasia at \geq 150 ppm and an increase in extramedullary hematopoiesis in the liver.) ACCEPTABLE. (Kishiyama & Silva, 12/22/93).

Subchronic Study:

029 069429 "Thirteen-Week Toxicity Study with Thiram in Rats", (Kehoe, D.F., Hazleton Laboratories America, Inc., Project I.D. HLA 6111-110, March 23, 1988). Thiram technical (purity = 99.43%; LOT #: 117) was administered in feed at concentrations of 0 (vehicle = feed), 50, 500 or 1000 ppm for 13 weeks to Charles River (CrL:CD*(SD)BR) albino rats (10/sex/group). **No adverse effect indicated.** Nominal NOEL = 50 ppm, actual mean NOEL = 37.5 ppm (Bodyweights, cumulative bodyweight gain, food consumption, red blood cell count and absolute liver weights were reduced in both sexes at \geq 500 ppm. Females showed a significantly increased kidney/bodyweight % at 1000 ppm in both kidneys. Chloride at 1000 ppm and BUN at \geq 500 ppm were increased in females while hemoglobin, hematocrit and albumin in females at \geq 500 ppm were reduced. Total protein was reduced in males at \geq 500 ppm. Thiram increased mean corpuscular volume--females at 1000 ppm and males at \geq 500 ppm and mean corpuscular hemoglobin--both sexes at \geq 500 ppm; increased white blood cell and corrected white blood cell counts--both sexes at \geq 500 ppm, absolute neutrophil, lymphocyte and monocyte counts--both sexes at 1000 ppm. Increased testis/epididymus-to bodyweight percentages at \geq 500 ppm was observed and histopathologically: red/mottled mesenteric lymph nodes and areas of erosion, ulceration, mucosal hyperplasia, accompanied by mucosal inflammation and edema were observed in both sexes in the nonglandular stomach at \geq 500 ppm). Thiram, in the low dose diet, averaged 75% of the targeted level. These data are supplemental. (Kishiyama & Silva, 5/30/90).

Chronic Study:

012 034451, Title not given: Midwest Research Institute, 8/75; Thiram (purity unknown) tested at 0, 5.3, 20.4 and 52.0 mg/kg/day for males and 0, 6.1, 25.5 and 66.9 mg/kg/day for females in the diet in an 18-month study with Charles River CD rats; 24 animals/sex/dose; 6-month interim sacrifice; toxicity observed at medium and high dose groups; decrease in body weight gains, food consumption; decrease in RBC and Hb conc. in females; decrease in brain weight in males and increase in thyroid weight; ataxia in females with 25% demyelination and 25% degeneration of axis cylinders of sciatic nerves; fatty infiltration of pancreas in males beginning at low dose; **possible adverse effect** in thyroid, pancreas and the nervous system; NOEL < 5.3 mg/kg/day for males and < 6.1 mg/kg/day for females; UNACCEPTABLE; not upgradeable (no purity and

stability of compound, no diet analysis, 18 months instead of 24 months study; incomplete data on tissue lesions and tumors in animals sacrificed at 6 and 18 months). (J. Remsen (Gee), 9/30/85).

005 020005, "Toxicity and Behavioral Effects of Thiram in Rats", is a published article of 012 034451.

Other records which contain a brief review of toxicity studies are as follows:

007 20007, "Chronic Oral LD₇₇ - Rat, 2 Year Study (Thiram). (JW, 4/12/85)

007 20012. "Behavioral Effects, Neurological Chronic Study of Thiram Fed to Female Rats". (JW, 4/12/85).

005 22054, "Oral Toxicity of Ferric Dimethyl-Dithiocarbamate (Ferbam) and Tetratmethylthiuram Disulfate (Thiram) in Rodents". (JW, 4/15/85).

CHRONIC TOXICITY, DOG

** 050 097911, "52-Week Dietary Chronic Toxicity Study with Thiram in Dogs", (D.F. Kehoe, Hazleton Laboratories America, Inc., Laboratory Project I.D. HLA 6111-112, 6/28/91). Thiram technical (purity 97.5%) was administered in diet to Beagle dogs (6/sex/dose) at 0, 30, 90, or 250 ppm/day for 52 weeks. NOEL = 30 ppm (There were significant effects on some hematological and clinical chemistry factors in both sexes, primarily at ≥ 90 ppm. Liver weights in males (absolute and relative) were increased at ≥ 90 ppm. Organ/brain % were increased at 250 ppm in males. Body weights weeks 36-52 were decreased 13.8% in males. ACCEPTABLE. (Kishiyama & Silva, 12/13/93).

044 088485 "13-Week Toxicity Study With Thiram in Dogs," (Kehoe, D.F., Hazleton Laboratories America, Inc., Lab I.D. #: HLA 6111-121, 3/26/90). Thiram technical (97.5% pure, LOT #: 117, sample # 70504831) was fed, in diet, to beagle dogs (4/sex/group) at 0 (vehicle = diet), 75, 250 and 500 ppm for 13 weeks. No adverse effect indicated. NOEL = 75 ppm (reduced bodyweight and food consumption in both sexes at 500 ppm; decreased RBC's in males at 500 ppm and in females at ≥ 250 ppm; decreased mean corpuscular hemoglobin concentration % in males and hematocrit % and hemoglobin in females at 500 ppm; significantly increased mean corpuscular volume and mean corpuscular hemoglobin in both sexes and platelets in males at ≥ 250 ppm; significantly decreased serum albumin in both sexes at ≥ 250 ppm; significantly increased cholesterol in males at ≥ 250 ppm; significantly decreased total protein at ≥ 250 ppm and calcium at 500 ppm in females; hepatocellular degeneration with granulomatous inflammation, bile duct hyperplasia, bile pigmentation and mononuclear cell infiltration were observed in males at ≥ 250 ppm and females at 500 ppm). NOAEL = 250 ppm. The animals were not completely healthy and displayed a low grade bacterial infection in the liver which may have been facilitated by thiram. These data are supplemental. (M. Silva, 6/12/90).

035 069640, "Four-Week Range-Finding Study with Thiram in Dogs", (Kehoe, D.F., Hazleton Laboratories America, Inc., HLA 6111-109, March 24, 1988) Thiram technical (purity = 99.43%; LOT #: 117) was administered in the feed at concentrations of 0 (vehicle = feed), 125, 500 or 2000/1500 ppm (2000 during week 1 and 2 and 1500 ppm during week 3 and 4) for 4 weeks to Beagle dogs (2/sex/group). No adverse effect indicated. NOEL = 125 ppm (Thiram treatments reduced bodyweight and food consumption and increased urea nitrogen levels in both sexes at ≥ 500 ppm. Lowered RBC count, hematocrit and hemoglobin and increased platelet count, total bilirubin, alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase was observed in males at ≥ 500 ppm.) There were too few animals at start and termination of study. These data are supplemental. (Kishiyama & Silva, 5/30/90).

007 020006, "Dog Feeding Test with Thiram," (Haskell Laboratory, 4/24/57); Thiram (97.5%) tested at 0, 10, 50 and 200 ppm in the diet in a one year study in dogs; 3 dogs/dose group; insufficient information to assess health effect; UNACCEPTABLE (incomplete, not upgradeable, MTD not reached, no eye exam, no analyses of diet, other multiple major deviations from the EPA guidelines). (J. Wong, 4/12/85).

ONCOGENICITY, RAT

See combined, rat.

ONCOGENICITY, MOUSE

** 054 113674 "Oncogenicity Study in Mice with Thiram", (J.A. Trutter, Hazleton Washington Inc., HWA Study No. 798-223, 3/13/92). Thiram (purity = 97.6%) was administered in diet to CrI:CD-1* (ICR)BR albino mice (50/sex/group) at 0, 15, 150 or 300 ppm (males) and at 0, 15, 300, or 600 ppm (females) for 97 weeks. Systemic NOEL = 15 nominal for both sexes, although the actual dose may have been much lower due to low stability of thiram in diet (Decreased body weight and food consumption were observed at ≥ 150 ppm (males) and ≥ 300 ppm (females). There was a decrease in RBC mass (erythrocyte count, HB and/or HCT in females at ≥ 300 ppm), accompanied by an increase in platelet counts. Males showed a decrease in mean cell hemoglobin concentration at ≥ 150 ppm. Histopathologically, there was an increase in splenic pigment in females and evidence of extramedullary hematopoiesis in both sexes at ≥ 150 ppm. There was an increase in hyperkeratosis in the stomach of both sexes at ≥ 150 ppm. An increase in intracytoplasmic, protein-like droplets in the transitional epithelium of the urinary bladder and an increase in suppurative inflammation on the skin in both sexes occurred at ≥ 150 ppm. **Possible systemic adverse effect:** There was an increase in opaque eye, lacrimation and retinal atrophy in both sexes at 150 & 300 ppm (males) and 300 & 600 ppm (females). There were no treatment-related oncogenic effects at any dose. ACCEPTABLE. (Kishiyama & Silva, 12/23/93).

012 034449, "Toxicological Investigation of Thiram in the Chronic Feeding Study with NMRI Mice," (Advisory Board for Preventative Medicine and Environmental Protection Ltd., 6/27/80); Thiram (99.6%) tested at 0, 30, 100 and 300 ppm in the diet in a 104 weeks study in NMRI mice; 50 mice/sex/dose group; no adverse effect observed; NOEL ≥ 300 ppm; UNACCEPTABLE possibly upgradeable (needs dose justification and analyses of diet. Does not appear to have used the MTD). Initially reviewed as a chronic study but changed to an oncogenicity test type as a better category. All individual data submitted as microfiche and not all tables translated from German. (J. Gee, 10/1/85 and 11/4/87).

021 055700 (4 parts) Duplicate of 034449 plus individual data in hard copy plus tables translated. Study remains UNACCEPTABLE as above. (J. Gee, 11/4/87).

007 020008. A record which contains a brief review of another oncogenicity study, no data. (JW, 4/12/85).

REPRODUCTION, RAT

** 051, 056, 063 111058, 130815, 145157 "Two-Generation Reproduction Study in Rats", (R. G. York, International Research and Development Corporation, Lab Project ID 399-104, 10/16/91).

Thiram technical (purity = 97.5%) was administered orally in diet to Charles River Crl:CD* VAF/Plus * rats (26/sex/group/generation) at 0, 30, 60 or 180 ppm for two generations (3 litters were produced from F0 parents and 2 litters from F1 parents). Parental Systemic NOEL = 60 ppm (There were significant decreases in body weight & food consumption and an increase in hair loss at 180 ppm in F0 animals.) Reproductive NOEL = There did not appear to be thiram induced reproductive effects in the F1a & F2a & F2b generations. Pup NOEL < 30 ppm **Possible adverse effect indicated (not related to reproduction)**: Pup weights were decreased at all doses for all generations. There was a decreased mean litter size (day 0) in F2a pups at \geq 60 ppm. The study was previously reviewed as unacceptable (Silva, 12/13/93 & 10/17/94) it is upgraded to acceptable upon submission of requested information. (Silva, 3/25/96).

012 034455, "Toxicological Evaluation of Ferric Dimethyldithiocarbamate (Ferbam) and Dithiocarbamate (Thiram) ...Developmental Toxicity - Reproduction Study of Thiram in Rats," (Midwest Research Institute, 8/75); Thiram (purity unspecified) tested at 0, 0.04 and 0.1% in 20 female rats and 0, 0.05, 0.1 and 0.25% in male rats in the diet; 10 treated males/dose; half of females were examined on gestational day 13 and half delivered with pups examined on days 4 and 21; **possible adverse effect**; reduced litter size; reduced pup birth weight; viability; reduced parent fertility; possible hormonal imbalance in females; NOEL < 0.1%; incomplete; UNACCEPTABLE; not upgradeable (not a two-generation reproduction study). (J. Remsen (Gee), 9/30/85).

**** 132 - 075 181857**, "Two Generation Reproduction/Fertility Study in Rats with Thiram", (P.A. Turck, MPI Research (formerly International Research and Development Corporation), USA, Report # 399-180, 7/15/97). Thiram technical (99.4% pure) was fed in diet to Sprague-Dawley (Crl:CD®VAF/Plus®) rats (26/sex/dose/generation) at 0 (ground Certified Rodent Chow®, No. 5002), 20, 60, and 180 ppm through 2 generations (2 litters/generation). Treatment began at least 90 days prior to F0 mating and 81 days prior to F1 mating. Average mg/kg/day calculated for F0 and F1 pre-mating periods was 1.418 - 1.815, 4.221- 5.394 and 12.216 - 16.409 mg/kg/day at 20, 60 and 180 ppm respectively. Parental NOEL = 20 ppm (M: 1.4 - 1.7 mg/kg; F: 1.6 -1.8 mg/kg) (Bodyweights were statistically significantly decreased in both sexes of F0 parents at 180 mg/kg and F1 parents at \geq 60 mg/kg. There was a statistically significantly decreased mean bodyweight in F0 females (F1a generation) during gestation and lactation at 180 mg/kg. Decreases, though statistically significant, were minimal (\leq 10%, except day 0 lactation). These effects were not seen with the F0 females (F1b generation) during gestation or lactation. F1 females (F2a generation) had statistically significantly, but minimally decreased body weights during gestation and lactation at 180 mg/kg. Food consumption was statistically significantly decreased in both sexes of F0 and F1 parents at 180 ppm. Reproductive NOEL = 180 ppm (M: 12.21 - 14.9 mg/kg; F: 14.0 - 16.4 mg/kg) There were no treatment-related effects. Pup NOEL = 20 ppm (M: 1.4 - 1.7 mg/kg; F: 1.6 -1.8 mg/kg) (There was decreased body weight in pups at 180 mg/kg (F0) and \geq 60 mg/kg (F1) throughout lactation). Acceptable. (Green & Silva, 10/23/03)

005 020004 is a published article of 012 034455.

007 020009. A record which contains a brief review of "Reproduction Studies Rat, Chicken (Thiram)". (JW, 4/12/85)

TERATOLOGY, RAT

Pilot Study:

045 091041 "Thiram: Effects of Oral Administration Upon Pregnancy in the Rat - Preliminary Teratology Study," (Tesh, J.M., et al., Life Science Research, Suffolk, England, 4/27/90). Thiram technical (Lot # 860410/L; LSR #: TRK/001/THIRAM; purity = 99%) was administered by oral

gavage to mated (presence of a copulation plug, plus spermatozoa present in a vaginal smear = day 0 of gestation) Charles River CD rats (6/dose) at 0 (vehicle = 0.5% w/v carboxymethyl-cellulose & 0.5% w/v Tween 80), 5, 10, 20, 40 and 80 mg/kg/day during days 6-15 (inclusive) of gestation (volume-dosage = 10 ml). **Maternal NOEL = 20 mg/kg/day** (reduced bodyweight at ≥ 40 mg/kg; increased post-implantation loss and total # of resorptions/litter at 80 mg/kg). **Developmental NOEL =** No effects were reported in fetuses at any dose, however, few data were presented regarding fetuses beyond the # of viable young. Therefore, it is not possible to assess the effects of thiram on fetuses from the data reported. In the report it was stated that doses should not go above 40 mg/kg/day in the definitive rat teratology study. These data are supplemental. M. Silva, 7/19/90.

Definitive Studies:

**** 027 066516**, "Teratology Study in the Rat", (Tesh, J.M., McAnulty, P.A., Willoughby, C.R., et al., Life Science Research, LSR Report No. 87/TRK002/179, January 30, 1987). Thiram (purity = 99.82%; LOT #: 860410/L) was administered by gavage at concentrations of 0 (vehicle = 0.5% carboxymethylcellulose + 0.5% Tween 80), 7.5, 15 or 30 mg/kg/day to 25 mated female Sprague Dawley (Charles River CD) rats/group on gestation day 6 through 15 (day 0 = sperm positive vaginal smear or 3 copulation plugs). **Possible adverse effect. Maternal NOEL = 7.5 mg/kg/day** (reduced bodyweight and hair loss at ≥ 15 mg/kg/day). **Maternal NOEL > 30 mg/kg/day**. **Fetal NOEL = 7.5 mg/kg/day** (reduced 13th rib, smaller fetuses and an increased incidence in incomplete skeletal ossification). ACCEPTABLE. (Kishiyama & Silva, 7/19/90).

005 020003, "Teratogenicity Study in Rats with Disulfide, bis(dimethylthiocarbamoyl) (IN-793, Thiram)," (Haskell Laboratory, 7/8/80); Thiram (98.6%) tested at 0, 25, 125 and 625 ppm (43.5 mg/kg at the high dose) in ChR-CD rats in the diet days 6 - 15; 18-24 pregnant females/dose; decrease in maternal body weight and food consumption at 625 ppm; skeletal anomalies in fetuses increased in a dose-response fashion; nominal maternal NOEL = 125 ppm (body weight gain, decreased food consumption), developmental NOEL = 25 ppm; **possible adverse effects**; incomplete; UNACCEPTABLE; not upgradeable (no diet analysis, no individual data, incomplete necropsy observations). (J. Wong, 4/12/85).

005 020004, "Developmental Toxicity of Ferric Dimethyldithiocarbamate and Bis(dimethylthiocarbamoyl) Disulfide in Rats and Mice," (Midwest Research Institute, 4/5/75, published in Toxicology and Applied Pharmacology 35: 83 - 94 (1976)); Thiram (purity not specified - stated as "practical grade" and assumed to be 100%) tested at 0, 40, 90, 136, 164 and 200 mg/kg in 0.5% carboxymethyl cellulose by oral gavage during gestation days 6-15 with Charles River CD rats; 8-28 female rats/dose group; increase in mortality in high dose group - 33% survival; maternal NOEL < 40 mg/kg (reduced weight gain during gestation, decreased food consumption), developmental NOEL < 40 mg/kg (decreased mean fetal weight, decreased implants and increased resorptions at 136 and above, increased incidence of "anomalies" at 136 mg/kg described in the text as domed cranium (19/21 versus 0/267), slight (6/10 versus 3/146) or marked (4/10 versus 0/146) hydrocephalus, unossified sternabrae (11/11 versus 0/156), incompletely ossified supraoccipital (7/11 versus 0/156) and centra split (6/11 versus 0/156) or lobed (5/11 versus 0/156); summary only; **possible adverse effect**; incomplete; UNACCEPTABLE (no purity of test compound, no analysis of dosing solutions, not enough animals per dose group, no necropsy observations). Not upgradeable. (J. Wong, 4/12/85).

012 034453 was reviewed as 005 020004.

007 020010. A record which contains a brief review of "Teratogenicity-Rat, Mouse, Hamster Hen (Thiram). (JW, 4/12/85).

TERATOLOGY, RABBIT

Pilot Study:

045 091042 "Thiram: Preliminary Teratology Study in the Rabbit," (Tesh, J.M., Ross, F.W. and Crisp, V.C., LSR Report #: 87/TRK003/122, Life Sciences Research, Suffolk, England, 8/14/87). Thiram technical (Sample #: 860410/L; purity = 99.1%) was administered by gavage to artificially inseminated New Zealand White rabbits (4/dose) at 0 (vehicle = 0.5% w/v aqueous carboxymethyl-cellulose mucilage + 0.5% w/v Tween 80), 5, 10, 20, 40, 80, and (due to a high incidence of mortality and/or total litter loss at > 10 mg/kg) 0, 1, 3 and 7.5 mg/kg/day from day 6 to day 19 of gestation (day of artificial insemination = day 0 of gestation). **Maternal NOEL = 10 mg/kg/day** (Increased early and late resorptions, increased post implantation loss, transitional decreased body weight gain, decreased food intake and increased fecal retention and water intake was observed at 20 mg/kg/day. Increased death was observed for all animals at \geq 40 mg/kg/day.) **Developmental NOEL = \geq 20 mg/kg/day** (No fetal effects were observed at 20 mg/kg/day. Higher levels were toxic to dams.) These data are considered supplemental. M. Silva, 7/23/90.

Definitive Study:

028 067162, "Teratology Study in the Rabbit", (Tesh, J.M., Ross, F.W., Crisp, V.C., et al., Life Science Research, Eye, Suffolk IP23 7PX, England, Report no. 87/TRK004/541, June 29, 1987). Thiram (purity = 99.5%, LOT #: 860410/L) administered by gavage at concentrations of 0 (aqueous 0.5 carboxymethylcellulose plus 0.5% Tween), 1, 2.5 or 5 mg/kg/day during day 6 through 19 of gestation (insemination = day 0 of gestation) to artificially inseminated New Zealand White female rabbits. **Insufficient data to evaluate the possibility of an adverse effect.** Maternal NOEL > 5 mg/kg/day and Fetal NOEL > 5mg/kg/day (no effects were observed in dams or fetuses at the doses tested). UNACCEPTABLE (The dose level selection was too low, given the results of the pilot study 045 091042. (Kishiyama & Silva, 7/23/90).

048 095749 This volume, sent by the thiram task force, contains a letter from Life Science Research to Uniroyal Chemical Company Incorporated, which presents a justification for dose selection for study 028 067162 (definitive rabbit teratology study). Included is a figure showing bodyweight change (kg) of female rabbits during gestation (4 separate studies) and a table of the tabulated data. M. Silva, 1/16/91.

** 053 113161, "Developmental Toxicity Study in New Zealand White Rabbits", (R.G. York, International Research and Development Corporation, Laboratory Product I.D. 399-121, 2/18/92). Thiram technical (purity = 98.26%) was administered by gavage to artificially inseminated New Zealand White SPF females (20/group) at 0 (0.5% Tween 80 plus 0.5% low viscosity methylcellulose), 1.0, 5.0 or 10.0 mg/kg during gestation days 7 through 19. NOEL > 10 mg/kg/day (no evidence of maternal and/or developmental toxicity). ACCEPTABLE. (Kishiyama & Silva, 12/7/93).

TERATOLOGY, MOUSE

005 020004, "Developmental Toxicity of Ferric Dimethyldithiocarbamate and Bis(dimethylthiocarbamoyl) Disulfide in Rats and Mice," (Midwest Research Institute, 4/5/75, published in Toxicology and Applied Pharmacology 35: 83 - 94 (1976); Thiram (purity not stated but "practical grade" assumed to be 100%) tested at 0, 100 and 300 mg/kg in 0.5% carboxymethyl cellulose by oral gavage during gestation days 6-14 with Swiss-Webster mice; 18 pregnant mice/dose group; increase in mortality in high dose group - nominal maternal NOEL =

100 mg/kg; increase in anomalies in fetuses; summary only; initially reviewed as having a possible adverse effect but the anomalies occurred at 300 mg/kg where 4/18 dosed dams died; incomplete; UNACCEPTABLE; not upgradeable (no purity of test compound, no analysis of test compound, need 3 dose levels, no individual data.) (J. Wong, 4/15/85 and J. Gee, 11/5/87).

012 034454 was reviewed as 005 020004.

005 020001. A record which contains a brief review of "Influence of L-Cystine on Thiram (TMTD)-Induced Teratogenesis in NMRI-Mice" (written in German). (JW, 4-12-85).

005 020002. A record which contains a brief review of "Teratological Studies with Thiram (TMTD) on Two strains of Mice" (written in German). (JW, 4/12/85).

GENE MUTATION

Mammalian System

** 018 048604, "Evaluation of the Mutagenic Activity of TMTD Technical in an in vitro Mammalian Cell Gene Mutation Test with V79 Chinese Hamster Cells," (NOTOX, The Netherlands, Report #0174/EV 1, 5/1/1986); Thiram (100%, batch # S 94/06-85) tested at 0, 1, 3.3, 5.6 and 10 ug/ml without S9 and at 10, 18, 33 and 56 ug/ml with Aroclor 1254 induced rat S9 on Chinese hamster V79 cells; two trials with activation and two trials without activation; 2-hour exposures; 7-day expression time; mutants selected with 6-thioguanine at 5 ug/ml; no adverse effect; complete; ACCEPTABLE. (WN Choy, 11/20/86).

CHROMOSOME EFFECTS

** 025 065351, "Micronucleus Cytogenetic Assay in Mice", (Putman, D.L., Microbiological Associates, Inc., Laboratory study no. T5558.122, 11/9/87). Thiram (purity = 99.8%; LOT #: NR 860410/L) was administered to CD1 mice by a single IP injection at concentrations of 0 (vehicle = 1% carboxymethyl cellulose), 0.2, 0.4, 0.6, 0.8 or 1.0 g/kg (cytotoxicity assay-- 5 mice/sex/group) and 0, (1% CMC), 38, 189 or 377 mg/kg for the micronucleus assay. The micronucleus assay had 24, 48 and 72 hour post-dose sacrifice time points (5/sex/group/time point). Toxicity test: LD₇₇ (7th day) = 471 mg/kg. Micronucleus Assay: Incidence of micronucleated polychromatic erythrocytes/1000 polychromatic erythrocytes scored and the proportion of polychromatic erythrocytes/total erythrocytes were presented for each animal. Thiram produced no significant increase of micronuclei in the bone marrow of the mice. ACCEPTABLE. (Kishiyama & Silva, 6/20/90).

** 025 065352, "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells", (Putman, D.L., Microbiological Associates, Inc., Laboratory Study No. T5558.337, 11/2/87). Thiram (purity = 99.82%; Lot NR 860410/L) was used on duplicate cultures of Chinese hamster ovary cells (CHO-K1) at 0 (untreated or DMSO), 0.003, 0.006, 0.012, 0.023, or 0.05 ug/ml without S-9 activation for 14 hours and at 0 (untreated cells or DMSO), 0.2, 0.4, 0.8, 1.5 or 3 ug/ml with S-9 activation for 2 hours. 100 cells/dose were scored for chromosomal aberrations. A concurrent cytotoxicity assay was performed at 0.03, 0.1, 0.3, 1.0, 3.0, 10, 33, 100 and 330 ug/ml both with and without S-9 (incubation times: no S-9 = 6 hours; with S-9 = 2 hours). Thiram, with or without S-9 activation, did not show evidence of inducing chromosomal aberrations in this system. Cytotoxicity was observed at ≥ 1.0 ug/ml (no S-9) and ≥ 3.0 ug/ml (+ S-9). ACCEPTABLE. (Kishiyama & Silva, 6/15/90).

** **020 050380** "Evaluation of the Ability of TMTD Technical to Induce Chromosome Aberrations in Cultured Chinese Hamster Ovary (CHO) Cells, Using Multiple Fixation Times," (NOTOX, the

Netherlands, report # NOTOX 0174/EC108); Thiram (100%) tested at 0, 0.56, 1.0, 1.8 and 2.4 ug/ml without activation and at 0, 1.8, 5.6 and 18 ug/ml with Aroclor 1254 induced rat liver S9 activation; cytotoxicity evaluated by cell counts immediately and 18-20 hours after treatments; three harvests at 3, 8 and 12 hours after treatments; 2 replicates/dose; 100 metaphase/replicate examined; **possible adverse effect**; optimal harvest time was 10 hours; dose dependent increase of chromosome aberrations reported; mostly chromatid-type aberrations, i.e. chromatid gaps, breaks, fragments and terminal deletions; 8-10 fold more sensitive in non-activated than in activated trials, suggesting test compound can be metabolized into two molecules of dimethyl dithiocarbamate and further inactivated by the S9 enzymes; complete; ACCEPTABLE. (WN Choy, 12/8/86).

Conclusion: Although an adverse effect for chromosome aberrations was observed in study 050380, a similar study (065352) was performed using lower doses below and up to a dose that would produce an insufficient number of metaphase cells. Apparently in study 050380, the dose effects in the preliminary cytotoxicity assay were not reproducible and ultimately may have been too high, since in the CHO assay at 14 hours post treatment there were no metaphases. Study 050380 was performed so that the highest dose was considered cytotoxic, but the lower ones were not. Since in this repeat study and in a micronucleus assay (065351) there were no adverse effects, CDFA does not consider thiram to induce chromosome aberrations. M. Silva, 8/17/90.

DNA DAMAGE

**020 050379, "Evaluation of the DNA Repair Inducing Ability of TMTD Technical in a Primary Culture of Rat Hepatocytes, " (report # NOTOX 0174/ER156; NOTOX, the Netherlands, 12/9/85) Thiram (100%) tested at 0, 0.03, 0.1, 0.3, 1.0, 3.0 and 10 ug/ml for 18 hours with tritiated thymidine by an autoradiographic method in isolated hepatocytes from male wistar rats; 2 independent trials; 50 cells/replicate scored; 3 replicates/dose; no adverse effect; complete; ACCEPTABLE. (WN Choy, 12/5/86).

NEUROTOXICITY

012 034452, "Neurotoxicity of Thiram: Behavior and Neuropathology," Midwest Research Institute, 8/75. Thiram (purity unknown) tested at low, mid and high dose groups (dosage not stated) for 79-81 weeks in a behavioral study; **possible adverse effect**; statistically significant differences were observed in treated rats in 1. hindleg gait, 2. jump/climb ability and 3. open field behavior; no statistically significant differences were observed in active avoidance test; microscopic examination of 2 high dose females treated for 80 weeks showed some demyelination of sciatic nerve and degeneration in the lower lumbar regions of the spinal cord; incomplete; UNACCEPTABLE (multiple deviations from the EPA guidelines). (J. Remsen (Gee), 9/30/85).