

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

MANEB (Including Ethylenethiourea)

Chemical Code # 000369, Tolerance # 00110
SB 950 # 128

AUGUST 18, 1986

Revised date 7/6/89; 2/22/91; 10/25/91; 3/13/92; 1/11/93

I. DATA GAP STATUS

Chronic/onco rat: No data gap, possible adverse effect.
Chronic dog: No data gap, possible adverse effect.
Onco mouse: No data gap, possible adverse effect.
Repro rat: No data gap, possible adverse effect¹.
Terato rat: No data gap, no adverse effect².
Terato rabbit: No data gap, possible adverse effect.
Gene mutation: No data gap, possible adverse effect in inadequate studies with bacterial systems.

Chromosome: No data gap, possible adverse effect.

DNA damage: No data gap, no adverse effect.

Neurotox: Not required at this time.

-----1 - The adverse
effect is systemic and not related to reproduction.

2 - See conclusion for TERATOLOGY, RAT.

Note, Toxicology one-liners are attached

All record numbers through 117875 (volume 093) were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T930111

Revised by: Kishiyama and Gee, 7/6/89 and 2/21/91; Kishiyama & Silva, 10/25/91; Kellner and
Gee, 3/13/92; Kishiyama & Silva, 1/11/93.

See "Guidance for the Reregistration of Pesticide Products Containing Maneb as the Active
Ingredient," US EPA, October, 1988.

THESE PAGES CONTAIN SUMMARIES ONLY. EACH INDIVIDUAL WORKSHEET MAY CONTAIN ADDITIONAL EFFECTS.

II. TOXICOLOGY ONE-LINERS AND DISCUSSION

NOTE: Some of the studies listed below with adverse effects were performed using ethylenethiourea (ETU), a degradation product and contaminant of Maneb. ETU is classified by EPA as a Class B2 carcinogen, a teratogen, that is also weakly genotoxic. Gee, 5/18/89.

COMBINED, RAT

**** 026, 055 & 063, 043966, 097216 & 089839, "Chronic Oral Toxicity of Manganese-Ethylene-1,2-bis-Dithiocarbamate, 90% - Called for Short 'Maneb' - in Sprague-Dawley (SIV 50) - Rats."** (Leuschner, F., Laboratorium fuer Pharmakologie & Toxikologie, 4/9/79). Maneb technical (90% pure; ETU content not given) was fed to Sprague-Dawley (SIV 50) rats (90/sex/group) at 0, 30, 100, 300, or 1000 ppm in the diet for 31 months. Sacrifices were performed at 3, 6 and 12 months (5/sex/group). Systemic NOEL = 300 ppm. **Possible adverse effect indicated (increased retention of ¹³¹I at 6 and 12 months; increased thyroid weight at 6, 12, and term)** No oncogenic effects were reported. Rebuttal dated 9/28/90 addresses stability in the diet. Previously reviewed as unacceptable (Gee, 5/29/86, 5/18/89 and 2/20/91), upon submission of the requested information, the study is now acceptable. Kishiyama & Silva, 9/10/91.

EPA: NOEL = 300 ppm (15 mg/kg/day) based on thyroid effects and bladder epithelial dysplasia in males). Supplementary but possibly upgradeable with additional data and clarifications of analysis of diets.

044 066222 Duplicate of 043966.

055 097216. Supplemental to 043966. Additional microscopic examinations of the liver, kidneys, and urinary bladder; blood chemistry and body weight. M. Silva, 10/8/91.

063 089839. This volume contains the diet analysis (retrospective) for study 043966. M. Silva, 10/8/91.

022 020212, "S/Amitrol and Dithiocarbamates - Induction of Thyroid Tumors with Amitrole and Ethylene Thiourea (Degradation product of Maneb)." (Excerpt from Pesticide Residues in Food). No worksheet. (JSK, 3/6/89).

052 092526 Rebuttal for 043966. Replied to 2/21/91 by Gee.

CHRONIC, RAT

018 014769 "Two-Year Feeding Test with Rats." (Haskell, DuPont, 1956.) Maneb, multiple lots, 81.6 to 90%; 25/sex/group were fed 0, 0.0025, 0.025, 0.125, and 0.25% (2500 ppm) in the diet for 2 years; NOEL = not clearly established; thyroid toxicity and muscle damage at 0.25%. UNACCEPTABLE, insufficient number of animals; **positive for adverse effect on thyroid.** (Wong, 4/18/85)

EPA: Supplementary (inadequate number of animals). NOEL = 250 ppm (0.025%) based on thyroid effects.

022 019936 "Difference de sensibilite du hamster et du rat vis-a-vis des effets de l'administration a long terme de l'ethylene thiouree." (1976 Journal article in French with English summary in: European J. of Toxicol. 9: 303-312, Gak et al.) ETU tested at 0, 5, 17, 60, and 200 mg/Kg in the diet of rats and hamsters; onco effects reported in rats and **thyroid effects** noted in hamsters). No worksheet. UNACCEPTABLE. (Parker, 8/20/86).

CHRONIC, DOG

**** 110-071 112581** Corney, S. et al. "52-Week Oral Toxicity (Feeding) Study with Maneb Technical in the Dog" (RCC, Research & Consulting Company, Ltd., RCC Project # 206616,

1/16/92). Maneb Technical (batch # B1 280289, 89.2% purity) was administered in the feed at nominal concentrations of 0, 50, 200, 1000 and 2200 ppm to 5 beagle dogs/sex/dose for 52 weeks. Reduced food intake and weight gain was seen in high-dose animals. **Possible Adverse Effects:** Increases in thyroid weight and thyroid follicular cell hyperplasia were seen at 1000 and 2200 ppm; decreased thyroxine levels were noted at 2200 ppm. Possible anemia was suggested by lower RBC counts and hemoglobin concentrations at 200 ppm and above, although the values at 200 ppm were well within the reference range included in the report. Increased reticulocyte and platelet count and polychromasia at 2200 ppm and increased plasma bilirubin concentration at 1000 and 2200 ppm were noted. A NOEL based on thyroid effects = 200 ppm (6.77 mg/kg/day). **Acceptable.** Kellner and Gee, 3/2/92.

018 030283. "One-Year Feeding Test on Dogs." (Haskell, DuPont, 1956) Maneb, purity not stated.; mongrels, 2 males/group, were fed 0, 2, 20, 75, or 200 mg/Kg orally for 1 year (due to appetite problems, changed to capsules) apparent NOEL= 20 mg/kg (toxicity described by authors); **adverse effects noted were paralysis, cardiovascular effects, myopathy and degeneration in CNS at high dose;** cardiovascular effects, myopathy and weakness in hindlimbs at 75 mg/Kg; UNACCEPTABLE, not upgradeable (animal number, males only). No data. (Wong, 4/18/85).

EPA: Supplementary. Cannot be upgraded.

CHRONIC, MONKEY

027 043967, "Oral Toxicity of Manganese Ethylene-1,2-bis-dithiocarbamate, 90%, Internal No. WF 1172 - Called for Short 'Maneb' - in the Rhesus Monkey." (Subchronic study in which potential adverse effect on thyroid identified--Lab. fuer Pharmakol. Toxikol., Germany, 1977). Maneb, 90% in the diet to 4/sex/group of rhesus monkeys at 100, 300 or 3000 ppm for 6 months. **Positive adverse effect on ¹³¹I-¹³¹I-absorption was decreased, serum thyroxine decreased, thyroid enlarged and ¹³¹I-bound to protein also decreased at 3000 ppm.** NOEL = 300 ppm based on lack of microscopic findings and marginal increase in thyroid organ weight. Unacceptable for chronic study. (Gee, 5/29/86 and 5/19/89)

EPA: NOEL = 100 ppm (5 mg/kg/day) based on increase in thyroid weight in males.
Acceptable as a 90-day non-rodent feeding study.

ONCOGENICITY, RAT

020 019933 (1977 RPAR, no worksheet).

ONCOGENICITY, MOUSE

** 093 117875, "18-Month Dietary Oncogenicity Study in Mice with Maneb Technical", (E.C. Tompkins, WIL Research Laboratories, Inc., WIL-134008, 11/8/89). Maneb technical (purity = 89.5%) was fed in diet at 0, 60, 240 or 2400 ppm to Crl:CD*-1(ICR) mice (75/sex/group) for 18 months. **Systemic NOEL = 60 ppm** (Decreased food consumption and body weight gain were observed in both sexes at 2400 ppm. The decreases were statistically significant but were usually less than 10%. Decreased RBC, HB and HCT were observed in females at 2400 ppm. Decreased RBC was observed in both sexes at interim sacrifice at 2400 ppm. Interim and terminal thyroxin RIA were significantly decreased in males and interim females at 2400 and in females at all doses at terminal sacrifice. An increased incidence in hepatic masses was observed in males at \geq 240 ppm and in females at 2400 ppm. Terminal absolute and relative thyroid weights were increased in both sexes at 2400 ppm. Relative heart, liver and kidney weights were increased at 2400 ppm in both sexes. Absolute and relative brain weights were increased in females at \geq 240 ppm. Testes weights were decreased at \geq 240 ppm.) **Oncogenicity NOEL = 240 ppm/day** (Hepatocellular and lung alveologenic adenomas were increased at 2400 ppm in both sexes.) **Possible adverse effect:** There was an alteration in thyroid function (increased thyroid weight & decreased thyroxin RIA values) and an increase in hepatocellular adenomas and lung alveologenic adenoma observed in both sexes at 2400 ppm. ACCEPTABLE. (Kishiyama & Silva, 12/9/92).

022 019935 "Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note." (1969 Journal article of the NCI which refers to onco effects of ETU, Innes, J. R. M. et al., J. Nat. Cancer Inst. 42: 1101-1114 (1969)) No protocol, no data. Screen of 120 compounds for tumorigenesis. J. Wong (4/18/85) identified possible adverse effect for ETU, but not mane. Insufficient information for evaluation. (J. Parker, 8/20/86).

ONCOGENICITY, GENERAL

022 019937 "Living with Carcinogens." (1974 Journal article which refers to thyroid tumors and terata in rats exposed to ETU; also epidemiology obs for humans.) positive but UNACCEPTABLE as a SB950 study. (Wong, 4/18/85; Parker and Martz, 8/20/86).

022 019938, "Ethylene Thiourea - a Study of Possible Teratogenicity and Thyroid Carcinogenicity." (1976 Journal article in: J. Soc. Occup. Med. 26: 92-94, D. Smith) on incidence of thyroid cancer in workers exposed to ETU in rubber. Results were negative for birth defects and thyroid cancer. No worksheet. Gee, 5/18/89.

REPRODUCTION, RAT

** 058 089631, "A Study of the Effect of Maneb (Technical) on Reproductive Function of Two Generations in the Rat", (P.R. Ryle, P. F. Bell, C. Parker, H. Farmer, J.M. Offer, A. Anderson and I.S. Dawe, Huntingdon Research Centre, Project I.D. No.: MNB/1, May 2, 1991). Maneb (purity = 89.6%) was administered at concentrations of 0 (basal diet), 75, 300, or 1200 ppm to 28 F0 generation and 24 F1 generation Sprague-Dawley rats/sex/group. Exposure time was 19 and 26 weeks for F0 and F1 generations, respectively. **Reproductive NOEL > 1200 ppm** (No effects reported). **Systemic NOEL = 75 ppm** (Adults of both sexes and both generations showed a decrease in body weight gain and a decrease in food consumption at 1200 ppm. F0 adults at 1200 ppm and F1 adults at ≥ 300 ppm showed an increase in water consumption. F0 (both sexes) thyroid, liver and kidney weights were increased at 1200 ppm. Thyroid in F1 females at 1200 ppm, and liver at ≥ 300 ppm and kidney at 1200 ppm weights in males were increased.) **Possible adverse SYSTEMIC effect:** Histopathology showed an increase in thyroid effects (diffuse hyperplasia, F1 & F2, both sexes and cystic follicular hyperplasia, F1 & F2 males), accompanied by thyroid follicular adenomas in 2/24 F1 males. F1 & F2 males also showed centrilobular hepatocyte enlargement at 1200 ppm.) **Pup NOEL = 75 ppm** (F1 weanling females at ≥ 300 ppm showed increased liver and kidney weights. F1 weanling male kidney weights were increased at 1200 ppm. F2 liver weights for both sexes were increased at ≥ 75 ppm and F2 male kidney weights were increased at 1200 ppm. However, the tissues were not examined microscopically.) ACCEPTABLE. Kishyama & Silva, 9/13/91.

018 014768 "Three-Generation Reproduction Study (with Manzate D)." (Haskell, 5/11/66).
Three generation study in CHR-CD rats with maneb (88%) at 0, 0.0125% and 0.025% of diet;
16/sex/group; UNACCEPTABLE, not upgradeable. Inadequate number of animals, no histopathology
data, no histopath. on F0 or F1 parents, only 2 dose levels with no justification of dose
selection. Summary. No adverse effect identified. (Wong, 4/18/85)
EPA: Unacceptable.

025 038465, Exact duplicate of 14768.

025 038466, Appendix of 038465.

028 043968, "Chronic Toxicity of Manganese Ethylene-1,2-bis-dithiocarbamate - called Maneb -
in Three Succeeding Generations of Sprague-Dawley Rats at Oral Administration." (Lab fuer
Pharmakol. & Toxikol., 12/27/78). Maneb no purity stated; 40/sex/group were fed 0, 30, 100 or
500 ppm, Sprague-Dawley; 3 generations, 2 litters (1/2 of 2nd litter for terata at day 19);
NOEL not established-->500 ppm; no adverse effect on reproduction, teratology or other
including thyroid; UNACCEPTABLE and not upgradeable. Histopathology on 10/sex/group of F3.
No purity of test article, no analysis of diet although it was sampled, no justification of
dose selection and no evidence MTD was approached. (Gee, 5/29/86).
EPA: Unacceptable.

042 066219 Exact duplicate of 043968.

TERATOGENICITY, RODENT

** 092 117021, "A Developmental Toxicity Study of Maneb Technical in Rats", (Nemec, M.D.,
WIL Research Laboratories, Inc., Report # WIL-134011, 26 June 1992). Maneb technical (90.4%
pure) was administered by gavage to mated Sprague-Dawley Cr1:CD*BR rats (25/group) at 0 (0.5%
carboxymethylcellulose), 20, 100, and 500 mg/kg/day on gestation days 6 through 15. **Maternal**
NOEL = 20 mg/kg/day (Significantly decreased body weights and food consumption were observed

at \geq 100 mg/kg. Clinical signs of impaired mobility, dragging hindlimbs, hunched body, unkempt appearance, excessive chewing, prostration and red or yellow urogenital staining were observed at 500 mg/kg. Soft stool was increased at \geq 100 mg/kg.) **Developmental NOEL = 100 mg/kg/day** (Reduced litter size was observed at 500 mg/kg. Bent ribs and delays in several sites of ossification were also observed at 500 mg/kg.) **Adverse effects are not indicated** at less than maternally toxic dosing levels. **Acceptable.** (H. Green & M. Silva, 12/8/92).

022 019937 (See this record # in general section above.)

022 019939, "Preliminary Report on the Fetotoxic Potential of Maneb and Ethylenethiourea in the Rat and Mouse." (1977, preliminary report by N. Chernoff.) Refers to repro and teratogenic effects on mice (CD-1) and rats (CD) of ETU and mane-80% plus "inerts" (Dithane M-22, lot 6810). Animals were given 120, 240 or 480 mg/kg in water by oral gavage, days 6-20, to CD rats or at 300, 600 or 1200, days 6-15, to CD-1 mice. Insufficient information to fully evaluate. **Possible adverse effect in rat, UNACCEPTABLE.** (J. Wong, 4/18/85 and J. Parker, 8/20/86).

025 038467. Partial duplicate of 019939.

020 019934. Duplicate of 019939.

025 038468. Partial duplicate of 019939.

019 019929, "Ethylenethiourea-Induced Hydrocephalus: Pre- and Postnatal Pathogenesis in Offspring from Rats Given a Single Oral Dose during Pregnancy." (1976 Journal article: Toxicology and Applied Pharmacology 42: 85-97, Khera and Tryphonas) Reports reproductive and teratogenic effects of ETU in rat. Pregnant Wistar rats (5 - 10 per group) given a single oral dose on day 15 of gestation of 0, 15, 30 or 45 mg/kg. (J. Wong, 4/18/85. J. Parker, 8/20/86).

020 019933, (1977 response to RPAR). (Wong, 4/18/85).

019 019930, "A Comparison of the Distribution, Metabolism and Excretion of Ethylenethiourea in the Pregnant Mouse and Rat." (1977 Journal article in Toxicology 16: 159 - 162, Ruddick et al.) The distribution of ETU in maternal and fetal tissues after a single oral dose of 240 mg/kg with radiolabeled ETU. No worksheet. Gee, 5/19/89.

NOTE: Studies 061/089633-089635 were combined in study 059/089632.

061 089633, "Study to Determine the Prenatal Toxicity of Manganese Ethylene-1,2-bis-dithiocarbamate in Rats", (R.W. Kapp Jr., L.J. Schellhaas, & V.J. Piccarillo, BASF Gewerbehygiene und Toxikologie, Laboratory Study Number 88/0522, 3/4/77). Maneb technical (<0.01% ETU; 99.99% pure) was administered by gavage at concentrations of 0 (untreated), 0 (0.5% CMC), 20, 100 or 500 mg/kg/day to 23-25 Sprague-Dawley mated rats/group on days 5 through 16 of gestation. **Developmental NOEL** = 20 mg/kg/day (Numerous malformations, variations and retardations, including skull retardation--dose related increase at \geq 100 mg/kg--were reported. Increased percent in % of dead implantations/animal and decreased mean fetal weights were reported at 500 mg/kg). **Maternal NOEL** = 100 mg/kg/day (Lower body weight (10-16%) and increased incidence of paresis (in rear limbs of 14/25 animals).) Unacceptable, but possibly upgradeable (Analysis of dosing solution and maneb technical are requested. Indicate method for randomizing animals into groups. Clarify whether animal #117 aborted or had dead fetuses.) (Kishiyama & Silva, 10/1/91).

061 089634, "Study to Determine the Prenatal Toxicity of Manganese Ethylene-1,2-bis-dithiocarbamate Containing 0.75% ETU in Rats", (R.W. Kapp Jr., L.J. Schellhaas, & V.J. Piccarillo, BASF Gewerbehygiene und Toxikologie, Laboratory Study Number 88/0523, 6/12/78). Maneb Technical + 0.75% ETU (99.99% pure), was administered by gavage at concentrations of 0 (untreated), 0 (0.5% CMC), 133.33 or 500 mg/kg/day to mated Sprague-Dawley rats (23-25/dose) on days 5 through 16 of gestation. **Maternal NOEL** = 133.33 mg/kg/day (Reduced body weight and perirenal fat, increased incidence of paresis and increased mortality.) **Developmental NOEL** < 133.33 mg/kg/day (Increased incidence of fetal malformations and variations/retardations, including skull retardation at \geq 133.33 mg/kg. Significantly decreased fetal body weight and

length at 500 mg/kg.) UNACCEPTABLE (Analysis of dosing material is required and maneb technical are requested.) These data are supplemental. (Kishiyama & Silva, 10/2/91).

061 089635, "Study to Determine the Prenatal Toxicity of Manganese Ethylene-1,2-bis-dithiocarbamate Containing 2% ETU in Rats", (R.W. Kapp Jr., L.J. Schellhaas, & V.J. Piccarillo, BASF Gewerbehygiene und Toxikologie, Laboratory Study Number 88/0524, 5/26/78). Maneb Technical + 2% ETU (99.99% pure) was administered by gavage at concentrations of 187.5 or 500 mg/kg/day to 23-25 Sprague-Dawley mated rats/group on days 5 through 16 of gestation. (NOTE: Untreated and 0.5% CMC controls were from 089634 and were not run with this study.) **Possible adverse effect:** Developmental NOEL < 187.5 mg/kg/day based on increased malformations and variations/retardations (96% and 50%, respectively) at \geq 187.5 mg/kg. Increased dead implantations at \geq 187.5 mg/kg; decreased mean fetal body weight (35%), mean litter size (12%) and mean body length (18%) at 500 mg/kg. Maternal NOEL < 187.5 mg/kg/day based on lower body weight (from 9 to 26%). UNACCEPTABLE. Not upgradeable (There were no controls and many inconsistencies in data reporting, among numerous other deficiencies.) (Kishiyama & Silva, 10/4/91).

059 089632, A single summary of three teratogenicity studies. "Prenatal Toxicity Study of Maneb in Rats: BASF Study Numbers 88/0522; 88/0523; 88/0524" (R.W. Kapp Jr., L.J. Schellhaas, & V.J. Piccarillo, BASF Gewerbehygiene und Toxikologie, Ludwigshaven, Germany, Laboratory Study Number 88/0522, 88/0523; 88/0524, 5/6/91). **Summary of 3 studies:** Maneb technical (99.99% pure) was administered by gavage to mated Sprague Dawley SPF rats at concentrations of 20, 100, or 500 mg/kg maneb containing less than 0.01% ethylene thiourea (ETU); 133.33 or 500 mg/kg maneb + 0.75% ETU and 187.5 or 500 mg/kg maneb + 2.0% ETU in 3 separate tests, on days 5 through 16 of gestation (gestation day 0 = detection of vaginal sperm). Effects of different concentrations of ETU were compared. **Maternal NOEL** = 133.33 mg/kg; \geq 0.01% ETU (Increased mortality and clinical signs at 500 mg/kg. Decreased body weight and weight gain at \geq 187.5 mg/kg. Decreased implantations at 500 mg/kg + 2.0% ETU. Effects associated with ETU = loss of perirenal adipose tissue at \geq 0.75% ETU.) **Fetal NOEL** = 20 mg/kg; \geq 0.01% ETU (Decreased mean fetal body weight and mean body length at 500 mg/kg + 0.01% and 2.0% ETU. Increased incidence in litters with resorptions/total litters at 500

mg/kg + 0.75% & 2.0% ETU. An increase in malformations was observed at 500 mg/kg + \geq 0.01% ETU. **Possible adverse effect:** An increase in variations/retardations was observed at \geq 100 mg/kg.) **Not acceptable** (Numerous deficiencies were listed in the worksheet. No historical controls; no control with ETU alone; use of "concurrent controls" and combined controls is not acceptable.) NOT upgradeable. (Kishiyama & Silva, 9/23/91).

CONCLUSION: Maneb does not produce adverse developmental effects when used as it was in the most recent study (which is also acceptable--DPR document/record # 110-092/117021). On the other hand, adverse effects for "maneb" were indicated in previous developmental studies submitted to DPR by the Registrant (See DPR document/record #: 110-061/089633-089635). The difference between the older studies and study 117021 is that in the new study ETU contamination was carefully monitored. Maneb was prepared fresh each day and used within 1 hour of preparation, since it was shown that significant ETU contamination occurred after an hour. Therefore, it is likely in the new study that almost pure maneb was tested for developmental effects (rather than maneb contaminated with ETU). Regarding analysis of dosing material from previous reports, either a poor recovery of maneb (without careful monitoring of contaminants) was shown or the reports entirely lacked an analysis. Because of these deficiencies, it is not known from these older studies whether it was maneb or its contaminants that were actually responsible for inducing the adverse effects. ETU, as shown in studies mentioned above (DPR document/record #: 110-019/019929), is known to induce developmental adverse effects in animal studies. Thus when comparing information from the latest study with previous studies, it seems safe to conclude that induction of the developmental effects could be attributed to ETU contamination and not to maneb. Therefore it is concluded, based upon the results of this study, that "pure" maneb probably does not cause adverse developmental effects and that adverse effects in previous studies are probably due to ETU. M. Silva, 1/5/93.

TERATOGENICITY, RABBIT

**** 035, 063 072452, 089840**, "Study to Determine the Prenatal Toxicity of Manganous Ethylenebisdithiocarbamate) in Rabbits", (Piccirillo, V.J., BASF AG, Ludwigshafen Rhein, FRG, Lab project no. RZ-No.83/094, May 24, 1983). Maneb (purity = 90.6% + 2% ETU) was administered by gavage to inseminated Himalayan (Chbb) rabbits (15/group) at 0 (0.5% sodium carboxymethyl cellulose), 20 or 80 mg/kg body weight/day during days 6 - 18 post insemination. Possible adverse effect - decreased litter size, increased resorptions. Developmental NOEL = 20 mg/kg/day. Maternal NOAEL = 80 mg/kg/day and NOEL = 20 mg/kg/day (markedly decreased food intake). Previously reviewed as unacceptable (Gee, 5/17/89 & 2/21/91), after submission and review of the requested information, the study has been upgraded to acceptable. (M. Silva, 10/7/91).

043 066220. Partial duplicate of 072452.

Pages only. Rebuttal to 3/4 items in CDFA review of 072452.

063 089840. This volume contains animal distribution data, supplementary to 072452. M. Silva, 10/8/91.

GENE MUTATION

Microbial Systems:

019 019931, "Mutagenicity Testing on Ethylenethiourea." (1977 Journal article in: Mutation Research 56: 121-129, Teramoto et al.) Potential effects of ETU on B. subtilis, S. typhimurium and E. coli). Salmonella were tested at 10, 100, 1000 or 10,000 ug/plate. Also, in host-mediated assay in male rats. No mutagenic effect but ETU tumorigenic at 215 mg/kg. (Wong, 4/18/85).

019 019932, "A Comparative Study on the Mutagenicity of Ethylenethiourea in Bacterial and Mammalian Test Systems." (1977 publication in: Mutation Research 56: 111-120, Schupbach and

Hummeler) Summary of effects of ETU on Salmonella. Strains TA1532, TA1530, TA1964 and TA1531. **Positive adverse effect for reversion in host-mediated assay at 6000 mg/kg claimed in summary tables only.** UNACCEPTABLE. (Wong, 4/18/85).

- 022 019940, "Genetic Activity of Dithiocarbamate and thiocarbamoyl disulfide." (1976 Summary on effects of maneb on E. coli, S. typhimurium and S. cerevisiae.) Abstract. Positive effects in Salmonella ("weakly mutagenic") and E. coli (5-fold increase) stated by authors. UNACCEPTABLE. (Wong, 4/18/85).
- 022 019941 "The Mutagenic Effect of Pesticides on Escherichia coli WP2try." (1976 Summary on potential effects of maneb on E. coli.) Abstract. No data. (Wong, 4/18/85).
- 022 019942, "Attivita Mutagenica degli Antiparassitari." (1976 Italian article on effects of several pesticides, including maneb, on S. cerevisiae.) No worksheet.
- 022 019945, "Nitrosation in vitro and in vivo by Sodium Nitrite and Mutagenicity of Nitrogenous Pesticides." (1977 Journal article: Mutation Res. 48: 225-236, Seiler) 37 pesticides tested on Salmonella including ETU. Insufficient information to evaluate. (Wong, 4/18/85).
- 022 019946 "Mutagenicity Studies on Ethylenethiourea. I. Microbial Assay." (1976 abstract - Summary of ETU effects on Salmonella.) (Wong, 4/18/85).
- 022 019949 "Evaluation of the Mutagenicity of Ethylenethiourea, using Bacterial and Mammalian Test Systems." (1976 abstract - Summary of ETU effects in several systems.) (Wong, 4/18/85).
- 029 043969, "Salmonella/Microsome Mutagenesis Assay on Technical Grade Maneb." (American Biogenics Corp., 11/26/85). Maneb (88.1%, 11.9% "inerts"); TA1535, TA1537, TA1538, TA98, and TA100 +/- S9 (rat and mouse were used) at 0, 3, 10, 15, 30, 50, or 100 ug/plate; no increase in reversion rate was reported; UNACCEPTABLE, not upgradeable (single trial, duplicate plates.) (Gee, 5/28/86).
- 030 043970, "Host-Mediated Assay in Mice with Compound Maneb Technical - Final Report." (Hazleton, 6/14/85). Maneb (88%); host-mediated assay in male B6C3F1 mice; TA 1530 injected

i.p.; 10 mice/group were given 0, 0.5, 2.0 or 5.0 g/Kg body weight by gavage and sacrificed after 4 hrs; DMN as positive control; no evidence for mutagenesis reported; UNACCEPTABLE, not upgradeable. (Gee, 5/28/86).

The studies above identifying a mutagenic effect in Salmonella used ETU as the test article, suggesting that the adverse effect is due to the degradation product of maneb rather than to maneb itself. Because ETU is inherent in the pesticide, it is included in the toxicity evaluation.

Drosophila:

022 019950 and 019951 (1976 abstract - ETU potential effects on Drosophila.) (Wong, 4/18/85).

Mammalian Cells:

**031 043971, "Final Report: CHO/HGPRT in vitro Mammalian Cell Mutation Assay on Technical Grade Maneb." (Bioassay Systems Corp., 7/31/85). CHO/HGPRT; Maneb (88.1%); +/- S9 (rat and mouse liver) at 0-25 ug/ml (8 conc.) for 16 hrs. without S9; 0-50 (trial 1) or 0-30 (trial 2), 8 conc., 4 hrs with rat liver S9; 0-20 ug/ml, 4 hrs., mouse S9; no increase in MF reported to toxic levels; ACCEPTABLE. (Gee, 5/28/86).

EPA: Clarification of percent of active ingredient required [Reregistration standard].

CHROMOSOMAL ABERRATION

022 019944, Russian article: potential effects of manebe on mouse bone marrow cells. No worksheet.

022 019947 (1976 -Summary of ETU studies with CHO and bone marrow cells.) (Wong, 4/18/85).

019 019931, "Mutagenicity Testing on Ethylenethiourea." (1977 Journal article in: Mutation Research 56: 121-129, Teramoto et al.) Potential effects of ETU in CHO micronucleus and dominant-lethal systems. For micronuclei, Wistar rats were given 200 or 400 mg/kg in a single dose or in 2 to 5 consecutive daily doses. Summary table only. No adverse effect was identified. UNACCEPTABLE. For dominant lethal, ICI-ICR male mice were given 300 or 600 mg/kg on 5 days. For chromatid aberrations, Chinese hamster Don cells were given 1000 or 3200 ug/ml. 200 cells were examined per dose. (Wong, 4/18/85).

022 019948, "Mutagenicity Studies on Ethylenethiourea. III. Dominant-lethal Assay." (1976 - Summary of mouse dominant-lethal study with ETU.) (Wong, 4/18/85).

019 019932, "Comparative Study on the Mutagenicity of Ethylenethiourea (Metabolite of Manzate) in Bacterial and Mammalian Test Systems: The Dominant Lethal Test in Mice." (1977

Summary of ETU study using dominant-lethal and micronucleus systems.) Mice were given 500, 1000 or 3500 mg/kg in a single dose. No effect was reported for dominant lethal. For micronucleus test, Swiss Albino mice were given 2 doses 24 hours apart or 700, 1850 or 6000 mg/kg. No adverse effect reported. UNACCEPTABLE with insufficient information to evaluate. (Wong, 4/18/85).

022 019945 "Nitrosation in vitro and in vivo by Sodium Nitrate and Mutagenicity of Nitrogenous Pesticides." (1976 Journal article: Mutation Res. 48: 225 - 236, Seiler) Deals with effects of 37 pesticides including ETU in micronucleus system.) Mice were used with the Schmid protocol. Insufficient information. No adverse effect and UNACCEPTABLE. (Wong, 4/18/85).

032 043972, "Clastogenic Evaluation of Maneb Technical in the Rat Bone Marrow Cytogenetic Assay - Final Report." (Litton Bionetics, 8/14/85). In vivo chromosomal aberrations in rats; Maneb (88%); males only, 10/group were given a single dose of 0, 0.5, 1.7 or 5.0 g/Kg and sac. at 6, 24, or 48 hours; 10 were given 5 doses of 5 g/Kg (9/10 died), 1.7 or 0.5 g/Kg; no evidence for chromosomal aberrations reported; UNACCEPTABLE (males only without justification), possibly upgradeable. (Gee, 5/28/86).

** 033 043973, "Final Report: In vitro Sister Chromatid Exchange Assay in Cultured Chinese Hamster Ovary (CHO) Cells Treated with Technical Grade Maneb." (American Biogenics Corp., 2/26/86). CHO in vitro sister chromatid exchange; Maneb (88%); +/- S9 (rat and mouse) at 0, 0.5, 1.5, 3, or 5 ug/ml without S9 (28 hrs); + rat S9 at 0, 3, 10, 15, or 30 ug/ml (trial 1) or 0, 5, 15, 20 or 30 ug/ml (trial 2) for 2 hrs followed by 28 hrs; positive effect with >20% increase +S9 (rat) at 15 and/or 30 ug/ml in two trials; +S9 (mouse) at 5 ug/ml (trial 1) but not at 10 ug/ml; ACCEPTABLE. (Gee, 5/29/86).

DNA DAMAGE

022 019943. "Genetic Effects of Fungicides." (1970 Journal article: Mutation Res. 10:533 - 543) 14 fungicides tested on S. cerevisiae. (Wong, 4/18/85).

**034 043974 "Final Report: In vitro Unscheduled DNA Synthesis Assay in Rat Hepatocytes using Technical Grade Maneb." (Bioassay Systems Corp., 8/5/85)₃ Rat hepatocytes UDS; Maneb (88.1% in DMSO); 0, 0.15, 0.5, 1.5, 5.0 and 15.0 ug/ml, 18 hrs - ³H-TdR; no increase in net grains per nucleus; >15 ug was toxic; ACCEPTABLE. No information on the initial viability of the hepatocytes. (Gee, 5/29/86).

019 019931 (Journal article, 1977, on several tests.) B. subtilis rec assay. No adverse effect reported but no data. UNACCEPTABLE. (Wong, 4/18/85).

EPA: Individual data are required [Reregistration standard, 1988].

NOTE: The reregistration standard mentions two cell transformation studies with C3H-10T 1/2. Concentrations in one study ranged from 0.05 to 0.20 µg/ml. Both studies were negative under the conditions used. These studies are not on file at CDFA and should be submitted. Gee, 5/18/89.

NEUROTOXICITY

Not required at this time.