CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
MANCOZEB

Chemical Code # 000211, Tolerance # 00176
SB 950 # 062

December 1, 1986
5/7/87; 6/16/88; 4/19/90; 2/11/91; 11/6/91; 2/14/92, 10/12/95, 7/28/98, 2/10/00

I. DATA GAP STATUS

Combined, Rat :	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, mouse :	No data gap, possible adverse effect (not onco)
Reproduction, rat:	No data gap, possible parental (not reproductive) 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, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time[a].

Toxicology one-liners are attached.

All record numbers through 172566 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T000210
Revised by: [redacted], 2/11/91; [redacted], 11/6/91 and 2/14/92; [redacted] 10/12/95; [redacted], 7/28/98 & 2/10/00.

a - A rat subchronic neuropathology study with a possible adverse effect is on file.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Each individual worksheet may contain additional effects.

COMBINED, RAT

Subchronic Studies:

**** 145 169927** "Three-Month Dietary Toxicity in Rats (Final Report)," (Goldman, P.R., Bernaski, H.J., Quinn, D.L.; Rohm & Haas Company, Spring House, PA; Protocol #: 85P-134; Project #: 85R-167, 2/27/86). Mancozeb (purity = 84%) was fed in diet to Crl: CD(SD) rats (14/sex/dose) at 0, 15, 30, 62.5, 125, 500 ppm a.i. or ETU at 125 ppm (1-2 weeks). Then treatment was: 0, 21, 42, 87.5, 175, 700 ppm mancozeb or ETU at 175 ppm (weeks 3-4) and finally: 0, 30, 60, 125, 250,1000 ppm mancozeb or ETU at 250 ppm (weeks 5-13). NOEL = 125 ppm (Both sexes at 1000 ppm mancozeb showed significantly decreased body weights. Both sexes fed 250 ppm ETU in diet showed increased serum cholesterol levels after 13 weeks. After 13 weeks, serum T_4 levels were decreased, while serum TSH levels were increased at 250 and 1000 ppm mancozeb (females) and at 1000 ppm mancozeb (males). Serum T_4 levels were decreased and both T_3 and TSH levels were increased in rats fed ETU at 250 ppm. Liver (relative-both sexes) and thyroid (relative-M) weights were significantly increased at 1000 ppm mancozeb. At 1000 ppm (mancozeb), MFO activity was decreased in both sexes (not significant), when measured by aniline hydroxylation. Histopathological effects were observed in liver (hepatocyte hypertrophy), adrenal gland and thyroid at 1000 ppm. Pituitary showed an increased amount of large, hypertrophied cells with basophilic tinctorial appearance in the anterior lobe of males at 1000 ppm mancozeb. Cells with similar morphology were seen in other groups, including the controls, however the amount and severity was increased in the males at 1000 ppm mancozeb.) Acceptable. Possible adverse effect (decreased serum T_4 and increased TSH in females at 250 ppm and multiple effects at 1000 ppm) . [redacted], 8/30/99.

** 146 169928 "Mancozeb: Subchronic Inhalation Toxicity Study in Rats (Final Report)," (Hagan, J.V., Fisher, J.R. and Baldwin, R.C.; Toxicology Dept., Rohm & Haas Company, Spring House, PA; Protocol #: 85P-136; Report #: 86R-003; 4/24/86). Mancozeb (purity = 83.35%) was administered to Crl:CD(SD)BR rats by aerosol in air (nose only) for 6 hours/day, 5 days/week. Four groups (#'s: 1, 2, 3, 4 with 38 rats/sex/group) were each subdivided into 3 groups: A, B and C, corresponding to different necropsy intervals. Subgroup A: necropsied at 4 weeks; Subgroup B necropsied after 13 weeks of treatment and Subgroup C was necropsied after 13 weeks of exposure and 13 weeks of recovery. Group #'s: 1, 2 3 & 4 were exposed to total mancozeb aerosol at: 0, 22, 86 and 308 mg/m^3 (4 weeks) and 0, 18, 79 and 326 mg/m^3 (13 weeks), which corresponds to respirable concentrations of 0, 8, 40 and 127 mg/m^3 (4 weeks) and 0, 8, 36 and 144 mg/m^3 (13 weeks), respectively. NOEL = 36 mg/m^3 (Absolute bodyweights and bodyweight gains were significantly decreased at 144 mg/m^3 in males after 13-weeks. T_4 was significantly decreased in females after13-weeks at 144 mg/m^3. Males at 144 mg/m^3 showed significantly decreased heart and kidney weights after 13 weeks (reversed during recovery). Triglycerides in males at 144 mg/m^3 were significantly decreased after 13 weeks. Females after 13 weeks of exposure showed significantly increased MCV and significantly decreased MCHC at 144 mg/m^3.) No adverse effect. [redacted], 9/13/99.

096 124253 "Toxicology and Carcinogenesis Studies of Ethylene Thiourea in F344/N Rats and B6C3F1 Mice," (Alden, C.J., Boorman, G.A., Chhabra, R.S., Eustis, S.L., Goehl, T.J., Griesemer, R.A., Haseman, J.K., Jokinen, M.P., McDonald, M.M., Rao, G.N., Walters, D.B. and Witt, K.L.; U.S. Department of Health and Human Services; Batelle Columbus Labs for National Toxicology Program, Research Triangle Park, NC, NTP TR 388; NIH Publication #: 92-2843; 3/92). Ethylene thiourea (99% pure) was fed in diet to F344/N rats (10/sex/dose) at 0, 60, 125, 250, 500 or 750 ppm for 13 weeks, and B6C3F1 mice (10/sex/dose) at 0, 125, 250, 500, 1000 or 2000 ppm for 13 weeks. NOEL Rat < 60 ppm (Relative and absolute rat body weights (both sexes) were decreased by 10% or more at $\geq$ 500 ppm. Rat mean food consumption was decreased in males at $\geq$ 500 ppm and in females at $\geq$ 250 ppm. Males at $\geq$ 250 ppm and females at $\geq$ 500 ppm showed increased thyroid focal follicular cell hyperplasia and increased follicular cell adenomas. Both sexes at all doses showed increased thyroid diffuse follicular cell hyperplasia. Cellular vacuolization of pituitary gland pars distalis was increased in males at $\geq$ 250 ppm and in females at $\geq$ 500 ppm. In both sexes liver centrilobular cytomegaly was increased at 750 ppm.) NOEL Mouse = 250 ppm (Male mouse body weights were somewhat decreased at $\geq$ 1000 ppm and in females at 2000 ppm. Food consumption in mice was somewhat decreased in both sexes at 2000 ppm. Both sexes showed increased thyroid gland diffuse follicular cell hyperplasia and liver hepatocellular cytomegaly at $\geq$ 500 ppm.) **Possible adverse effects in thyroid (including adenomas in rats) and liver of both species and in pituitary of rats.** Unacceptable (No hematology, clinical chemistry, urinalysis or ophthalmology). [redacted] 7/28/98.

Complete Study:

**** 176-083 093142** Stadler, J. "Combined Chronic Toxicity/Oncogenicity Study with Mancozeb Two-Year Feeding Study in Rats" (Du Pont HLR 259-89, 9/13/90). Mancozeb technical (Dithane M-45), lot #: 56831, purity ranging from 83.8% at study start to 79.3% by the end, was fed to rats (72/sex/dose) at 0 (vehicle = diet), 20, 60, 125 and 750 ppm for 24 months. **Possible adverse effects:** At 750 ppm: diarrhea (males), lower body weight gains and enlarged thyroid with follicular cell carcinomas, adenomas and nodular hyperplasias (males and females); lower circulating T4 and elevated T3 and TSH and ocular abnormality (bilateral retinopathy) was noted in 750 ppm-dosed rats. A globular pigment in the kidneys was seen in males and females at 125 and 750 ppm. Nominal NOEL = 60 ppm (abnormal kidney pigmentation and bilateral retinopathy at 125 ppm). **Acceptable.** [redacted] and [redacted] 10/24/91.

** 158 172563 "Mancozeb Technical: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats," (Hooks, W.N., Offer, J.M., Hadley, J.C., Gibson, W.A., Gopinath, C. & Dawe, I.S.; Huntingdon Research Centre Ltd., Cambridgeshire, England; 9/16/92). Mancozeb technical (88.2 & 88.5% pure) was fed in diet to Sprague-Dawley CD rats (50/sex/dose--Main group; 20/sex/dose--Satellite group) at 0, 25, 100 and 400 ppm (mancozeb active ingredient equivalent to 28, 113 and 454 ppm technical at 88%) for 104 weeks (main group) and 52 weeks (satellite group/interim kill). There was a significantly decreased bodyweight gain in both sexes at 454 ppm (primarily during the first 13 - 26 weeks of treatment). Weeks 26 and 52 showed slightly lower than control thyroxine (T4) concentrations in both sexes receiving 454 ppm. Weeks 63 and 78, this trend continued at 454 ppm in females only. Females at 113 ppm also showed marginally lower T4 concentrations at week 78. The terminal kill showed increased masses in the thyroid in males at 454 ppm and testes showed increased unilateral blue and small testes in 6/22 males at 454 ppm. Both sexes showed an increased incidence in height of the follicular epithelium and prominent microfollicles in thyroid at 454 ppm, compared to the control. There was no evidence of oncogenicity

at any dose. Chronic NOEL = 113 ppm (M: 4.0 mg/kg; F: 5.1 mg/kg technical at 88% mancozeb). Acceptable. No adverse effect. [redacted], 2/8/00.

070 087577, Partial preliminary results of a rat chronic feeding study reported to EPA in accordance with FIFRA Section 6 (a) (2). Evaluations of thyroid tissue from a combined rat study have been completed, and a significant increase in follicular cell carcinoma in males, and combined follicular cell carcinoma and adenoma in females was observed at the high dose of 750 ppm. In the same study, a significant increase in bilateral retinopathy was observed in males at 750 ppm, and in females at 750 ppm and 125 ppm. This is a preliminary report only (G. Chernoff, 4/18/90). A final report for this study has been submitted and a worksheet has been completed; see -083 093142 above ([redacted], 11/12/91).

**** 138 169237** "Ethylene Thiourea 104 Week Chronic Toxicity (Feeding) Study in Rats (final report)," (Schmid, H., Tennekes, H., Janiak, T., Probst, D., Luetkemeier, H., Pappritz, G., Marki U., Vogel, O. and Heusner, W.; RCC Ltd. & PATCO AG, Itingen, Switz.; U. Mass. Medical School, Worcester, MA; Enviro-Biotech Inc., Bernville, PA; BRL Ltd., Fullinsdorf, Switz; EPS (UK) Ltd., Hereford, England; RCC Project #: 256803, 12/92). Ethylene Thiourea (ETU; purity = 96.2%) was fed in diet to Ico Ibm: OFA(SPF-Sprague-Dawley) rats (30/sex/dose) at 0, 0.5, 2.5, 5 and 125 ppm for 104 weeks (10/sex/dose sacrificed at 52 weeks). Blood chemistry was affected at 125 ppm: Males: Increase: bilirubin, cholesterol, G-GT, albumin, total protein; Females: Decrease: glucose & urea; Increase: uric acid. Both sexes showed significantly increased levels of T_3 and TSH and significantly decreased levels of T_4 at 125 ppm. At 52 weeks, both sexes showed increased thyroid weights at 125 ppm. At 104 weeks, both sexes showed increased thyroid weights at 125 ppm. In both sexes the thyroid gland showed an increased incidence in treatment-related diffuse or nodular enlargement at 125 ppm. Histopathology showed at 52 weeks: pituitary hypertrophic foci (M), thyroid nodular hyperplasia (M), diffuse hyperplasia (M/F) & follicular adenoma (M), thymic lymphoid atrophy (both sexes) and inflammation/cysts (M) at 125 ppm. At terminal kill, there were neoplastic and non-neoplastic effects in thyroid (congestion, diffuse & nodular follicular hyperplasia--M/F; M/F-benign + malignant follicular tumors M) at 125 ppm and combined effects in auditory sebaceous gland $\geq$ 125 ppm (M/F), lung round cell infiltration (M $\geq$ 5 ppm) and pancreatic effects (M-125 ppm). NOEL = 2.5 ppm; M: 0.17 mg/kg bwt; F: 0.25 mg/kg bwt (based on thyroid effects). This study is acceptable. **Possible adverse effect in thyroid.** [redacted], 11/1/99.

CHRONIC TOXICITY, RAT

005 032695, "Toxicologic Study on the Effect of Adding Dithane M-45 to the Diet of Albino Rats for a Period of Twenty-one Months", (Med. Coll. of Va., 10/14/65). Mancozeb, 86.2%, fed in the diet to 25/sex/group of Wistar rats at 0, 25, 50, 100 or 1000 ppm for 21 months. Report is a series of monthly reports. Decrease in body weight gain of 10% at 1000 ppm. Possible NOEL = 100 ppm. UNACCEPTABLE (no histopathology reported, many lost to autolysis, high mortality in first 5 months apparently not due to test compound, inadequate number of animals at risk.) Insufficient information for assessment [redacted], 4/3/85).

005 958821 Larson, P. "Toxicologic Study on the Effect of Adding Dithane M-22 and M-45 to the Diet of Rats for a Period of Three Months" (Medical College of Virginia, 3/64). Mancozeb technical (Dithane M-45, 88.3% A.I.) was fed to Wistar rats (10 sex/dose) at dietary concentrations of 0, 100, 1000 and 10,000 ppm. Survival of high-dose rats: 7/10 males and 6/10 females (10/10 and 8/10 for male and female controls, respectively). **Possible adverse effects:** depressed weight gain and

food consumption at 10,000 ppm. Heart, liver and kidney weight ratios of females at 10,000 ppm were significantly greater than controls; spleen ratios of males at 1000 ppm and testes ratios of 10,000 ppm rats were significantly increased. Thyroid follicular cell hyperplasia seen at 100 ppm and higher doses. Not a guideline study (no worksheet). [redacted], 2/14/92.

SUBCHRONIC TOXICITY, MONKEY

147 169929 "Effects of Feeding Ethylene Thiourea in the Rhesus Monkey," (Leber, A.P., Wilkinson, G.E., Persing, R.L. and Holzworth, D.A; Batelle Columbus Laboratories, Columbus, OH; 6/30/78; Contract #: 68-01-4171). Ethylene Thiourea (ETU; purity = 96.8%) was fed in diet to Rhesus Monkeys (5/sex/dose) at 0, 50, 150 and 450 ppm for 27 weeks in order to assess effects on the thyroid gland. A propylthiouracil (PTU; thyrotoxic hypothyroid goitrogen) group (5/sex/dose) was treated at 125 ppm for 3 months, then raised to 250 ppm when no suppression of thyroid hormone levels was observed. NOEL < 50 ppm (Mean absolute thyroid weights at $\geq$ 150 ppm ETU in males and all ETU-fed females were significantly greater than respective controls. Males at $\geq$ 150 ppm ETU and females at 450 ppm ETU showed increased serum TSH. Serum T_3 for males at $\geq$ 150 ppm ETU and for females at 450 ppm ETU was decreased. Serum T_4 for both sexes was decreased at $\geq$ 150 ppm ETU during week 20 (rebound effect observed at week 22). I^{125} uptake in thyroid was significantly increased in all treatment groups of both sexes. Both sexes showed increased thyroid/hypertrophy or hyperplasia. All treatment levels in both sexes showed increased thyroid weights. Hyperplasia of the thyroid follicules was increased in both sexes at all doses.) **Possible adverse effect.** These data are supplemental. [redacted], 9/16/99.

CHRONIC TOXICITY, DOG

**** 143 169925** "Three-Month Dietary Toxicity in Dogs (Final Report)," (Cox, R.H., Hazleton Laboratories America, Inc., Vienna VA; Project #: 417-416, 2/26/86). Mancozeb (purity = 83.35%) was fed in diet to Beagle dogs (6/sex/dose) at 0, 10, 1000 and 5000 ppm for 13 weeks. No dogs died on study, however 2 males and 1 female at 5000 ppm were sacrificed *in extremis*, due to a deteriorating physical condition resulting from anorexia. Clinical signs (dehydration, languid, few or no feces, pale) occurred primarily at $\geq$ 1000 ppm in both sexes. Bodyweights and food consumption were significantly decreased in both sexes at 5000 ppm. RBC, HGB and HCT were significantly decreased at $\geq$1000 ppm (females) and 5000 ppm (males). MCV and MCH were significantly increased in both sexes at 5000 ppm. Lymphocytes were decreased in both sexes at 5000 ppm (significant in males only). Macroscopically, effects were observed in thyroid and thymus (both sexes). Microscopically, effects were observed in testes, uterus, ovaries, sternum (marrow), spleen, liver and adrenals, primarily at 5000 ppm. Thyroid and thymus showed histopathological effects at $\geq$ 1000 ppm. Females showed significantly decreased calcium at 5000 ppm. Both sexes showed increased total bilirubin (significant at 5000 ppm, females only) and total cholesterol at $\geq$1000 ppm (females) and 5000 ppm (males). ALT, ALK P (significant in females only), T4 and T3 were significantly decreased in both sexes at 5000 ppm. A marked increase in thyroid weights (absolute, bodyweight and brain weight ratios) occurred at week 13 in both sexes (statistically significant for females) at 5000 ppm. Absolute testes and heart (males) weights were significantly decreased at 5000 ppm. Relative (body) weights for kidneys (5000 ppm, females), liver/gallbladder (both sexes; 5000 ppm males; $\geq$ 1000 ppm females), brain ($\geq$ 1000 ppm females) were increased. Relative (brain) weights for liver/gallbladder were increased in males at 5000 ppm. NOEL = 100 ppm (Based on bodyweight, thyroid effects and hematology. Acceptable. **Possible adverse effect.** [redacted], 8/20/99.

**** 077 095501** "Mancozeb: 52 Week Oral (Dietary Administration) Toxicity Study in the Beagle," (Shaw, D.C., HUK Report #: 5913-616/3, HUK Report issued: 8/90). Mancozeb technical (Dithane M-45, lot #: 74222, purity = 80.6%) was fed to Beagle dogs (4/sex/dose) at 0 (vehicle = diet), 59-62, 237-248, 947-993 or 1893-1985 ppm (w/w--actual, or 0, 50, 200, 800 and 1600 ppm target) for 52 weeks. **Possible adverse effect** (Increased thyroid weight was observed in both sexes--significant in males--accompanied by follicular cell distension and decreased T4 levels, at 1600 ppm). NOEL = 800 ppm (An increased mean cell volume, thyroid weight and liver/brain ratio was observed in males at 1600 ppm. Increased Kupffer cell pigment deposits (liver) were observed in females at 1600 ppm.) ACCEPTABLE. [redacted], 12/28/90.

154 172557 "Mancozeb Technical: Toxicity Study by Oral (Capsule) Administration to Beagle Dogs for 52 Weeks," (Broadmeadow, A.; Life Science Research Ltd., Suffolk, England; LSR Report #: 90/PTC029/0197; LSR Schedule #: PTC/029/MANC; 1/28/91). Mancozeb Technical (purity = 88.1%) was administered in gelatin capsules to Beagle dogs (4/sex/dose) at 0 and 40 mg/kg (actual dosage of a.i. was 35.4 mg/kg in the gelatin capsules, based on analysis) for 52 weeks. NOEL < 40 mg/kg (Bodyweight gain was statistically significantly decreased in females at 40 mg/kg (79% lower) as an average throughout the study. Food consumption was also significantly decreased in females at 40 mg/kg. Two females (at 40 mg/kg) showed thin appearance at different times during the study. One female at 40 mg/kg also had a splenic enlargement. Plasma alkaline phosphatase and phosphorous were high in both sexes at 40 mg/kg. Females showed an associated lowered plasma alanine amino-transferase and aspartate amino-transferase at 40 mg/kg. Cholesterol levels were increased in both sexes at 40 mg/kg. T3 and T4 were decreased in both sexes at 40 mg/kg. The specific gravity of urine in females was decreased at 40 mg/kg. Thyroid weights (absolute, bodyweight and brain weight ratios) were increased in both sexes at 40 mg/kg. There was an increase in pigment in Kupffer cells in females at 40 mg/kg. There was also an increase in periacinar hepatocytes with lipofuscin in males at 40 mg/kg.) No adverse effect. These data are supplemental. [redacted] 1/21/00.

154 172558 "Mancozeb Technical: Toxicity Study by Oral (Capsule) Administration to Beagle Dogs for 52 Weeks," (Broadmeadow, A.; Life Science Research Ltd., Suffolk, England; LSR Report #: 89/PTC004/0015; LSR Schedule #: PTC/004/MANC; 6/25/91). Mancozeb Technical (purity = 88.6%) was administered in gelatin capsules to Beagle dogs (4/sex/dose) at 0, 2.3, 22.6 and 113 mg/kg (actual mancozeb technical = 2, 20 & 100 mg/kg) for 52 weeks. Emesis, yellow/green feces & pallor (associated with torpor & deterioration) occurred at 113 mg/kg. Both sexes were underactive, thin and pale (inappetence & weight loss), with cold pinnae and sclera (females) at 113 mg/kg. One male was killed, due to treatment (113 mg/kg). The condition of the females at 113 mg/kg was poor weeks 24 - 26 before this group was terminated at the request of the sponsor (week 26). Bodyweight gain was decreased at 22.6 mg/kg in females over the 52 week treatment. Food consumption was decreased at 22.6 mg/kg. After 24 weeks, many blood parameters were affected in female #2069 (decreased PCV, Hb, RBC, platelet, leukocyte count, short activated partial thromobplastin time; increased reticulocyte count, MCV, MCHC, MCHb) at 113 mg/kg. The remaining females at 113 mg/kg showed decreased PCV, Hb and RBC. One male (#2132) at 113 mg/kg showed a similar trend (low Hb, RBC & high MCV). Plasma thyroxine in males at 22.6 mg/kg after 50 weeks were decreased significantly. Thyroid weights (absolute, bodyweight and brain weight ratios) were increased in 2 males at 22.6 mg/kg and liver weights were increased in females at 22.6 mg/kg. Pallor of some organs and yellow contents of the GI tract were observed in the male (#2106) killed *in extremis* (attributed to the anemia). A male had large and dark thyroids at 22.6 mg/kg. Autoimmune thyroiditis was observed in 1 male at 22.6 mg/kg (#2104) and 2 females at 2.3 mg/kg (#'s 2089 &

2075). NOEL = 2.3 mg/kg. Possible adverse effect. Not acceptable and not upgradeable (The highest dose exceeds the MTD). [redacted], 1/25/00.

155 172558 "Mancozeb Technical: Toxicity Study by Oral (Capsule) Administration to Beagle Dogs for 52 Weeks," (Broadmeadow, A.; Life Sciences Research Ltd., Suffolk, England; LSR Report #: 89/PTC004/0015; LSR Schedule #: PTC/004/MANC; 6/25/91). Mancozeb Technical (purity = 88.6%) was administered in gelatin capsules to Beagle dogs (4/sex/dose) at 0, 2.3, 22.6 and 113 mg/kg (actual mancozeb technical = 2, 20 & 100 mg/kg) for 52 weeks. NOEL = 2.3 mg/kg (Emesis, yellow/green feces & pallor (associated with torpor & deterioration) occurred at 113 mg/kg. Both sexes were underactive, thin and pale (inappetence & weight loss), with cold pinnae and sclera (females) at 113 mg/kg. One male was killed, due to treatment (113 mg/kg). The condition of the females at 113 mg/kg was poor weeks 24 - 26 before this group was terminated at the request of the sponsor (week 26). Bodyweight gain was decreased at 2.3 mg/kg and 22.6 mg/kg in females over the 52 week treatment. Food consumption was decreased at 22.6 mg/kg. After 24 weeks, many blood parameters were affected in female #2069 (decreased PCV, Hb, RBC, platelet, leukocyte count, short activated partial thromobplastin time; increased reticulocyte count, MCV, MCHC, MCHb) at 113 mg/kg. The remaining females at 113 mg/kg showed decreased PCV, Hb and RBC. One male (#2132) at 113 mg/kg showed a similar trend (low Hb, RBC & high MCV). Plasma thyroxine in males at 22.6 mg/kg after 50 weeks were decreased significantly. Thyroid weights (absolute, bodyweight and brain weight ratios) were increased in 2 males at 22.6 mg/kg and liver weights were increased in females at 22.6 mg/kg. Pallor of some organs and yellow contents of the GI tract were observed in the male (#2106) killed *in extremis* (attributed to the anemia). A male had large and dark thyroids at 22.6 mg/kg. Autoimmune thyroiditis was observed in 1 male at 22.6 mg/kg (#2104).) No adverse effect. Possible adverse effect. Not acceptable and not upgradeable (not enough treatment groups). [redacted], 1/25/00.

005 958826, "Toxicologic Study on the Effect of Adding Dithane M-45 to the Diet of Beagle Dogs for a Period of Two Years", (Med. College of Virginia, 12/1/65). Mancozeb, 86%, fed to 4/sex/group at 0, 25, 100 or 1000 ppm; NOEL $\geq$ 1000 ppm (not established). UNACCEPTABLE (no histopathology, dose selection needs justification since a NOEL was not established, no analysis of diet). No toxicological effects are reported but insufficient information for independent assessment [redacted], 4/3/85).

026 040239 Identical to 958826

**** 142 169923** "ETU 13 Week Oral (Dietary) Toxicity Study in the Beagle Dog," (Briffaux, J.P., Hazleton France (HF), L'Arbresle Cedex, France; 6/6/91; Laboratory Project ID #: 616/504). Ethylene Thiourea (ETU; purity = 98%) was fed in diet to Beagle dogs (4/sex/dose) at 0, 10, 150 and 2000 ppm for 13 weeks. NOEL = 10 ppm; M: 0.39 mg/kg; F: 0.42 mg/kg (High dose dogs showed pale mucous membranes, decreased activity/subdued behavior, blood in feces and bilobed swelling in pharyngeal area. Bodyweights were significantly decreased in males (killed) at 2000 ppm. Food consumption was reduced significantly in both sexes at 2000 ppm. Both sexes showed significantly decreased mean hemoglobin levels at 2000 ppm. A decrease in Hb, PVC and RBC was also observed in the moribund males at 2000 ppm. A marked decrease in blood levels of T_3 and T_4 was observed in both sexes throughout the study at 2000 ppm. A marked increase in absolute and relative thyroid weights and increase in anemia occurred in both sexes. Two males at 2000 ppm were killed moribund on day 51. All surviving animals showed enlarged thyroid glands at 2000 ppm. Hypertrophy of the basophilic cells of the pituitary with microvacuolization and severe follicular hyperplasia of the thyroid

gland occurred in all surviving dogs at 2000 ppm.) See worksheet for a discussion of the NOEL. Acceptable. **Possible adverse effect in thyroid and anemia at 2000 ppm (both sexes).** [redacted], 8/16/99.

**** 137 169236** "ETU 52 Week Oral (Dietary) Toxicity in the Beagle Dog," (Briffaux, J.P., Hazleton France (HF), L'Arbresle Cedex, France; 5/20/92; Laboratory Project ID #: 616/505). Ethylene Thiourea (ETU; purity = 98%, w/w) was fed in diet to Beagle dogs (4/sex/dose) at 0, 5, 50 and 500 ppm for 52 weeks. NOEL = 5 ppm; M: 0.18 mg/kg; F: 19 mg/kg (At 500 ppm, 3 animals died or were killed moribund (deaths attributed to severe anemia). At 500 ppm, all males and 1/4 females showed pale mucous membranes, subdued behavior and a change in feces color. Bodyweights and weight gain were decreased in males at 50 ppm and at 500 ppm. Although these effects were not statistically significant, they appeared to be both dose and treatment-related. A statistically significant decrease in RBCs occurred in both sexes at 500 ppm. Hemoglobin and PCV were decreased, primarily in males at 500 ppm. Platelet counts, bilirubin, globulin and triglycerides were significantly increased in the combined group at 500 ppm. WBC count and albumin/globulin ratio were significantly decreased in males at 500 ppm. ALAT and ASAT were increased (not statistically significant) in males at 500 ppm. A marked decrease in blood levels of T_3 and T_4 was observed in dogs at 500 ppm that died or were terminated prematurely. A dose-related increase in thyroid weights occurred in both sexes at $\geq$ 50 ppm. A male at 500 ppm showed an enlarged thyroid gland. High dose dogs that died on study showed centrolobular hepatocellular necrosis that was associated grossly with pale carcasses. Other changes seen in the liver were minimal or slight pigment accumulation in Kupffer cells at $\geq$ 50 ppm. Thyroid changes showed follicular dilatation (hypertrophy) and colloid retention in both sexes at $\geq$ 50 ppm.) This study is acceptable. **Possible adverse effect in thyroid.** [redacted] 8/24/99.

ONCOGENICITY, MOUSE

Subchronic Study (see COMBINED RAT).

**** 095, 096 124276, 124277, 124251** "Mancozeb: 18-Month Dietary Oncogenicity Study in Mice", (T.E. Shellenberger, Tegeris Laboratories, Inc., TL Project No. 85051, Rohm and Haas Report No. 86RC-029, 6-4-91; Supplementary data: 6-23-93 and 7-7-93). Mancozeb, purity 82.2%-77%, was administered in the feed at nominal concentrations of 0, 30, 100 or 1000 ppm to 94 CD-1 mice/sex/dose for 18 months. Body weights were reduced in high-dose mice an average of 5% in males and 6% in females, compared to controls. **Possible Adverse Effect:** Thyroid function (the level of circulating T4 was reduced 25% to 76% for high-dose mice). NOEL = 100 ppm/day (decreased body weight gains and decreased levels of circulating T4 at 1000 ppm and supportive evidence from NTP study). **ACCEPTABLE;** the dose selection was based on the sub- chronic study (176-084 112072) and is supported by the findings of the NTP study on ethylene thiourea submitted in 096, 124251, 124253 and 095 124276 ([redacted], 10/12/95).

** 157 172562 "Mancozeb: 78 Week Dietary Carcinogenicity Study in Mice with 52 Week Interim Kill," (Everett, D.J., Atkinson, C., Perry, C.J., Strutt, A., Millar, P. and Hudson, P.; Inveresk Research International, Tranent, Scotland; Report #: 7561; 5/14/90). Mancozeb (purity = 88.6%) was fed in diet to CD-1 mice (Study 1: 50/sex/dose, 78 weeks--carcinogenicity & 10/sex/dose, interim kill) at 0, 100, 1000 and 7000 ppm. At week 60, due to excessive toxicity, the 7000 ppm mancozeb group was removed and 0 and 25 ppm mancozeb groups were added (Study 2: 50/sex/dose--carcinogenicity study, 78 weeks & 10/sex/dose, interim kill). Achieved intake was approximately 0, 4, 14 & 144

mg/kg (males) and 0, 5, 17 & 187 mg/kg (females) at 0, 25, 100 and 1000 ppm, respectively, over 78 weeks. Systemic NOEL = 100 ppm; Males: 14 mg/kg/day; Females: 17 mg/kg/day (Both sexes at 1000 ppm showed decreased body weight gain (approximately 15%). The incidence of liver nodules was 4/50 (control), 3/50 (100 ppm) and 10/50 (1000 ppm) in males (not significant). Liver masses were increased in males (5/50 control & 100 ppm; 9/50 1000 ppm) but the increase was not significant. Males at 100 and 1000 ppm mancozeb had a statistically significantly lower incidence in cortical cysts in the kidney (4/50 & 5/50, respectively), compared to controls (15/50). Males showed a slight increase in hepatocellular tumors at 1000 ppm (17/50 versus 10/50 control) which was not significant by Fisher's Exact. Acceptable. No adverse effect. [redacted], 1/27/00.

082 092994 "Mancozeb: 18-Month Dietary Oncogenicity Study in Mice", (T.E. Shellenberger, Tegeris Laboratories, Inc., TL Project No. 85051, Rohm and Haas Report No. 86RC-029, ending June 4, 1991). Mancozeb, purity 82.2%-77%, was administered in the feed at nominal concentrations of 0, 30, 100 or 1000 ppm to 94 CD-1 mice/sex/dose for 18 months. Body weights were reduced in high-dose mice an average of 5% in males and 6% in females, compared to controls. **Possible Adverse Effect:** Thyroid function (the level of circulating T4 was reduced 25% to 76% for high-dose mice). NOEL = 100 ppm/day (decreased body weight gains and decreased levels of circulating T4 at 1000 ppm). Evaluated as **UNACCEPTABLE;** due to dosing errors that occurred in the last 30 weeks of the study (concentrations averaged 61%, 63% and 81% of the targeted 30, 100 and 1000 ppm doses, respectively) and inadequacy of dose levels that were selected after the range-finding study (see -084 112072, below). Sponsor's rebuttal comments in -084 112071 (no worksheet). [redacted] and [redacted] 10/5/92. Upgraded with submission of 095, 096 (See above) [redacted] 10/12/95).

176-084 112072 O'Hara, G. and DiDonato, L. "Dithane M-45 and Ethylenethiourea (ETU) 3 Month Dietary Study in Mice" (Rohm and Haas Company, Report # 80R-124, 2/18/85). Mancozeb technical (Dithane M-45, lot no. 2-8767, 83.1% A.I.) was fed to CD-1 mice (15 sex/dose group) at dietary concentrations of 0, 10, 100, 1000 and 10,000 ppm. Decreased weight gain in males and females at 10,000 ppm; scattered significant decreases in weight gain in males at 1000 ppm. Decreased hepatic mixed function oxidase (MFO) and increased pigment deposits in the adrenal cortex at 10,000 ppm. Thyroid lesions seen at 10,000 ppm were follicular cell hypertrophy and hyperplasia, increased vacuolation, interstitial congestion and decreased colloid density. NOEL (non-thyroid effects) = 1000 ppm (Males = 167 mg/kg/day; Females = 234 mg/kg/day). NOEL (thyroid effects) = 100 ppm (Males = 18 mg/kg/day; Females = 22 mg/kg/day; slightly increased incidence of thyroid follicular cell hypertrophy/hyperplasia at 1000 ppm). Although slight increases over control levels of thyroid follicular cell hypertrophy and scattered decreases in male weight gain were seen at 1000 ppm, the study did not demonstrate that 1000 ppm constituted an MTD for the 18-month dietary oncogenicity study (-082 092994). Purified ethylenethiourea (ETU, recrystallized, Matheson, Coleman and Bell, catalog #IX0010) was administered to male and female CD-1 mice (15/sex/group) for 3 months at levels of 1, 10, 100 and 1000 ppm. Increased thyroid weight was seen at 1000 ppm and thyroid follicular cell hyperplasia, hypertrophy, vacuolation, and decreased colloid density was reported at 100 and 1000 ppm. Livers showed increased weight, centrilobular hypertrophy, nuclear pleomorphism and intranuclear inclusions. Deposits of brownish pigments in the zona reticularis of the adrenal cortex were seen at 1,000 ppm. NOEL = 10 ppm ETU (1.7 mg/kg/day in males and 2.4 mg/kg/day in females). [redacted], 2/12/92.

REPRODUCTION, RAT

**** 071, 074 087576, 091357**, "Mancozeb: Two-Generation Reproduction Study in Rats", (Rohm and Haas Toxicology Department, Report No. 87R-020, 3-17-88). Mancozeb (Dithane M-45), Lot D56530, 84.0%, was administered in the diet to groups of 25 male and 25 female CRL:CDBR rats from 10 weeks pre-mating through 2 generations, 2 litters per generation, at dose levels of 0 (vehicle control), 30, 120 or 1200 ppm. At 1200 ppm, both sexes of the P-1 and P-2 generations had depressed body weights, increased liver, kidney and thyroid relative weights, and microscopic changes in the thyroid, kidney and pituitary. The thyroids of both sexes had diffuse hyperplasia of follicular cells, nodular/cystic follicular cell hyperplasia and follicular cell adenoma. Males at 1200 ppm had hypertrophy and/or vacuolation of cells in the adenohypophysis of the pituitary. Kidneys of both sexes at 120 and 1200 ppm had brown globular pigment within the lumen of the proximal tubules without associated changes in the tubular epithelium. Parental NOEL = 30 ppm (2.0 mg/kg/day), brown globular pigment within the lumen of the proximal tubules in the kidney; initial review found the reproductive NOEL could not be determined because data on male fertility is missing. **Possible Parental (Not Reproductive) ADVERSE EFFECTS** (thyroid, kidney, and pituitary histopathology) are indicated. Previously reviewed as unacceptable (Chernoff, 4/17/90: require methods for randomization at culling and methods for selection of the P-2 generation, mating histories and male fertility data). Upon submission of the required information, the study has been upgraded to ACCEPTABLE**.** Reproductive NOEL = 1200 ppm. [redacted], 1/2/91.

** 161 172566 "Final Report: Penncozeb Technical: Two-Generation Oral (Dietary Administration) Reproduction Toxicity Study in the Rat (One Litter Per Generation)," (Muller W.; Hazleton Deutschland GmbH, Munster, Germany; HD Report #: 852-683-001; HD Project #: 683-001; 6/19/92). Penncozeb (mancozeb technical; purity = 88.4%) was fed in diet to Sprague-Dawley Crl:CD (SD)BR rats (25/sex/dose) at 0, 25, 150 and 1100 ppm for 2 generations (P & F1, 1 litter/ generation). Systemic NOEL = 25 ppm (P and F1 generation males showed decreased bodyweight gain at ≥ 150 ppm. P female bodyweight gains were decreased during mating (1100 ppm) and gestation (≥ 150 ppm). The F1 females had significantly decreased bodyweight gain from premating through lactation at 1100 ppm. P males at 1100 ppm and F1 males at ≥ 150 ppm had a decreased food consumption during mating. P females at 1100 ppm had decreased food consumption during mating and F1 females at ≥ 150 ppm had decreased food consumption during mating, gestation and lactation. Mean thyroid weights were significantly increased in both sexes of P and F1 parental generations at 1100 ppm. In both sexes of P and F1 adults, there were increases in follicular hypertrophy, hyperplasia and follicular adenoma at 1100 ppm. Thyroid cysts lined by stratified squamous epithelium were associated with stimulation of the thyroid gland at 1100 ppm.) Reproductive NOEL > 1100 ppm (There were no reproductive effects at any dose.) Pup NOEL = 25 ppm (Post partum day 4, F1 litter sizes were slightly decreased at 1100 ppm (7.4 pups at 1100 ppm, versus 9.1 pups in control). A treatment-related weight decrease in pups at 1100 (day 21, F1 pups) was observed at 21 days post-partum was observed. At 1100 ppm, delayed eye opening was observed in pups at 1100 ppm (F1 & F2 pups). It is stated in the report that the F1 decrease in viability from day 14 to 21 of lactation was treatment-related. There was a decreased mean F2 pup weight from days 14 to 21 at 1100 and on day 21 at 150 ppm. No adverse effect. Acceptable. [redacted], 2/4/00.

005 031126, "Three Generation Reproduction Study on Rats Receiving Dithane M-45 in Their Diet", (Medical College of Virginia, 11/12/65). Mancozeb, no purity stated; fed to groups of 20/sex at 0, 25, 100 or 1000 ppm a.i.; F0 animals were part of a chronic study and returned to that study when finished breeding; fed on diet for 11 weeks, then mated 1:1, 2 litters, 3 generations; UNACCEPTABLE

(no description of test article or analysis of diet, histopathology on 10/sex in the F3b litters and gross necropsy only for F0 and F1 parents, decreased fertility in all groups in F3a and F3b matings suggestive of a husbandry problem, no individual data.) Apparent reproductive NOEL = 100 ppm (decreased fertility). [redacted], 4/4/85.

Summary: The initial study (031126) had no adverse effect indicated, where study 087576 showed a possible adverse effect (not reproductive). The more recent study (087576--acceptable and performed according to FIFRA Guidelines) had a high dose, where thyroid effects were evident, which was higher than that used in study 087576. This may be one reason why effects were detected. On the other hand, thyroid effects were also observed in preliminary rat combined (070 087577) and chronic dog (077 095501) studies. Therefore, the adverse effect for mancozeb in thyroid will remain for study 087575, even though the effect is not a reproductive effect.

** 144 & 150 169926 & 169932 "Ethylene thiourea: Two-Generation Reproduction Study in the Rat," (Dotti, A., Kinder, J. & Wright, J.; RCC AG, Itingen, Switzerland; RCC (UK); Enviro-Biotech Inc., Bernville, PA; RCC Report #: 252360; 1/15/92). Ethylene thiourea (purity = 98%) was fed in diet to IcoIbm:OFA (SPF) Sprague-Dawley rats (25/sex/dose) at 0, 2.5, 25 and 125 ppm for 2 generations (P & F1, 1 litter/ generation). Systemic NOEL = 2.5 ppm (Body weight and bodyweight gain was decreased in males at 125 ppm (P generation. Both parental generations showed increased anterior pituitary cell hypertrophy, thyroid follicular cell hypertrophy and hyperplasia at $\geq$ 25 ppm. F1 generation both sexes showed increased kidney mononuclear infiltration and reduced colloid at $\geq$ 25 ppm.) Reproductive NOEL > 125 ppm (There were no reproductive effects at any dose.) No adverse effect. Acceptable. [redacted], 9/28/99.

156 172561 An exact duplicate of volumes 144 & 150 169926 & 169932

TERATOLOGY, RAT

015 958829, "Teratologic Evaluation of Dithane M-45 in the Albino Rat", (Booz, Allen and Hamilton, Florham Park NJ, 5/29/80). Mancozeb, 83%, lot 4268 (no information on the contaminant/metabolite ethylenethiourea (ETU) content in mancozeb technical, if any); given by oral gavage to 26 females/group on days 6-15 of gestation at 0, 2, 8, 32, 128 or 512 mg/kg/day. Positive control = ETU (50 mg/kg/day). Maternal NOEL = 32 mg/kg/day (decreased food consumption and body weight gain at 128 and 512 mg/kg/day; gravid uterine weight was decreased). Developmental NOEL = 128 mg/kg (increased resorptions and fetal teratogenic effects were observed at 512 mg/kg/day). ETU functioned as a teratogen and fetal findings at 512 mg/kg/day of mancozeb resembled those in the ETU positive controls in type and incidence. No adverse effect was observed, since the developmental NOEL was greater than the maternal NOEL. Although a possible adverse effect was noted previously, after re-review and consideration of Hazard Evaluation Division Standard Evaluation Procedure: Teratology Studies (EPA Office of Pesticide Programs, June, 1985) it was decided there were no adverse effects for mancozeb. The study was initially reviewed as unacceptable [redacted] 4/3/85 and [redacted] 12/1/86; lack of information regarding dosing material preparation, analysis and incomplete dose calculation and mixing records). Upon receipt and evaluation of the requested information (Record #065388), the study is now ACCEPTABLE.** D. Shimer, 4/18/88; [redacted]. [redacted], 6/14/88.

** 160 172565 "Mancozeb:Teratology Study in the Rat." (Tesh, J.M., McAnulty, P.A., Willoughby, C.R., Enticott, J., Wilby, O.K., Tesh, S.A.; Life Science Research, Suffolk, England; LSR Report #:

87/0365; 3/2/88). Mancozeb (purity = 88.6%) was given by gavage to mated CD (Sprague-Dawley) rats (25/dose) at 0 (1% aqueous methylcellulose mucilage), 10, 60 and 360 mg/kg from days 6 to 15 of gestation (gd 0 = sperm positive vaginal smear or 3+ copulation plugs). **Maternal NOEL =** 60 mg/kg (One female at 360 mg/kg showed piloerection from gd 12 with slight hindlimb paralysis from gd 13. Other signs included hunched posture, pallor, staining on the coat and around the eyes, frequent urination and thin build (killed in extremis on gd 16). Four females at 360 mg/kg had a reeling gait and 3 of these females had slight paralysis of the hindlimb after the last dose. Bodyweight gain of dams at 360 mg/kg was significantly decreased during treatment. Food consumption was significantly decreased at 360 mg/kg, during treatment. **FETAL NOEL** = 60 mg/kg (Skeletal examinations showed a dose-related decrease in degree of ossification of the interparietal bone (significant at 360 mg/kg) and an increase in incidence of "large" anterior fontanelle at 360 mg/kg. There was a statistically significant decrease in degree in ossification of the thoracic vertebral centra at 360 mg/kg.) No adverse effects. ACCEPTABLE. [redacted], 1/28/00.

Guidance for the Reregistration of Pesticide Products Containing Mancozeb (EPA, Office of Pesticide Programs, April, 1987): Maternal NOEL = 32 mg/kg/day (decreased body weight). The NOEL for fetal toxicity = 128 mg/kg/day (increased resorptions). Developmental NOEL = 128 mg/kg/day (dilated ventricles, spinal cord hemorrhage, delayed/incomplete ossification of skull and ribs).

028 040254, Identical to 958829

035 050831, Supplement to 958829, containing statements by Dr. P.K. Chan (attachment to letter by David R. Streelman, 12/1/86) regarding dosing levels, statistical methods and additional records.

036 050832, Supplement to 958829; Volume II, individual body weights, clinical observations, randomization records, dosage calculations and mixing record (JAP 5/7/87).

037 050833, Supplement to 958829; Volume III, Caesarean section sheets with individual fetal gross examination and weight data (JAP 5/7/87).

038 050834, Supplement to 958829; Vol. IV, Individual fetal visceral and skeletal data (JAP 5/7/87).

054 065388, Supplement to 958829, containing rebuttal information regarding dosing material preparation, analysis, calculation and mixing records [redacted], 6/16/88).

** 034 050252, "Teratogenic Evaluation of Mancozeb in the Rat Following Inhalation Exposure", (In: Toxicology and Applied Pharmacology, 84:335-368, 1986). Mated Crl:CD rats (37-38/group in study 1 and 27/group in study 2) were exposed to mancozeb (80%) at 0, 1, 17, 55, 110, 890 or 1890/500 mg/m^3 for 6 hours/day, days 6-15 of gestation (presence of sperm = day 1 of gestation). Maternal NOEL = 17 mg/m^3 (decreased weight gain, hindlimb weakness, general debilitation; maternal toxicity observed at 55-1890 mg/m^3). Developmental NOEL = 17 mg/m^3 (increase in resorbed litters, external hemorrhage and wavy ribs; no embryotoxicity in absence of maternal toxicity). No adverse effect. The study was initially reviewed by [redacted] (12/1/86) as unacceptable due to lack of individual data. Record# 058531, subsequently received at CDFA provided individual litter data including number of resorptions per dam, weight and sex of fetuses and external, visceral and skeletal exam results. Upon evaluation of these data the study has been upgraded to ACCEPTABLE (D. Shimer, 4-12-88; [redacted], 6/14/88).

045 058531, Supplemental to 050252 containing individual litter data, including number of resorptions/dam, weight and sex of fetuses and external, visceral and skeletal exam results [redacted] 6/16/88).

TERATOLOGY, RABBIT

049 064267, "Range-Finding (Gavage) Developmental Toxicity Study in Rabbits", (Rohm and Haas, 3-9-87). Mancozeb (lot D56530; purity = 83.0%) was given to inseminated New Zealand White rabbits by gavage on days 7-19 of gestation (day of insemination = day 0 of gestation) at 0 (vehicle = 0.5% methylcellulose), 50, 100, 200, 400 or 1000 mg/kg (8/group). Dosing solutions were analyzed (there was good correlation with the target concentrations) and were prepared daily. Dams were weighed days 0, 7-11, 14, 17, 20 and 29. Clinical signs were taken daily (days 7-19 twice daily). Morbidity and mortality checks were performed days 0-6 and days 20-28. Live fetuses were weighed but had only external exams. Maternal NOEL = 50 mg/kg (deaths were 3, 6, 4, 6 at 100, 200, 400, 1000 mg/kg, respectively; increased clinical signs included anorexia, blood beneath cage, soft and scant feces; abortions were 3, 4, 3 at 200, 400, 1000 mg/kg, respectively). Developmental NOEL = 100 mg/kg, (no fetuses survived at 200 mg/kg or higher; no increase in incidence of developmental variations at 50 or 100 mg/kg). No adverse effects observed in this supplemental range-finding study (Shimer, 4-18-88; [redacted], 6/14/88).

**049 064268, "Mancozeb: Oral (Gavage) Developmental Toxicity Study in Rabbits", (Rohm and Haas, Report No. 86R-021, 3-31-87). Mancozeb (Lot D56530; purity = 83%) was given to inseminated New Zealand White rabbits by gavage on days 7-19 of gestation (day of insemination = day 1 of gestation) at 0 (vehicle = 0.5% methylcellulose), 10, 30 or 80 mg/kg (20/group). Maternal NOEL = 30 mg/kg (2 deaths and 5 abortions were observed at 80 mg/kg; does with abortions exhibited decreased body weight gains and decreased food consumption; at 80 mg/kg clinical signs such as alopecia, anorexia, scant or no feces, ataxia, anuria and red discharge on the cage liner were observed). Developmental NOEL > 80 mg/kg (no treatment-related fetal effects at any dose). No adverse effects. ACCEPTABLE ([redacted], 6-14-88).

** 159 172564 "Penncozeb Technical Oral (Gavage) Teratogenicity Study in the Rabbit," (Muller, W.; Hazleton Laboratories Deutschland GmbH, Munster, Germany; HLD report #: 853-683-002; HLD Project #: 683-002; 4/15/91). Penncozeb (mancozeb technical; 88.4% pure) was administered by gavage to mated New Zealand white rabbits (18/dose) at 0 (1% methylcellulose), 5, 30, 55 mg/kg for days 6 - 18 post-coitum. After results of groups 1 - 4 were evaluated, a second high dose group (100 mg/kg) and concurrent control were added. **Maternal NOEL =** 55 mg/kg (Mean bodyweight change during treatment was significantly decreased at 100 mg/kg. Mean daily food consumption was markedly decreased at 100 mg/kg throughout the treatment period on each single day. Abortions occurred at 100 mg/kg.) **FETAL NOEL =** 100 mg/kg (There were no significant effects at any dose.) Acceptable. [redacted], 2/1/00.

028 040255, "Somers Test on Dithane M-45", (Brown Biol. Labs, Thornhill, Ontario, 8/8/68). Mancozeb 80% (20% "inerts"), given by oral gavage to 10 New Zealand White rabbits per group at 0, 25, 250 or 400 mg/kg/day, day 7 through 16 of gestation; 6-mercaptopurine as positive control to 5 rabbits; at 400 mg/kg, weight loss and diarrhea were seen - no other information; 1/2 for visceral and 1/2 for skeletal; no clinical observations are reported; NOEL = 250 mg/kg; UNACCEPTABLE (no MTD was used, insufficient number of animals and too few fetuses for visceral and skeletal exams.) No teratogenic effect reported at the doses used ([redacted] 3/10/86).

GENE MUTATION

003 031862, "Microbial Mutagenicity Test of Mancozeb", (Inst. of Environmental Toxicology, Japan for Rohm & Haas, 5/24/79). Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 tested with mancozeb, 85.0%, at 0, 0.05, 0.1, 0.5, 1, 5, 10, 50, 100 or 500 ug/plate with and without rat liver activation, duplicate plates, single trial, with cytotoxicity at higher concentrations; initially reviewed as acceptable but since only one trial was run, the study does not meet guidelines. The data gap, however, is considered filled by the collective microbial studies and by the mammalian study. No increase in reversion rate is reported ([redacted], 4/3/85 and [redacted] 12/1/86).

027 040244, "Microbial Mutagen (Ames) Test with Dithane M-45 Fungicide (S-9 Prepared from Aroclor 1254 Induced Fischer 344 Rats)", (Rohm and Haas, 6/21/84). Salmonella tested with mancozeb, 88%, Lot 0842, strains TA1535, TA1537, TA98 and TA100, at 0, 2.5, 7.5, 25, 75 or 250 ug/plate (inhibition of growth at 75 and 250 ug/plate) with and without rat liver activation, triplicate plates, one trial. UNACCEPTABLE (no individual plate counts, single trial.) No increase in reversion rate is reported ([redacted] 3/7/86).

027 040245, "Microbial Mutagen (Ames) Test with Dithane M-45 Fungicide (S-9 Prepared from Aroclor 1254 Induced B6C3F1 Mice)", (Rohm & Haas, 6/21/84). Mancozeb, 88%, Lot 0842, tested with Salmonella strains TA1535, TA1537, TA98 and TA100 with and without mouse liver activation at 0, 2.5, 7.5, 25, 75 or 250 ug/plate; inhibition of growth at 75 and 250 ug/plate; no increase in reversion rate. UNACCEPTABLE (single trial, no individual plate counts). [redacted], 3/7/86.

027 040246-040247, "Host-Mediated Assay in Mice with Dithane M-45 Fungicide. Protocol 83P-083 and Protocol 85P-167", (Hazleton, 3/7/84-85). Host-mediated assay in mice with Salmonella. Mancozeb, 88%, 0842 and 83-224; given by oral gavage at 0, 0.5, 2.0 or 5.0 mg/kg (040246) or 200, 2000 or 5000 mg/kg (040247) to 10 male mice per group; i.p. injection of TA1530 with harvesting after 4 hours. No increase in mutation frequency is reported. DMN as positive control. UNACCEPTABLE (no evidence of metabolism or body distribution is presented to indicate exposure of the Salmonella.) [redacted], 3/7/86.

Summary: Although no one report is acceptable in itself, the reports 31862, 40245 and 40244 are, in essence, repeat trials and, taken together, provide sufficient data on mutagenicity in Salmonella to allow evaluation of the genotoxicity of mancozeb. All studies were negative for mutagenicity.

**027 040248, "Gene Mutation Assay in CHO cells with Dithane M-45 Fungicide", (Rohm & Haas, 2/11/85). CHO cells; mancozeb, 88%, lot 0842, tested in CHO-K1-BH4 cells with and without rat liver activation; tested at 0 to 45 ug/ml with activation, 5 hours, and 0 to 15 ug/ml without activation, for 20 hours; 5 plates per group for mutation, 2 replicates per group, replicate trials; no consistent evidence for increase in mutation frequency. ACCEPTABLE ([redacted] 3/7/86).

CHROMOSOME MUTATION

027 040250, "Dithane M-45 In Vivo Cytogenetic Study in Fischer 344 Rats", (12/21/1984, Rohm & Haas, 12/21/84). In Vivo cytogenetics in rats given mancozeb, 88%, Lot 0842, by oral gavage at 0.44, 1.76 or 4.4 g/kg as a single dose or for 5 consecutive days; 10 males/group; after the single dose, animals were sacrificed at 6, 24 or 48 hours and at 6 hours only after the 5 day dosing; TEM as positive control; 4 slides per animal were prepared but only those from the high dose were scored, 50

metaphases per animal; no increase in chromosomal aberrations is reported; lethargy was noted in 12/30 of the high dose group given the single dose. UNACCEPTABLE (use of only males should be justified). [redacted] 3/7/86.

027 040251, "Mutagenicity Evaluation of Dithane M-45 Fungicide Lot. No. 0842 (TD 83-224) in an In Vitro Sister Chromatid Exchange Assay in CHO Cells", (Litton Bionetics, 3/25/85). Mancozeb, 88%, Lot No. 0842, tested with CHO at 0 to 17.5 ug/ml with and without rat and mouse liver activation, 2 hours followed by approximately 26 hours of growth; scored 50 cells per concentration; increase in SCE's in two trials without activation. An increase was seen in one trial with mouse liver activation but was not repeatable. ACCEPTABLE [redacted], 3/7/86).

DNA DAMAGE

003 031862 (formerly 958832), "Microbial Mutagenicity Test of Mancozeb", (Inst. of Environmental Toxicology, Japan, for Rohm and Haas, 5/24/79). Bacillus subtilis strains H17 and M45, exposed to mancozeb, 85.5% purity, at 0, 0.1, 0.5, 1, 2, 5, 10, 25 or 50 ug/disk without activation only, one plate per concentration; UNACCEPTABLE (no activation, single plate); inhibition of growth at the two highest concentrations but no differential inhibition ([redacted], 4/3/85).

**027 040252, "Dithane M-45 Mammalian Cell Transformation Test. Protocol No. 83P-056", (Rohm & Haas, 11/19/84). Mancozeb, 88%, lot 0842, tested with C3H 10T1/2 cells at 0, 0.05, 0.15, 0.25, 0.4 or 0.5 ug/ml, 24 hours; 20 plates per concentration; no activation, DMBA as positive control. No Type III foci were observed in any treated plate. ACCEPTABLE ([redacted], 3/10/86).

027 040253, "Dithane M-45 Mammalian Cell Transformation Test for Promotion. Protocol No. 83P-057", (Rohm & Haas, 5/29/85). Transformation test with C3H 10T1/2 cells; mancozeb (Dithane), 88%, Lot No. 0842, with MNNG to initiate for 4 hours followed by mancozeb for 5 weeks to promote; tested with mancozeb at 0, 0.001, 0.033, 0.066, 0.1, 0.25 or 0.5 ug/ml, 20 plates per concentration; TPA as positive control for promotion; no evidence is presented that mancozeb acts as a promoter. UNACCEPTABLE as an 844 test - see 40252 above for an acceptable study [redacted] 3/10/86).

027 040249, "Dithane M-45 In Vitro Unscheduled DNA Synthesis Assay. Protocol No. 83-055. Report No. 84R-280", (Rohm and Haas, 5/29/85). Mancozeb, 88%, lot no. 0842, tested at 0, 0.25, 0.5, 1.0, 2.5, 5.0 and 10.0 ug/ml; 18 - 20 hours of incubation; autoradiography to score. UNACCEPTABLE but possibly upgradeable (data in graphic form, cytotoxicity at most concentrations, increase in net grain counts attributed to decrease in cytoplasmic counts due to toxicity - another test should be performed to verify this). [redacted], 3/7/85.

Related Studies (DNA damage)

027 04022, "Ethylenethiourea Mammalian Cell Transformation Test. Protocol No. 83P-058", (Rohm & Haas, 11/19/84). Test article ETU Transformation test. Ethylenethiourea, 99.8%, lot DB8-36, tested with C3H 10T1/2, clone 8, at 0, 100, 330 or 1000 ug/ml, 24 hours with no activation included; 20 plates per concentration except for 1000 where 80 plates were made; scored for types I, II and III foci; no cytotoxicity at 1000 ug/ml, no type III foci in any treated plate; DMBA as positive control; test run on ethylthiourea, a degradation product of mancozeb ([redacted], 3/6/86).

027 040243, "Ethylenethiourea Mammalian Cell Transformation Test for Promotion", (Rohm & Haas, 5/29/85). Cell transformation with C3H 10T1/2 cells tested with ethylenethiourea, 99.8%, with MNNG to initiate for 4 hours followed by ethylenethiourea at 333 ug/ml for 5 weeks to promote; TPA as positive control for promotion; 20 plates per group; scored for Type I, II and III foci; no evidence for promotion. Supplementary information on a degradation product of mancozeb ([redacted], 3/6/86).

NEUROTOXICITY

**** 148 169930** "Neurotoxicity Study in Rats With Mancozeb," (Stadler, J.C.; E.I. du Pont de Nemours & Company; Haskell Lab for Toxicology & Industrial Medicine; Medical Research Project #: 8486-001; Haskell Lab Report ID#: 217-89; 4/19/91). Mancozeb (purity = 72.7%) was fed in diet to Crl:CD®BR rats (10/sex/dose) at 0, 20, 125 or 750 ppm for 90 days. Another group of 10 female rats was also fed diet containing 5000 ppm for 14 days, but due to mortality, the surviving rats were then fed diets that contained 0 ppm mancozeb for the remainder of the study. Subsequently, 2 groups of females (16/group) were fed 5000 ppm mancozeb for 14 days to duplicate effects observed in the initial feeding study. NOEL = 125 ppm (Mean body weights of males at 5000 ppm were significantly decreased (44.7%) throughout the test. Females at 5000 ppm for the first 2 weeks of the 90-day treatment showed decreased mean body weight (days 7 & 14). Food consumption was decreased in both sexes at 5000 ppm. All rats at 5000 ppm showed clinical signs. Males showed an abnormal gait or mobility with limited or no use of the rear legs and a reluctance to walk. There was also a noticable lack of muscle in the rear legs. Females at 5000 ppm also showed hind limb effects. In weeks 2-4 1/10 males and 4/10 females at 5000 ppm died. Males at 5000 ppm fed for 90 days showed increased intrasheath ellipsoids, myelin phagocytosis, Schwann cell proliferation, demyelinated nerves, myelin sheath thickening, myelin bubbles and neurofibrillary degeneration in nerve tissues. In addition, there was singificant atrophy of the posterior thigh muscles. Demyelinated fibers and myelin ovoids or debris were observed in teased nerve fibers taken from rats in this group. In tissues from males at 750 ppm there were incidences of myelin bubbles, myelin phagocytosis and Schwann cell proliferation; and in the teased nerve fibers, there were demyelinated lengths and myelin ovoids and/or myelin debris. Females at 5000 ppm fed for 2 weeks at the beginning of the 90 day treatment showed myelin bubbles, myelin sheath thickening, myelin phagocytosis and Schwann cell proliferation. Posterior thigh muscle atrophy was observed in 9/10 of these females at 5000 ppm. Teased muscle fibers had demyelinated lengths and myelin ovoids or debris. When the effects in the 2 groups of females at 5000 ppm were compared, only 2 differences were observed. Rats allowed to recover for 11 weeks had a low incidence of muscle atrophy and low incidence of myelin ovoids or debris. However, microscopic lesions in the 2 groups were similar, and these effects were considered to be irreversible. Females at 750 ppm showed teased nerves with demyelinated lengths and myelin ovoids/debris.) **Possible adverse effect.** Acceptable. Possible adverse effect. [redacted], 10/5/99.

SUPPLEMENTAL

** 149 169931 "Mancozeb: 4-Week Repeat Dermal Toxicity Study in Rats," (Trutter, J.A.; Hazleton Laboratories, America, Inc., Vienna, VA; HLA Study #: 417-432; R & H Report #: 88RC-0007; 4/6/88). Mancozeb (purity = 82.4%) was administered dermally to Crl: CD®(SD)BR rats (10/sex/dose) at 0, 10, 100 and 1000 mg/kg for 4 weeks (6 hour/day exposure; 20-21 treatments). The treatment site was occluded (covered with a porous bandage). Rats were inhibited from grooming the application site by a cardboard collar. NOEL > 1000 mg/kg (There were no significant treatment-related effects at any dose). The limit test was performed, therefore the study is acceptable in the absence of toxic

effects. No adverse effects. [redacted], 9/21/99.

** 151 & 152 169933 & 169934 "Mancozeb Pharmacokinetic Study in Rats," (DiDonato, L.J., Longacre, S.L.; Report #: 85R-123 for vol. 152; Nelson, S.S.; Laboratory Project ID: 31C-87-24 for vol. 151; Rohm & Haas Company, Spring House, PA; 5/21-22/86). The pharmacokinetics of 14C-mancozeb (11.54 mCi/g = 25,619 dpm/ug; suspended in 0.5% methylcellulose in distilled water) were studied in Sprague-Dawley CD rats (both sexes) treated with a single oral dose of 1.5 (Group A) or 100 mg/kg (Group B) or a pulse (oral) dose of 1.5 mg/kg 14C-mancozeb (Group C) which followed 2 weeks of dietary administration of nonradiolabelled mancozeb (84% pure; 15 ppm a.i.). Rats were terminated 96 hours after 14C-mancozeb treatment. Bile cannulation occurred in both sexes of rat treated at 1.5 (Group D) and 100 mg/kg (Group E) for assessment of excretion in bile at 24 hours. Approximately half of the oral dose of mancozeb was absorbed in rats. Results showed non-linear kinetics occurred between 100 and 1.5 mg/kg. Absorption was moderately rapid (peak levels in 3 & 6 hours at 1.5 & 100 mg/kg, respectively). Elimination was biphasic. Most of the oral dose was eliminated in excreta within 24 hours--evenly divided between feces and urine. Small amounts were excreted in the bile (2-9%). Thyroid contained the greatest concentrations and peak concentrations in thyroid were not proportional to dose. Thyroid 14C-concentrations were disproportionately less than the respective peak blood levels after 100 mg/kg than after 1.5 mg/kg 14C-mancozeb indicating saturation at the high dose. Pretreatment with dietary nonradiolabelled mancozeb did not significantly affect the disposition or excretion of 14C-mancozeb. The in vivo conversion of mancozeb to ETU was determined to be 6.8% (record #: 169933, volume 151). Acceptable, [redacted], 10/12/99.

096 124253, NTP Technical Report on the Perinatal Toxicology and Carcinogenesis Studies of Ethylene Thiourea in F344/N Rats and B6C3F_1 ice. Supplemental.