SUMMARY OF TOXICOLOGY DATA

ZIRAM

Chemical Code # 000629, Tolerance # 00116  
SB 950 # 124

August 4, 1986
Revised 4/16/87, 8/10/88, 4/17/91, 1/31/96 and 5/22/96

I. DATA GAP STATUS

Combined rat: No data gap, possible adverse effect
Chronic dog: No data gap, possible adverse effect
Onco mouse: No data gap, possible adverse effect (non-oncogenic)
Repro rat: No data gap, no adverse effect
Terato rat: No data gap, no adverse effect
Terato rabbit: No data gap, no adverse effect
Gene mutation: No data gap, possible adverse effect
Chromosome: No data gap, no adverse effect
DNA damage: No data gap, no adverse effect
Neurotox: Not required at this time

All record numbers through volume 105, record 145950 were examined.
** indicates an acceptable study.
**Bold face** indicates a possible adverse effect.

File name: T960522
Revised by: M. Silva, 8/88; J. Kishiyama & M. Silva 4/17/91; M. Silva, 1/31/96 & 5/22/96.
II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

Subchronic Study:

081  117647,  "Ziram (Technical) Preliminary Toxicity to Rats by Dietary Administration for 13 Weeks",  (L.A.J. Powell, D. Crook, R. Gregson, C. Gopinath, W.A. Gibson & A. Anderson, Huntingdon Research Centre Ltd., Study Report ZIR 5/901840, 8/19/92).  Ziram (purity = 98.7%) was fed in diet to Crl:CD(SD)BR rats (10/sex/dose) at 0, 100, 300 or 1000 ppm for 13 weeks. NOEL = 100 ppm (Body weights and food consumption were decreased at ≥ 300 ppm. Brain, spleen, testes and ovarian weights were increased at ≥ 300 ppm. Adrenal, pituitary and heart weights were decreased at ≥ 300 ppm. Histopathologically, there was an increase in hyperplasia of stomach non-glandular epithelium in both sexes (males at 1000 ppm & females at ≥ 300 ppm).) Based on test results, the following doses were suggested for a 2 year combined toxicity study: 540, 180 and 60 ppm. These data are supplemental. No adverse effect indicated. (Kishiyama & Silva, 1/8/96).

Combined Study:

** 084 132753,  "Combined Chronic Toxicity and Oncogenicity of Ziram (Technical) administered in the Diet to Rats",  (L.A.J. Powell, S.M. Bottomley, D. Crook, R.L. Gregson, J.M. Offer, W.A. Gibson & A. Anderson, Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, UK; Report # ZIR 9/942098, 27 September 1994).  Ziram technical (98.7% pure) was fed in diet to Crl:CD(SD)BR rats (70/sex/dose) at 0, 60, 180, and 540 ppm for 104 weeks (20 per sex per group were sacrificed after 52 weeks of treatment). Oncogenicity NOEL = 180 ppm (Hemangiomata in mesenteric lymph nodes and spleens were observed at 540 ppm in males). Chronic NOEL < 60 ppm (Pancreas showed replacement by adipose (males only), hemosiderosis was increased in spleen,
thyroids showed prominent ultimobranchial cysts and C-cell hyperplasia (males only) were observed in both sexes at all doses. Adrenal cortical hypertrophy/degeneration/vacuolation increased in males at all doses. Females showed adrenal cortical cystic degeneration at all doses. Decreased body weights (and gain) at $\geq 180$ ppm. Food consumption was also decreased in males at 540 ppm and at $\geq 180$ ppm. Both sexes showed hematology and serum biochemistry effects at $\geq 180$ ppm. Urinary pH increased and volume was decreased in both sexes at 540 ppm. Liver, thyroid and testes/epididymus weights were increased at 540 ppm. Pituitary, kidney and ovarian weights were decreased at 540 ppm. There was an increase in sciatic nerve axonal degeneration and lipofuscin in tubular kidney epithelium in both sexes at 540 ppm. Increased adipose replacement and narrowing of peripheral muscle fiber bundles occurred in skeletal muscle; nonglandular stomach showed increased hyperplasia, subepithelial edema and ulceration and bile duct hyperplasia and pigmented sinusoidal cell incidence increased in both sexes at $\geq 180$ ppm.) Possible adverse effect: Histopathology revealed increased hemangioma in mesenteric lymph nodes and spleens at 540 ppm. Acceptable. (Green & Silva, 1/16/96).
CHRONIC, RAT

013/014  000231, 035021, "Chronic Oral Toxicity of Ferric Dimethyldithiocarbamate (Ferbam) and Zinc Dimethyldithiocarbamate (Ziram)," (1956, Univ. of Rochester, publication in: Toxicology, pg 174, by Hodge, H. C., et al). Ziram, purity not indicated, fed at 0, 0.0025, 0.025 or 0.25% in diet to 25/sex/group for 2 years; adverse effects include neurological effects, and thyroid adenomata which may be compound related: NOEL = 0.025%. UNACCEPTABLE (insufficient observations, serum and histo. data, inadequate number of animals per group). (Remsen (Gee), 4/17/85).

CHRONIC, DOG

Subchronic Study:

080  116115, "13-Week Dietary Toxicity Study in Beagle Dogs", (T.A. McLean, S.A. Horner, D.P. Buist, D.V. Crook, R.M. Read, C. Gopinath, A. Anderson, I.S. Dawe, S.F. Johnson and S. Patel, Huntingdon Research Centre Ltd., HRC Report No. 8/901813, 5/5/92). Ziram technical (purity = 98.5%) was fed in diet to Beagle dogs (4/sex/dose) at 0 (untreated diet), 100, 300, or 1000 ppm for 13 weeks. NOEL = 100 ppm (A male died at 1000 ppm. Body weight and food consumption were decreased in males at 1000 ppm. Females had decreased food consumption at 1000 ppm. Hematology and biochemistry parameters were affected at ≥ 300 ppm in both sexes. Liver weights were increased in both sexes and lung weights were decreased in females at 1000 ppm. Liver histopathology (pigment in Kupffer cells and focal necrosis--both sexes & cell loss/dilated sinusoids--females) was increased at ≥ 300 ppm). Based on the results, 50, 185 and 700 ppm were selected for the definitive chronic dog study. These data are supplemental. (Kishiyama & Silva, 12/12/95).

Chronic Studies:
"Chronic Oral Toxicity of Ferric Dimethylthiocarbamate (Ferbam) and Zinc Dimethylthiocarbamate (Ziram)," (1956, Univ. of Rochester, publication in: Toxicology, pg. 174, by Hodge, H. C. et al.) Reviewed as record #231, subsequently changed by library; Ziram, purity not indicated, fed at 0, 0.5, 5.0 or 25 mg/kg/day in diet to 1/sex/group for 1 year; epileptic seizures at high dose only; nominal NOEL = 5 mg/kg. UNACCEPTABLE, not upgradeable (too few animals, insufficient observations, serum and histo. data). (Remsen (Gee), 4/17/85).

"Ziram Toxicity to Dogs by Repeated Administration for 52 Weeks", (T.G. Smith, D.P. Buist, D. Crook, J. Morrow, C. Gopinath; Huntingdon Research Centre Ltd., ZIR 10/920533, 6/8/93). Ziram technical (purity = 98.5%) was fed in diet to Beagle dogs (4/sex/dose) at 0, 50, 185 or 500/700 ppm (700 ppm reduced to 500 ppm at week 12) for 52 weeks. NOAEL = 50 ppm/day (Females showed decreased body weights and body weight gains at > 185 ppm. Males showed increased GPT at > 185 ppm. Both sexes showed increased AP and cholesterol at > 185 ppm. Decreased albumin was observed in males at 500 ppm and in females at all treatment levels. Male liver and prostate weights were decreased at 500 ppm. Female gonad and uterus weights were decreased at all treatment levels. Liver histopathology was increased at all treatment levels (primarily in males). Increased incidence in pigmented macrophages in spleen was observed in males at > 185 ppm. Females showed decreased corpora lutea and increased pituitary cysts at all doses.) ACCEPTABLE. Possible adverse effect: Ziram induces pituitary cysts which affects estrus regulatory hormones. (Kishiyama & Silva, 12/13/95).

"Epiphyseal Lesions of the Femur and Tibia in Rats Following Oral Chronic Administration of Zinc Dimethylthiocarbamate (Ziram)," Enomoto, A., Harada, T., Maita, K. and Shirasu, Y., Toxicology, 54(1989): 45-58. Ziram technical (97.5% pure) was fed in diet (standard laboratory chow) to Fischer 344 rats (80/sex/group) at 0 (feed), 20, 200 or 2000 ppm for 104 weeks. Eight/sex/group were sacrificed at 26, 52 and 78 weeks. Possible adverse
Effect. NOEL = 200 ppm (Partial paralysis of the hind limbs, observed clinically was noted in 3 males (2000 ppm). In 11/34 males (2000 ppm) at 104 weeks, a marked curvature of the proximal end of the crus (possibly causing a restricted extension of the tibio-femoral joint) was observed. Females did not have clinical signs or gross abnormalities, however histopathology showed retardation of the epiphyseal closure of the proximal end of the tibia (this was also observed in males) at 2000 ppm. In addition, females showed the epiphyseal lesion at the distal end of the femur. Marked proliferation of epiphyseal cartilaginous tissue, along with irregular arrangement of chondrocytes was observed in the more severely affected rats. The severe changes were noted primarily in aged animals. Lesions observed in males and females was 22/77 (29%) and 13/73 (18%), respectively at 2000 ppm. Thyroid follicular hypertrophy was observed in males at 2000 ppm and in females at ≥ 200 ppm. Muscle atrophy occurred in both sexes at ≥ 200 ppm. Sciatic nerve degeneration occurred in both sexes at 2000 ppm.) It was concluded in the study that the bone effects were treatment-related. (No worksheet, summary only). These data are supplementary. (M. Silva, 4/8/91)

** 018 926450 "Carcinogenesis Bioassay of Ziram in F344/N Rats and B6C3F1 Mice," (4/1983, Southern Research Inst., NTP report no. 238, NIH Publication No. 83-1794). Ziram, 89% with 6.5% thiram, 2% "other", fed at 0, 300 or 600 ppm in diet for 103 weeks to 50/sex/group; oncogenic effect in thyroid: C-cell carcinomas with a dose-related trend in males, also with C-cell adenomas; ACCEPTABLE. Apparent oncogenic NOEL < 300 ppm; systemic NOEL > 600 ppm. C-cell carcinomas of the thyroid occurred at 0/50 for control males, 2/49 (NS) in low dose males and 7/49 (S) in high dose males. Combined adenomas/carcinomas were 4/50, 9/49 (NS) and 12/49 (S). No evidence for follicular cell changes. The notations for significance are S = significant by Fisher’s Exact with no corrections for dose numbers, NS = not significant. NOTE: This is an early review and when sent for risk characterization, the report may not be considered acceptable. One problem is the legibility of some of the tables in the copy on file. (Remsen (Gee), 4/18/85).
ONCOGENICITY, MOUSE

** 085 133419, “Ziram (Technical) Potential Oncogenicity to Mice by Repeated Dietary Administration for 80 Weeks”, (L.A.J. Powell, S.M. Bottomley, D. Crook, S.K. Majeed, C. Gopinath, W.A. Gibson and A. Anderson; Huntingdon Research Centre Ltd., England ZIR 12/932311, 8/19/94). Ziram Technical (purity 98.7%) was fed in diet to Crl: CD-1 (ICR) BR mice (50/sex/dose) at 0, 25, 75, 225 or 675 ppm and fed αδλιβυµ for at least 80 weeks. NOAEL = 25 ppm (There was decreased food consumption, body weight and body weight gain in both sexes at > 225 ppm. Brain weights were decreased at > 225 ppm. Male kidney weights were increased at 675 ppm and testes/epididymides weights were increased at ≥ 225 ppm. Centrilobular hepatocyte enlargement, vacuolation and generalized enlargement were increased at ≥ 25 ppm. Urinary bladder epithelial hyperplasia was increased at ≥ 225 ppm.) Oncogenicity NOEL = 675 ppm (No oncogenicity observed at any dose.) Possible adverse non-oncogenitic effect: There was an increase in centrilobular hepatocytic enlargement at all doses. ACCEPTABLE. (Kishiyama & Silva, 1/16/96).

013 000233 "Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note," (4/19/1969, Bionetics Research Labs, publication in: J. National Cancer Institute 42: 1101-1114, 1969). Ziram, no purity stated, 0 and 4.6 mg/kg/day by gavage from day 7 to 4 weeks, then by diet at 0 or 15 ppm to 90, 36 and 36 mice (2 strains/group from crosses with 18/sex from each cross per group), for 18 months; ETU (ethylene thiourea) at 215 mg/kg = 646 ppm was oncogenic; Insufficient data to evaluate an adverse effect. UNACCEPTABLE, incomplete (only one dose level used, no rationale for selection, insufficient clinical, histo. data). Ziram was not oncogenic at 15 ppm. Not upgradeable. (Remsen (Gee), 4/17/85).

037 050888 Exact duplicate of 000233.

** 018 038181 "Carcinogenesis Bioassay of Ziram in F344/N Rats and B6C3F1 Mice (Feed Study)," (4/1983, Southern Research Inst., NTP report no. 238, NIH Publication No. 83-1794.) Reviewed as record #926450, subsequently changed by library; Ziram 89% with 6.5% thiram, 2% "other", fed at 0, 600 or 1200 ppm in diet for 103 weeks to 49-50/sex/group; oncogenic effect in lung:
Alveolar/bronchiolar adenomas in females, also carcinomas; systemic NOEL < 600 ppm (body weight). Possible oncogenic NOEL < 600 ppm. Alveolar/bronchiolar adenomas were increased in female mice with 2/50 in controls, 5/49 (NS) in low dose and 10/50 (S) in high dose. Combined adenomas/carcinomas was 4/50, 6/49 (NS) in low dose and 11/50 (S) in high dose group. See under Rat oncogenicity for comment on S and NS. ACCEPTABLE. NOTE: This is an early review and when sent for risk characterization, the report may no longer be considered acceptable. Some of the tables are difficult to read. (Remsen (Gee), 4/18/85).

Conclusion: No adverse oncogenic effects were noted in study 085 133419, which was acceptable and completed in 1994 (according to current FIFRA Guidelines). Study 018 038181 (also acceptable), performed in 1983, used ziram at higher doses and an adverse effect was noted. The adverse effect may have been due to exceeding the MTD. The more recent study will be the one used to assess possible adverse effects for oncogenicity in mice. (M. Silva, 1/18/96).
REPRODUCTION, RAT

** 105 145950  "A Dietary Two-Generation Reproduction and Developmental Neurotoxicity Study of Ziram in Rats," (Nemec, M.D., WIL Research Laboratories, Inc., Ashland, OH; Laboratory Study #: WIL-223003; 1/30/96). Ziram technical (97.8% pure) was administered in diet to Sprague-Dawley Crl:CD BR rats (30/sex/dose) at 0, 72, 207 and 540 ppm (target level at 72 and 207 ppm were 60 and 180 ppm) for 2 generations. Thirty pups/sex/dose were selected for developmental landmarks and behavioral testing, neuropathology and brain weight measurements. Designated F0 and F1 parents and F2 pups were examined for neuropathology and brain weight measurements. Systemic NOEL = 72 ppm (There was decreased body weight and body weight gain in both sexes of F0 and F1 at 540 ppm. F0 food consumption was decreased in females, but F1 food consumption was decreased in both sexes at 540 ppm (> 207 ppm in F1 females during gestation and lactation). F0 females had decreased absolute brain weight and male relative liver weights were increased at 540 ppm. F1 males had absolute brain weight decrease, relative brain weight increase and absolute liver weight increase at 540 ppm. Relative epididymal and testes weights were increased at 540 ppm. Female absolute kidney weights were decreased at ≥ 207 ppm. Female relative brain weights were increased at 540 ppm.) Reproduction NOEL = 207 ppm (There was a significantly decreased live litter size in F0 generation at 540 ppm. F1 generation mean pup weights were significantly decreased at 540 ppm.) Pup NOEL = 207 ppm (F1 mean pup weights were significantly decreased on day 14 and F2 mean pup weights were significantly decreased on day 14 post partum at 540 ppm.) Neurotoxicity NOEL > 540 ppm (There were no significant neurotoxic effects observed at any dose.) No adverse effect. This study is acceptable for filling the rat reproduction data gap and also satisfies FIFRA Guideline recommendations for developmental neurotoxicity in rats (supplementary). M. Silva, 5/21/96.

** 013 000235 & 041 057818  "A Three Generation Reproduction Study of Vancide MZ-96 (Lot No. GP-26-24M), Zinc Dimethyldithiocarbamate in Sprague-Dawley Rats," (5/1/79, Cannon Labs, Inc.; revised 3/3/82 by Vanderbilt; revised 5/21/87 by Vanderbilt). Ziram (lot GP-26-24M, purity = 98%) was fed in diet to Sprague-Dawley rats (10 males and 20 females/group) at 0, 280, 1260 or 2800 ppm for 119 days, then reduced to 140, 770 or 1400 ppm because of toxicity. Parental
NOEL = 140 ppm (decreased body weight gain ≥ 770 ppm in males and in females during pregnancy and lactation). Reproductive NOEL = 140 ppm. **Adverse effect** (reproductive effects on fertility index, decreased lactation index at > 770 ppm; decreased pup body weights at ≥ 770 ppm; decreased pup survival at ≥ 770 ppm; decreased litter size at 2800 ppm). The study was initially reviewed as unacceptable (missing pages for record #000235). Remsen (Gee), 4/17/85 and 3/5/86. The information requested, however, was received by DPR (116/041/057818) and the status of the study is changed to ACCEPTABLE. (M. Silva, 7/27/88).

EPA 1-liner: NOEL = 140 ppm; LEL = 770 ppm (body wt. decrease in pups and young animals, and increased mortality during lactation); core grade - minimum (upgraded). Brief summary of 40310, reviewed.

**026-33 040310-17** (1979, Cannon) Supplements to 235 containing copies of laboratory notebooks of raw data and handwritten tables. The pages missing from report with Record # 235 are not included. (Remsen (Gee) 3/5/86).

037 Letter of November 14, 1986, from R. T. Vanderbilt with statement of purity as 98%. (Remsen (Gee), 4/16/87).
CONCLUSION: There were two acceptable rat reproduction studies submitted by the registrant. The earlier study (116-013 000235 & 041 057818) was from 1979, before current FIFRA Guidelines. Doses used in this study were highly toxic at the upper levels (770 & 1400 ppm) and which was reflected in effects observed in parents and offspring. The recent study (116-105 145950), performed according to FIFRA Guidelines showed no adverse effect. The doses were lower (72, 207 and 540 ppm) and there were no indications of having exceeded the MTD. Therefore, DPR concludes that ziram does not cause adverse effects in rat reproduction when used at or below the MTD.

** 063 095478 "A Study of the Effect of Ziram on the Pregnancy of the Rat", (J. A. Smith, A.M. Bryson, D.M. John and A. Anderson, Huntingdon Research Centre Ltd., HRC Report No. ZIR15/24/891371. Ziram Technical (purity 98.9%, batch #: 8331 AA) was administered by oral gavage at concentrations of 0 (1% methylcellulose), 1, 4, 16, or 64 mg/kg to 25 mated female rats (Crl: CD (SD) BR VAF/plus)/group on day 6 through 15 of gestation. Maternal NOEL = 4 mg/kg/day (Body weight and food consumption were reduced while water consumption and incidence of salivation and hair loss were increased at > 16 mg/kg.) Fetal NOEL = 16 mg/kg/day (Fetal body weights were lower than controls and an increased incidence of unossified sternebrae was observed at 64 mg/kg/day.) ACCEPTABLE. (Kishiyama & Silva, 3/18/91)

013 000234 "Investigation of Teratogenic and Toxic Potential of Vancide," (12/15/1976, Cannon Labs). Ziram (98%, lot GP-26-24M); 0, 14, 56, 98 and 140 mg/kg by oral gavage day 6-15 to 20/group; NOEL > 140 for teratogenicity, nominal maternal NOEL = 14 mg/kg (body wt); NO adverse effects UNACCEPTABLE (analysis of dosing solutions needs to be submitted, only 1/3 of fetuses for visceral exam, no clinical observations, no necropsy, wide range in fetal
weights in high dose group). Upgradeable (analysis of dosing solutions, clinical observations and necropsy data must be provided). Remsen (Gee), 4/17/85 and 3/5/86.

EPA 1-liner: Teratogenic and fetotoxicity NOEL > 140 mg/kg/day (HTD); maternal NOEL = 14 mg/kg/day; maternal LEL = 56 mg/kg/day; Core grade - minimum.

025 040309 (1976, Cannon Labs) Supplemental data to 000234 containing individual data. Remsen (Gee), 3/5/86.

041 A letter from R.T. Vanderbilt was submitted May 21, 1987 (no record#) in support of the above studies (000234 and 040309). The points discussed in the letter are regarding the rebuttal of 4/16/87. The study is still UNACCEPTABLE. M. Silva, 7/26/88.
** 045 062428  "Ziram: Oral (Gavage) Teratology Study in the Rabbit," (Hazleton Laboratories Europe Ltd.). Ziram technical (purity = 98%) was administered by gavage to mated New Zealand White rabbits (16/group), at 0 (vehicle = 1% aqueous methyl cellulose), 3, 7.5 and 15 mg/kg/day during days 7 to 19 of gestation (day of mating = day 0 of gestation). No adverse effect. Maternal NOEL = 7.5 mg/kg/day (decreased body weight gain, decreased food consumption, increased post-implantation loss). Developmental NOEL = 7.5 mg/kg/day (decreased mean litter weight). ACCEPTABLE. (M. Silva, 7/26/88).

045 062427. Range-finding study is supplementary to 062428.  "Ziram: Oral (Gavage) Range-Finding Study in the Pregnant Rat," (Hazleton Laboratories Europe Ltd., 9/85). Ziram technical (purity = 98%) was administered by gavage to mated New Zealand White rabbits at 0 (vehicle = 1% w/v aqueous solution of methyl cellulose), 5, 10, 20 mg/kg/day (5/group) from day 7 to day 19 of gestation (day of mating = day 0 of gestation). No adverse effect indicated. Maternal NOEL = 10 mg/kg/day (decreased body weight gain and food consumption were observed). Developmental NOEL > 20 mg/kg/day (no effects were observed at any level). (M. Silva, 7/25/88).

MUTAGENICITY, GENE

** 060 095481, "Ziram Technical: Bacterial Mutation Assay", (E. Jones, G.S. Cook, R.A. Gant and J. Kitching, Huntingdon Research Centre Ltd., HRC Study Report No. ZIR 25/891914, 8/22/90). Ziram, technical, purity 98.5%, at concentrations of 0 (DMSO), 0.5, 1.5, 5.0, 15.0 or 50 µg/plate were assayed in 2 independent tests, in the presence and absence of liver S-9 prepared from Aroclor 1254 induced rats, using Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538. Increases in revertants were observed at the 2 higher doses in one test (the repeat test). Additional tests followed which included Salmonella typhimurium strain TA100 and S-9 mix at various concentrations. Repeat Test #1 (TA100): 2 groups were tested with Ziram concentrations at 0, 15, 25, 50, 100, or 150 µg/plate with S-9
concentrations of 5, 10, or 20%. One group included a 60 minute pre-incubation and the other did not. **Repeat Test #2 (TA100):** TA100 was treated with Ziram at 0, 25, 50, 75, or 100 µg/plate with 20% and 30% S-9 mix with no pre-incubation. Exposure time in all tests was 3 days. **Adverse effect:** an increase in TA100 revertants was observed with Ziram in the presence of S-9. ACCEPTABLE. (Kishiyama & Silva, 3/21/91).

**063 095477** "Salmonella/Mammalian-Microsome Plate incorporation Mutagenicity Assay (Ames Test)", (T. Cascieri, Study Director, FMC Corporation, Genetic Toxicology Laboratory, Study no. A84-1317, 10/31/84). Ziram technical (purity 93.6%) was used at concentrations of 0 (DMSO), 10, 33.3, 66.7, 100, 333.3, 666.7, 1000, 3333.3, 6666.7, or 10000 µg/plate (triplicate plates) in the presence and absence of metabolic activation (S-9 from Aroclor 1254 induced rat livers) with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA 1538 (exposure = 48-72 hours). **Adverse effect:** FMC13581(Ziram) induced an increase in revertant colonies with Salmonella typhimurium strain TA100 (both with and without S-9). ACCEPTABLE. (Kishiyama & Silva, 3/19/91).
063 095479, "Salmonella Mutagenicity Test Results for 250 Chemicals", (S. Haworth, T. Lawlor, K. Mortelmans, W. Speck and E. Zeiger, SRI International, Environmental Mutagenesis, 5 (Supplement 1):3-142 [1983]). Ziram technical (purity 86.2%) was used at concentrations of 0 (DMSO), 10, 33.3, 66.7, 100, 333.3, 666.7, or 10000 µg/plate (triplicate plates), in the presence and absence of metabolic activation (S-9 from Aroclor 1254 induced rat and Syrian hamster livers), with Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537. Exposure time was for 48 hours, after a 20 min. preincubation. **Adverse effect:** increase in the number of revertants with Ziram/TA100 treatments. These data are supplemental information to support the positive findings with ziram and TA100 in study 063 095477. The entire report was not presented, only pages 3-5, 16-17, 49 & 142. (Kishiyama & Silva, 3/20/91).

**MUTAGENICITY, CHROMOSOME**

**060 095482, "Analysis of Metaphase Chromosomes Obtained from CHO Cells Cultured In Vitro and Treated with Ziram", (P. C. Brooker and L. C. Akhurst, Huntingdon Research Centre Ltd., HRC Study Report No. ZIR 7/89675, 5/9/89).** Ziram technical (purity = 98.5%) was used at concentrations of 0 (DMSO), 125, 500, and 1000 ng/ml in the presence of metabolic activation (S9 from Aroclor 1254-induced rat liver) and at 0 (DMSO), 3.1, 12.5 and 25 ng/ml (no S9) on Chinese hamster ovary cells (K1-BH4) which were evaluated for chromosome aberrations (duplicate cultures with 100 cells/culture evaluated). Exposure time was 4 and 21 hours in the presence and absence of metabolic activation, respectively. No significant increases in chromosome aberrations were observed at any dose. ACCEPTABLE. (Kishiyama & Silva, 4/5/91)

**MUTAGENICITY, DNA**

**060 095483, "Autoradiographic Assessment of DNA Repair after In Vitro Exposure of Rat Hepatocytes to Ziram", (R. J. Proudlock, Huntingdon Research Centre Ltd., HRC Study Report No. ZIR 6/89820, 5/21/89).** Ziram, technical, 98.5% pure at concentrations of 0 (DMSO), 0.316,
1.0, 3.16, 10, 31.6, 100, 316, 1000, 3160, 10000, 31600, or 100000 ng/ml was assayed using primary cultures of rat hepatocytes (triplicate cultures, 50 nuclei/culture were evaluated). A repeat was performed with a similar protocol, except the exposure time was 19 hours, instead of 20. Net nuclear grain count was not increased in any of the Ziram treatments. ACCEPTABLE. (Kishiyama & Silva, 4/8/91).

NEUROTOXICITY

A developmental neurotoxicity study was performed in rats (see DPR volume/record #: 116-105/145950, section on reproductive toxicity in this summary). There were no neurotoxic effects observed in the study. M. Silva, 5/22/96.
SUPPLEMENTAL STUDIES

"Twenty-one Day Dermal Toxicity Study in Rabbits With Ziram," (Edwards, J.A., Baldrick, P., Gibson, W.A., Crook, D., Offer, J.M. & Gopinath, C., Huntingdon Research Centre Ltd., Cambridgeshire, UK; Report #: ZIR 4/89689, 11/2/89). Ziram technical (98.5% pure) was administered to intact skin of New Zealand white rabbits (5/sex/dose) at 0 (distilled water), 100, 300 and 1000 mg/kg/day (limit test), daily for 21 days. Application was 24 hours after the hair was clipped and areas treated were not abraded. After treatment, the site was covered with an impervious bandage for 6 hours (before being washed with warm tap water). NOEL = 100 mg/kg/day (No skin reactions occurred from treatment. Females showed decreased body weight and food consumption at 1000 mg/kg. Lymphocyte counts were decreased in females at 1000 mg/kg. Liver GPT & GOT in females were increased at ≥300 mg/kg and increased levels of bilirubin (females) and cholesterol (both sexes) occurred at 1000 mg/kg.) No adverse effect. These data are supplemental. M. Silva, 1/18/96.

A volume was submitted by the R.T. Vanderbilt Company, Inc. (no volume or record number) which was a request to waive the 90 day dermal study in lieu of the 90 day feeding study (rat) and the 21 day dermal study (rabbit). No worksheet. M. Silva, 1/31/96.