Mancozeb

Document History
Published: 2008
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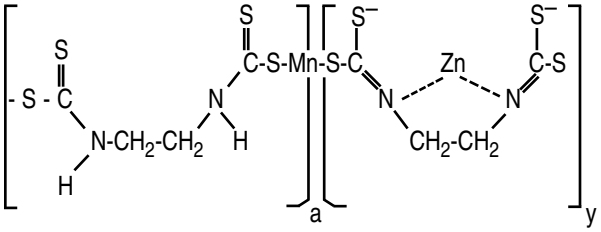
I. IDENTIFICATION

Chemical Name: Mancozeb, a coordination product of zinc cation
and manganese ethylene bisdithiocarbamate (EBDC)
Synonyms: Manganese zinc complex of ethylene bisdithiocarbamate
CAS Number: 8018-01-7
Molecular Formula: $(C_4H_6N_2S_4Mn)_a \cdot (C_4H_4N_2S_4Zn)_y$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1–5]

Physical State: Standard formulation is a gray-yellowish powder containing 80% of the coordination product and 20% other ingredients including surfactants and other diluents.
Odor Description: Musty odor
Molecular Weight: 212.4
Conversion Factors: 1 ppm = 0.115 mg/m³
1 mg/m³ = 8.67 ppm
Boiling Point: No data located
Melting Point: 192–204°C (378–399°F)
Vapor Pressure: No data located.
Specific Gravity: 0.35–0.50 g/cc bulk density
Flash Point: 146°C (295°F) Tagliabue open-cup
Flammability Limits: Minimum explosive concentration 0.16 oz/ft³
Auto-ignition Temperature: 132°C (270°F)
Solubility in Water: Practically insoluble in water and most organic solvents; slightly soluble in dimethyl sulfoxide (DMSO), but chemically unstable in this solvent. Powder formulations are manufactured so they are dispersible in water.
Stability and Reactivity: Stable under normal storage conditions and essentially inert in ambient air. Degradation increases with both the presence of oxygen and elevation of temperature and humidity. Decomposes at 192–204°C.
Incompatibilities: Must be kept dry; excessive heat (>49°C [120°F]) and ignition sources must be avoided. Hazardous decomposition products include hydrogen sulfide, carbon disulfide, plus oxides of carbon, nitrogen, and sulfur.

III. USES

Mancozeb is a commercial protective-eradicant and nonsystemic fungicide for various crops.[6]

IV. TOXICOLOGY DATA

A. Acute Toxicity

1. Oral Toxicity

Rat: LD_{50} 5000–15,000 mg/kg[7–11]

Mouse (male): LD_{50} >5000 mg/kg[10]

Guinea Pig: LD_{50} 3400 mg/kg[11]

2. Eye Irritation

Application of 0.1 g of ground mancozeb powder into the conjunctival sac of the rabbit eye resulted in substantial to severe eye irritation in the most severely responding animal.[8–11] Washing the treated eyes with water shortly after exposure dramatically reduced or prevented the ocular effects. Application of 0.1 g of ground mancozeb directly to the cornea resulted in moderate conjunctivitis that was reversible within 7 days after exposure.[13]

3. Skin

a. Irritation

Mancozeb powder was prepared as a paste with saline in a 1:1 ratio and held in

continuous contact with intact and abraded skin of New Zealand rabbits for 24 hours.[8] No skin reactions were seen on intact skin, and only barely perceptible erythema was seen on the abraded skin.

b. Absorption

Rabbit:	LD_{50}	>5000 mg/kg[8]
Rat:	LD_{50}	>4000 mg/kg[14]

c. Sensitization

Mancozeb has been demonstrated to be a strong skin sensitizer in guinea pigs by the Guinea Pig Maximization Test.[15,16] Induction concentrations of 5% (intradermal) and 25% (topical), and challenge concentrations of 2 and 0.5% (topical), produced responses in all mancozeb-treated female guinea pigs.

4. Inhalation

Rats:	4-hr LC_{50}	>5.1 g/m^3[11,17]

5. Other

Rats:	LD_{50} ip	380 mg/kg[11]

B. Subacute Toxicity

No data located

C. Subchronic Toxicity

Four groups of 38 male and 38 female rats received nose-only exposures to mancozeb airborne dust concentrations of 0, 18, 79, or 330 mg/m^3 for 6 hours per day, 5 days per week, for 13 weeks.[11,18] These total dust concentrations corresponded to respirable dust levels of 0, 8, 36, and 140 mg/m^3. The mass median diameter of the exposure aerosol was 3.7 to 4.4 micrometers and the mean geometric standard deviation was 2.1 to 2.3. Male animals in the highest exposure group experienced significant reductions in body weight gain and terminal body weights. A significant reduction in thyroxine levels and a treatment-related hyperplasia of the thyroid follicular epithelium in females were reported at the 330 mg/m^3 exposure level. These thyroid effects correlated well with the increased levels of ethylene thiourea (ETU) and ethylene bis-isothiocyanate sulfide (EBIS) seen in the urine, and ETU levels seen in the blood and thyroids. No significant histopathologic alterations were observed in either the 18 mg/m^3 or 79 mg/m^3 exposure groups. Tissue residue analysis showed that ETU did not accumulate in the thyroids of animals exposed to 79 or 330 mg/m^3. No treatment-related ophthalmologic changes were observed in any group after 12 weeks of exposure. The NOAEL is 79 mg/m^3 and the LOAEL is 330 mg/m^3. No treatment-related effects were observed after the 13-week postexposure recovery period in any of the exposed animals, indicating that the observed effects were reversible.

Groups of 14 rats/sex were given 0, 30, 60, 130, 250, or 1000 ppm in the diet for 13 weeks (male doses: 0, 1.8, 3.5, 7.4, 15, 57 mg/kg/day; female doses: 0, 2.2, 4.4, 9.2, 18, 75 mg/kg/day).[11] Thyroid toxicity was noted at 250 ppm in females and at 1000 ppm in males. Liver toxicity was noted in females at 1000 ppm. The NOAEL in females was 130 ppm (9.2 mg/kg/day) and in males was 250 ppm (15 mg/kg/day). The LOAEL in females was 250 ppm (18 mg/kg/day) and in males was 1000 ppm (57 mg/kg/day).

Groups of 6 dogs/sex were fed diets containing 0, 10, 100, 1000, or 5000 ppm for 13 weeks (male doses: 0, 0.29, 3, 29, or 100 mg/kg/day; female doses: 0, 0.32, 3.4, 29, or 110 mg/kg/day).[11] Two males and one female fed the 5000 ppm diet died on study. Depressed body weight gain, anemia in females, and prostate hypogenesis in males were noted at 1000 ppm or more. The NOAEL was 100 ppm (3 and 3.4 mg/kg/day male and female), respectively and the LOAEL was 1000 ppm (100 and 110 mg/kg/day, male and female, respectively).

Groups of 50 male rats were given 400, 630, 1000, or 10,000 ppm in the diet (16, 25, 40, or 400 mg/kg/day) for 12 weeks and held for a 4-week recovery period. At the end of dosing, the rats exhibited increased thyroid weights or thyroid-to-body weight ratios at 40 mg/kg/day or more.[7,19,20] Levels of thyroid stimulating hormone (TSH) were elevated only sporadically at 40 mg/kg/day. Histopathologic examination of the thyroid gland revealed minimal to moderate thyroid hyperplasia in the rats fed mancozeb at 40 mg/kg/day or more. Most of the effects were resolved by the end of the recovery period. Based on these data, the 12-week NOAEL for thyroid effects in the rat is 16 mg/kg/day.

In mice given diets containing 0, 10, 100, 1000, or 10,000 ppm (male doses: 0, 1.8, 18, 170, or 1700 mg/kg/day; female doses: 0, 2.3, 21, 230, or 2200 mg/kg/day), an increase in thyroid weight was seen in both sexes of the mouse after 13 weeks at 10,000 ppm mancozeb but not at lower concentrations. Thyroid follicular hyperplasia was seen at 1000 ppm.[11,20,21] The NOAEL for thyroid effects in the mouse was 100 ppm mancozeb (18 and 21 mg/kg/day for male and female respectively) and the LOAEL was 1000 ppm (170 and 230 mg/kg/day for males and females, respectively).

In a 90-day feeding study with rats at dietary mancozeb concentrations of 0, 100, 1000, or 10,000 ppm in the diet male doses: 0, 4, 40, or 400 mg/kg/day; female doses: 0, 5, 51, or 510 mg/kg/day produced an increase in liver-to-body weight ratios in females at 510 mg/kg/day.[22] The NOAEL for this effect was 51 mg/kg/day. No histopathologic changes were observed.

D. Chronic Toxicity and Carcinogenicity

Groups of 72 male and 72 female rats were fed diets containing 0, 20, 60, 130, or 750 ppm for 24 months.[23] Males were dosed at 0, 0.77, 2.3, 4.9, and 31 mg/kg/day and females were dosed at 0, 1.1, 3.1, 6.7, and 40 mg/kg/day, respectively. The authors concluded that the increased relative liver weight and testes weight were due to slightly lower body weights in treated males. T4 (thyroid hormone) levels were decreased and thyroid stimulating hormone levels were increased in males and females fed 750 ppm. At this dosage, males and females exhibited an increase in thyroid follicular cell carcinomas, adenomas, and hyperplasia. These tumors were thought to be related to ethylene thiourea, a metabolite of mancozeb. Bilateral retinopathy was also present in these animals. The NOAEL for this study was 4.9 mg/kg/day for males and 6.7 mg/kg/day for females.

Groups of 25 male and 25 female rats were fed 0, 25, 50, 100, or 1000 ppm mancozeb for 90 weeks. The males were dosed with 0, 1, 2, 4, or 40 mg/kg day and the females were dosed at 0, 1.3, 2.5, 5, or 50 mg/kg/day, respectively. Thyroid hyperplasia was seen after 90 weeks of dosing at 50 mg/kg/day for females and 40 mg/kg/day for males, but not at 5 mg/kg/day or lower concentrations.[24] No differences in tumor incidence were noted. The NOAEL was 5 mg/kg/day and the LOAEL was 50 mg/kg/day.

Chronic toxicity and oncogenicity were studied in male and female Sprague-Dawley rats fed dietary levels of 0, 20, 60, 130, and 750 ppm (male doses: 0, 0.77, 2.3, 4.8, or 31 mg/kg/day; female doses: 0, 1.1, 3.1, 6.7, or 40 mg/kg/day) for two years.[25] A statistically insignificant increase in thyroid follicular cell carcinoma and adenoma in females was observed only in the 60 ppm group. There was also a statistically significant increase in the incidence of bilateral retinopathy observed in male and female rats in the 750 ppm level. These ocular effects were not observed at the lower dietary levels of 20, 60, or 130 ppm. The NOAEL was 130 ppm or 4.8 and 6.7 mg/kg/day (males and females, respectively) and the LOAEL was 750 ppm (31 and 40 mg/kg/day for males and females, respectively).

[It should be noted that EPA states that the thyroid tumors are the result of prolonged elevated thyroid stimulating hormone levels resulting from internal concentrations of the metabolite ETU.[11]]

Groups of 4 beagle dogs/sex were fed 0, 50, 200, 800, or 1600 ppm for one year (male doses: 0, 1.8, 7.3, 27, or 54 mg/kg/day; female doses: 0, 1.8, 7, 29, or 70 mg/kg/day).[11] Two males fed 1600 ppm were sacrificed moribund. Thyroid toxicity and increased cholesterol levels were noted in animals fed 1600 ppm. Depressed body weight gain was noted in males fed 200 or 800 ppm and anemia was noted in females fed 800 ppm or more. The NOAEL was 50 ppm (1.8 mg/kg/day) in males and 200 ppm (7.3 mg/kg/day) in females. The LOAEL was 200 ppm (7.3 mg/kg/day) in males and 800 ppm (29 mg/kg/day) in females.

No effects were seen in dogs after 2 years of exposure to mancozeb at 5 mg/kg/day.[26] A slightly reduced mean ^{131}I uptake in the thyroid and slight thyroid hyperplasia were seen at 20 and 200 mg/kg/day; however, all ^{131}I uptake values were within the normal range.

No effects on the liver, body weight gain, feed consumption, or mortality were seen in either the rat or the dog after 90 weeks and 2 years, respectively, of exposure to mancozeb at dietary concentrations up to 1000 ppm (40 mg/kg/day).[24,25]

In an unverifiable, non-GLP study, groups of 150 male and 150 female rats were given 0, 10, 100, or 1000 ppm of mancozeb in the diet (0, 0.8, 8, or 80 mg/kg/day). Increased incidences of mammary, osteosarcoma, liver, pancreas, and Zymbal gland tumors were noted. The results may suggest that mancozeb is a carcinogen; however, the data cannot be used for quantitative evaluation.[27]

E. Reproductive/Developmental Toxicity

Groups of 23–38 pregnant rats were exposed to 0, 1, 17, 55, 110, 890, or 1900/500 mg/m^3, 6 hours/day on days 6-15 of gestation.[28] After one exposure to 1900 mg/m^3, several deaths and considerable weight loss resulted to exposing the group to 500 mg/m^3 for 5 more days. Among the surviving dams, decreased body weight, hindlimb paralysis, and general debilitation were noted. At 55 and 110 mg/m^3, decreased body weight and hind limb weakness were noted in the dams. No maternal effects were noted at 1 or 17 mg/m^3. An increase in total litter resorption, external hemorrhage, and wavy ribs were noted in fetuses from the 55 mg/m^3 or higher groups. There was no dose related incidence of malformations. Mancozeb was considered embryotoxic, but it may be a teratogen since there was an increase in total litter resorption as was seen with thalidomide.

In a two-generation study in rats given 0, 30, 120, or 1200 ppm of mancozeb in the diet (0, 1.7, 7, or 69 mg/kg/day for males; 0, 1.8, 7.5, or 79 mg/kg/day for females) there were no differences noted for mortality or clinical signs.[11] Increased thyroid weight and pathology were noted in both generations fed 1200 ppm. An increase in liver weight without histopathological lesions was noted in animals fed 1200 ppm. There were no effects on reproduction noted in this study. The NOAEL for systemic toxicity was 120 ppm (males: 7 mg/kg/day; females: 7.5 mg/kg/day) and the LOAEL was 1200 ppm (males: 69 mg/kg/day; females: 79 mg/kg/day). The NOAEL for reproductive toxicity was >1200 ppm (males: 69 mg/kg/day; females: 79 mg/kg/day).

Groups of 20 pregnant rabbits were administered 0, 10, 30, or 80 mg/kg/day via gavage on days 7–19 of gestation.[11] Maternal toxicity consisting of alopecia, anorexia, and ataxia was noted in two does given 80 mg/kg/day, while 5 does from this group aborted their litters. There were no signs of developmental toxicity in the fetuses of any group. The NOAEL for maternal toxicity is 30 mg/kg/day and the LOAEL is 80 mg/kg/day. The NOAEL for developmental toxicity is 80 mg/kg/day.

Repeated oral administration of mancozeb was given to rats at doses of 0, 2, 8, 32, 130, or 510 mg/kg on days 6–15 of gestation. The 512 mg/kg dosage level produced an increased incidence of abortion or resorbed litters and developmental toxicity.[11,29] Toxic effects reported included a normal number of live but smaller fetuses and an increased frequency of anomalies of the face, head, tail, and limbs at 510 mg/kg body weight, including hydrocephaly, and atrophy of brain. Exencephaly was reported as an anomaly, but is generally considered a malformation. Maternal toxicity was observed at both 130 mg/kg and 510 mg/kg. The NOAEL for developmental toxicity is 128 mg/kg/day and the LOAEL is 510 mg/kg/day. The NOAEL for maternal toxicity is 32 mg/kg/day.

Groups of 50 male rats were given oral doses of 0, 500, 1000, or 1500 mg/kg/day for 30, 90, 180, or 360 days. An increased incidence of mortality was noted in all treatment groups with 4/50, 10/50, 14/50, and 21/50 dying by Day 360, respectively. Beginning at 90 days, an increase in relative testes weight, but not absolute testes weight, was noted in all treatment groups. A decrease in absolute and relative epididymis weight was noted at 180 days and 360 days. This was accompanied by a degeneration of the seminiferous and epididymal tubules and reduced numbers of sperm. The LOAEL was 500 mg/kg/day and a NOAEL was not established.[30,31]

In a non-GLP study, groups of 6 pregnant female mice were given 0, 18, 24, 30, or 36 mg/kg/day for the first 8 days of pregnancy. Complete inhibition of implantation was noted in animals receiving 36 mg/kg/day. Partial implantation loss was seen at 24 and 30 mg/kg/day. When the treatment at 36 mg/kg was reduced to 5 days, there was still 100% implantation loss, whereas, in animals treated for 3 days, only 2% implantation loss was noted. The NOAEL was 18 mg/kg/day and the LOAEL was 24 mg/kg/day.[32]

In a comparative mechanistic teratology study, groups of 7 or 8 pregnant mice on Gestation Day 9 or Gestation Day 13 and groups of 7 pregnant rats on Gestation Day 11 were give a single oral dose of 0, 380, 730, or 1300 mg/kg.[33] There were no remarkable effects in mice at any dose level. In rats, 25% of the fetuses from dams given to 1300 mg/kg exhibited several types of malformations including cleft palate, hydrocephaly, adactyly or oligodactyly, meromelia, and short tail. These effects were not observed at doses of 730 mg/kg or less, nor were maternal toxic effects observed at any dose in this study. These results were compared to maneb, in which 100% of the fetuses exhibited malformations and the authors concluded that the difference in results for maneb and mancozeb was that the zinc in mancozeb as dithiocarbamates chelate zinc. By adding additional zinc to the diet, the incidence of fetal effects for the treatment groups was not different.

F. Genotoxicity/Mutagenesis

Mancozeb has been tested for genotoxic potential in a number of *in vitro* and *in vivo* systems. The weight of the evidence indicates that mancozeb does not cause point or gene mutations, does not induce chromosomal aberrations in vivo, and does not induce DNA damage.[11,34–39]

G. Metabolism and Pharmacokinetics

Mancozeb is poorly absorbed from the gastrointestinal tract and by the dermal route. Elimination of mancozeb and its metabolites, by contrast, is rapid and complete. Essentially all of an orally administered dose is eliminated within a 3-day period, with the majority excreted in the first 24 hours after exposure.[11,40]

In rats, after 7 consecutive days of oral dosing of ^{14}C-mancozeb at 100 mg/kg/day, 91.8% of the administered dose was recovered within 24 hr after the last dose.[11,41] Of the recovered dose,

77% was in the feces (47% of this was parent compound), 16.9% in the urine, 1.6% in the carcass, and 4.2% in the cage washings.

In the rat, percutaneous penetration occurred slowly from the thin layer of mancozeb on the skin. Less than 1% of a dermal dose of mancozeb was actually absorbed over a 6-hour period.[11,42]

Mancozeb is metabolized in the rat.[11,40] The principal metabolites found in the urine are ethylene thiourea (ETU) and ethylenebisisothiocyanate sulfide (EBIS). The extent of conversion of mancozeb to ETU in the rat has been estimated to be between 7.5% and 11.9% of the administered oral dose.[29, 43] ETU is also a chemical degradation product of mancozeb. A commercial grade of mancozeb contains approximately 0.06% of ETU.

Minor metabolites include ethylene urea, N-acetyl ethylene diamine, N-formyl ethylene diamine, urea, oxalic acid, glycine, ethylene diamine, and some unidentified polar metabolites.[11,40]

Distribution of absorbed radioactivity derived for ^{14}C-labeled mancozeb was found to be highest in the thyroid and uniform in all other tissues of animals.[11,40,41,44] The thyroid contained the highest concentration of the absorbed radioactivity and retained it the longest. The liver and kidney also contained significant amounts of radioactivity. ETU was detected in the thyroid tissue.[11,45]

H. Other

1. Neuropathology

Groups of 10 rats/sex were fed 0, 20, 130, 750, or 5000 ppm in the diet (male doses: 0, 1.4, 8.2, 50, or 340 mg/kg/day; female doses: 0, 1.7, 11, or 63 mg/kg/day) for 90 days.[11] One male and four females fed 5000 ppm died on study. Depressed body weight gain was noted in males at 5000 ppm and in females at 750 ppm and above. Peripheral nerve injury, including degeneration or demyelination of the sciatic and tibial nerves, was noted in males and females fed 750 ppm or more. The NOAEL for neuropathology was 130 ppm (males: 8.2 mg/kg/day; females: 11 mg/kg/day) and the LOAEL was 750 ppm (males: 50 mg/kg/day; females: 63 mg/kg/day).

2. Endocrine Modulation

Groups of eight female rats were given oral doses of 0, 500, 600, 700, or 800 mg/kg/day for 30 days. An increase in diesterus, reduced numbers of healthy follicles, reduced numbers of corpora lutea, reduced ovary weight and effects on the thyroid were noted at 600 mg/kg/day or more.[46]

The endocrine modulation of mancozeb was studied in groups of 75 male rats given oral doses of 0, 500, 1000, or 1500 mg/kg/day for 30, 90, 180, or 360 days. Increased thyroid weight and histopathology as well as reduced ^{125}I content, thyroxine, protein bound ^{125}I, and thyroid peroxidase activity were noted at all doses.[12,31]

In groups of nine or ten wild cotton rats exposed to 0 or 8 mg/kg/day mancozeb for 4 days, thyroid hormone concentrations were decreased, but this decrease was compensated by an increase in thyroxine turnover. In addition, no effects were noted in the ability of treated rats to acclimate to cold.[47]

3. Transplacental Carcinogenisis

In a transplacental cancer promotion study utilizing groups of seven to ten pregnant mice, mancozeb was injected ip into pregnant female mice on the 14th day of gestation and the promoter 12-tetradecanoylphorbol-13-acetate was applied to the skin of groups of three male and three female F1 pups. In the treated pups, the tumor incidence was 72% while pups given mancozeb without the promoter had a tumor incidence of 10%.[48] The significance of this study to human toxicity is not known.

4. Studies using ETU

The metabolic conversion of mancozeb to ETU and reported toxicologic findings from direct administration of ETU in animals warrants further mention. The principal systemic effects in animals after subchronic or chronic exposure to ETU in the diet include depression of body weight gains, thyroid effects, changes in the liver, and increased serum cholesterol secondary to the thyroid effects. The mechanism by which ETU and other thioureas produce effects in the thyroid is well understood. These chemicals inhibit iodine uptake and activation by the thyroid. At low doses, a physiological and biological compensatory mechanism maintains normal levels of circulating thyroid hormone, and no adverse effects result. Prolonged exposure to high doses of the thyroid inhibitors causes severe hypertrophy and hyperplasia with reduced levels of circulating thyroid hormone. In rats, thyroid effects based on 2-year chronic feeding studies resulted in changes in

thyroid iodine uptake, depression of circulating thyroid hormones, increased thyroid weight, hypertrophy, hyperplasia, and adenoma and adenocarcinoma. The severity and reversibility of the effects were functions of dose and duration of exposure.[49–51]

Hepatic effects from direct exposure to ETU have also been observed, including oncogenic effects in mice.[52] In rats, no significantly increased incidence of liver tumors was noted after 2 years of feeding on ETU-treated diet at concentrations as high as 100 mg/kg/day[49] nor in hamsters after 20 months of dietary concentrations as high as 36 mg/kg/day.[50]

ETU, a metabolite as well as a degradation product of mancozeb, has produced fetal malformations in rats and possible embryo-fetoxicity in hamsters at extremely high doses. The type and frequency of teratogenic response to ETU depends on the dose, and the dose-response trend is nonlinear.[11,53,54]

V. HUMAN USE AND EXPERIENCE

A. Odor Data

No data located

B. Toxicity Data

A series of health studies, concentrating on thyroid function, were conducted in male workers involved in the production and packaging of mancozeb.[55,56] Some of these men had worked in the mancozeb manufacturing area for as long as 25 years. Exposure to mancozeb was confirmed by detecting ETU in the urine from these workers. The initial studies of workers conducted in 1965 and 1975 revealed no abnormalities in thyroid function tests, serum concentration of protein bound iodine and T3 uptake, T4, Free T4 Index, or TSH. A mortality study done in 1975 encompassing all known mancozeb production workers did not reveal any difference in rate or cause of death when compared with those for other plant personnel or a comparable population in the city of Philadelphia.[57] No quantitative exposure data were available for these studies.

The follow-up study in 1978 employed a larger, more sensitive battery of thyroid function tests (in order to detect subtle abnormalities in thyroid function) and a medical examination by physicians with expertise in the thyroid.[56] This study revealed no clinical or laboratory evidence of thyroid abnormalities, liver dysfunction, or changes in blood chemistry that could be related to occupational exposure to mancozeb. Airborne mancozeb dust concentrations that were measured in conjunction with this study ranged from <0.1 to 13.9 mg/m^3 and averaged 1.51 mg/m^3 based upon full-shift time-weighted average (TWA) personal samples.

Evidence indicates that mancozeb is a weak skin irritant or sensitizer in humans. In a patch test on orange growers, 4 of 121 workers exposed to agricultural chemicals responded to mancozeb at a concentration of 5% in vaseline.[58] A lower incidence of irritation or sensitization (1%) was seen in a patch test in a group of 54 lettuce growers.[59] In California, of 711 reported cases of skin irritation that physicians attributed to pesticides, 1.2% involved EBDC products.[60,61] No quantitative exposure data were available for these studies.

C. Workplace Experience

In a case report, a man exposed to mancozeb and two other fungicides developed urticaria and was sensitized to mancozeb in patch testing.[62] No quantitative exposure data were available for this study.

In 49 workers heavily exposed to mancozeb, including 14 workers lightly exposed and 31 non-exposed controls, an increase in thyroid stimulating hormone without a reduction in thyroxine was noted in the heavily exposed workers.[63] An increased incidence of sister chromatid exchanges (SCE's) and chromosome translocations were also noted in the heavily exposed workers. No quantitative exposure data were available for this study.

Immunomodulation was studied in 14 workers exposed to mancozeb, and the effects were compared to results in 13 workers from the same plant, but not exposed.[64] An increase in T-cell functional response was noted, suggesting a slight immunomodulator effect following low-level, chronic occupational exposure. No quantitative exposure data were available for this study.

Over a 10-year period, 12 cases of neurotoxicity among workers exposed to mancozeb were noted.[65] Signs included headache, dizziness, confusion, and seizures, all of which were reversible. No quantitative exposure data were available for this study.

In a biomarker study, urine ethylene thiourea (ETU) levels of 13 vineyard workers exposed to mancozeb were compared to levels in 13 non-exposed workers.[66] ETU levels were significantly increased in the urine of exposed workers as compared to baseline levels. ETU levels in controls were below the limit of detection. The concentration in the urine was proportional to the exposure level of the workers. No quantitative exposure data were available for this study.

VI. RATIONALE

The highest NOAEL for thyroid toxicity in rats by the inhalation route was 79 mg/m^3.[18] The highest NOAEL in studies that produced thyroid effects by the dietary route was 100 ppm.[24] This level corresponds on a body weight basis in rats to approximately 5 mg/kg/day. This daily dose is equivalent to an airborne concentration of approximately 35 mg/m^3 for a 55-kg person with a respiratory volume of 8 m^3 per 8-hour workday. An Occupational Exposure Limit (OEL) of 1 mg/m^3 as an 8-hour TWA provides a rea-sonable margin of safety in relation to these NOAELs. This OEL should also afford adequate protection from the effects of mancozeb on the liver, peripheral nerves, and developmental effects, all of which have been reported at higher levels than those associated with the thyroid. An OEL of 1 mg/m^3 as an 8-hour TWA is also supported by human studies showing no adverse effects in workers occupationally exposed to mancozeb and its degradation product and metabolite, ETU, at airborne concentrations equal to or below this level. Since dermal exposure to mancozeb produces sensitization in animals and in humans, a DSEN notation is added to the OEL.

VII. RECOMMENDED OEL

8-hr TWA (as ethylenebisdithiocarbamate): 1 mg/m^3, as total dust, DSEN

VIII. REFERENCES

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