Research and Development

HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR THIRAM

Prepared for

OFFICE OF SOLID WASTE AND EMERGENCY RESPONSE

Prepared by

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency
Cincinnati, OH 45268

DRAFT: DO NOT CITE OR QUOTE

NOTICE

This document is a preliminary draft. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comments on its technical accuracy and policy implications.

HEADQUARTERS LIBRARY
ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460
SUBJECT: Health and Environmental Effects Document for Thiram

FROM: William H. Farland, Ph.D.
     Director
     Office of Health and Environmental Assessment (RD-689)

TO: Matthew Straus
     Chief, Waste Characterization Branch
     Office of Solid Waste (OS-330)

I am forwarding copies of the Health and Environmental Effects Document (HEED) for Thiram.

The HEEDs support listings under RCRA, as well as provide health-related limits and goals for emergency and remedial actions under CERCLA. These documents represent scientific summaries of the pertinent available data on the environmental fate and mammalian and aquatic toxicity of each chemical at an extramural effort of about $10K. The attached document has been reviewed within OHEA, by staff in OPP and OTS, and by two external scientists.

Should you wish to see any of the files related to the development of the HEEDs, please call Chris DeRosa at FTS: 684-7531.

Attachment
This report is an external draft for review purposes only and does not constitute Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.
Health and Environmental Effects Documents (HEEDs) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained for Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched for in this document and the dates searched are included in "Appendix: Literature Searched." Literature search material is current up to 8 months previous to the final draft date listed on the front cover. Final draft document dates (front cover) reflect the date the document is sent to the Program Officer (OSWER).

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RFDs) for chronic and subchronic exposures for both the inhalation and oral exposures. The subchronic or partial lifetime RFD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval i.e., for an interval that does not constitute a significant portion of the lifespan. This type of exposure estimate has not been extensively used, or rigorously defined as previous risk assessment efforts have focused primarily on lifetime exposure scenarios. Animal data used for subchronic estimates generally reflect exposure durations of 30-90 days. The general methodology for estimating subchronic RFDs is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, RFDs are not estimated. Instead, a carcinogenic potency factor, or q_k (U.S. EPA, 1980), is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity, and acute mammalian toxicity). Chemical-specific RQs reflect the lowest of these six primary criteria. The methodology for chronic toxicity and cancer based RQs are defined in U.S. EPA, 1984b and 1986b, respectively.
EXECTIVE SUMMARY

Thiram (137-26-8) is a white crystalline solid at room temperature (Hawley, 1981). It is insoluble in water but soluble in benzene, chloroform and carbon disulfide. Thiram is manufactured by UCB Chemicals Corp. in Bucks, AL, and Goodyear Tire and Rubber in Akron, OH (SRI, 1987; USITC, 1987). During 1982, a minimum of 2.29 million pounds of thiram was consumed in the United States (HSDB, 1988); 97% of the thiram consumed in the United States is used as a rubber accelerator (IARC, 1976).

If released to the atmosphere, thiram is expected to exist partly in the vapor phase and partly in particulate form (Hartley and Kidd, 1983; Eisenreich et al., 1981). The dominant removal mechanism for thiram in the vapor phase appears to be reaction with photochemically generated hydroxyl radicals. The half-life for this reaction has been estimated to be 71 minutes (Atkinson, 1985; 1987). Dry deposition may be a significant route of removal for particulate-phase thiram. Because of its ability to absorb sunlight, direct photolysis is also a potential removal process for both vapor- and particulate-phase thiram. If released to water or soil, thiram is expected to decompose by chemical and microbial action to dimethyldithiocarbamate (Munnecke and Mickal, 1967; Richardson, 1954; Shirkot and Gupta, 1985; Kluge, 1969a,b; Rajagopal et al., 1984). Under acidic conditions, chemical processes should dominate. Under anaerobic conditions, thiram has been found to biodegrade to dimethylamine, carbon disulfide and hydrogen sulfide (Williams, 1977). Volatilization from water or soil surfaces is not expected to be an important fate process. This compound should adsorb moderately to suspended solids and sediments in water. In general, thiram is expected to have low mobility in soil, although potential exists for
movement through some soils (Rajagopal et al., 1984; Helling et al., 1974; Reinbold et al., 1979). The half-life of thiram in soil has been found to vary from <1 day to >32 weeks, with the rate of degradation depending upon such variables as pH, humus content and initial concentration of the compound (Shirkot and Gupta, 1985; Griffith and Matthews, 1969; Chinn, 1973; Richardson, 1954; Kluge, 1969a).

Pertinent data regarding human exposure to thiram were extremely limited. The U.S. EPA STORET data base contained no data regarding the detection of thiram in water, aquatic biota or sediment samples. Because thiram is used as a fungicide in fruit plants, it was analyzed for but not found in samples of sweet cherries and peaches grown domestically in Ontario, Canada, between 1983 and 1984. The detection limit for thiram in this study was 0.01 mg/kg (Frank et al., 1987).

The 96-hour TL_{50} of thiram in fingerling channel catfish was reported as 0.79 mg/l (McKee and Wolf, 1963). The 26-hour LD_{50} of thiram to Daphnia magna was 1.3 ppm (Frear and Boyd, 1967). The 48-hour LC_{50} of thiram to Tubifex tubifex was 0.67 mg/l (Voronkin and Loshakov, 1973). Tooby et al. (1975) reported a 96-hour LC_{50} of 0.007 mg/l (based on concentration of product) for harlequin fish, Rasbora heteromorpha, exposed to a thiram-containing product with 80% active ingredient under flowthrough conditions. Tooby et al. (1975) estimated a 3-month LC_{50} of 0.001 mg/l from an extrapolation of the acute test results.

Schneider (1979) reported 96-hour LC_{50}s of 0.13 and 0.4 ppm for rainbow trout, Salmo gairdneri, exposed to solutions of thiram (99 and 75% active ingredient, respectively). Exposure of bluegill sunfish, Lepomis macrochirus, to thiram (99 and 75% active ingredient) generated 96-hour LC_{50}s of 0.045 and 0.28 ppm, respectively. The 96-hour LC_{50}s (based on
active ingredients) for two products each containing an 80% level of thiram but 20% levels of dissimilar inactive ingredients to the freshwater mollusc, Lymnaea stagnalis, were 12 and 8.9 ppm for products A and B, respectively, in aqueous solutions (Bluzat et al., 1981). The 96-hour LC$_{50}$s for acetone suspensions of products A and B were 2.8 and 3.2 ppm, respectively.

Exposure of scud, Gammarus pulex, to 10, 5, 2 and 1 ppm of a commercial product containing 80% thiram resulted in 95, 79, 48 and 25% mortality after 10 days (Bluzat et al., 1982a). Groups of scud (n=130 and 190) exposed to 0.7 ppm aqueous suspensions of thiram 1, 48 and 96 hours after preparation of the test solutions experienced 84.6, 91.5 and 50% mortality levels, respectively, after 96 hours of treatment. The 96-hour LC$_{50}$s for two commercial thiram-containing products (80% active ingredient) to G. pulex were 0.20 ppm and 0.13 ppm for products A and B, respectively, in aqueous solutions (Bluzat et al., 1982b). The 96-hour LC$_{50}$s for products A and B in acetone were 0.22 and 0.06 ppm, respectively. The approximate median lethal times for G. pulex exposed to 0.02, 0.025, 0.035, 0.05 and 0.08 ppm solutions of thiram were 30, 8.5, 6.5, 4.5 and 5 days, respectively (Bluzat and Seuge, 1983). Scud offered bean seeds treated with 3000 and 10,000 ppm thiram demonstrated 90% survival after 3-3.5 days and 10% survival after 29-36 days. Scud offered mussels treated with 50-10,000 ppm thiram demonstrated 90% survival after 2.4-5.4 days and 10% survival after 9-27 days.

The 96-hour LC$_{50}$s for the flatworm, Dugesia gonocephala, the isopod, Asellus aquaticus, and the amphibian, Xenopus laevis, at two stages of development (47 and 53) were 0.048, 61, 0.013 and 0.021 ppm, respectively (Seuge et al., 1983). The 96-hour LC$_{50}$ for mayfly larvae, Cloeon dipterum, exposed to freshly prepared solutions of thiram was 1.01 mg/L.
Solutions of thiram aged for 1, 7 and 36 hours produced mortality levels among mayfly larvae of 79.5, 64.7 and 45.3%, respectively, after 96 hours of exposure (Seuge and Bluzat, 1983).

The respective EC₅₀, EC₅₀ and EC₁₀₀ for Daphnia magna exposed to tetrathiomethane disulfide were 0.05, 0.06 and 0.8 µg/l (Knie et al., 1983). Jouany et al. (1985) reported 0% mortality for the water flea, Daphnia magna, carp, Cyprinus carpio, and zebrafish, Brachydanio rerio, exposed to <0.1, 1.0 and 0.1 mg/l after 24 hours. Zebrafish fed thiram-contaminated daphnids experienced a linear increase in mortality from 0-100% between 4 and 8 days after the initiation of the experiment. The 96- and 48-hour LC₅₀'s for guppies, Poecilia reticulata, and daphnids, Daphnia magna, exposed to thiram were 0.27 and 0.21 mg/l, respectively (Van Leeuwen et al., 1985a). The 24-hour LC₅₀ of thiram (>98% purity) to rainbow trout, Salmo gairdneri, weighing 34.0 g was 0.26 mg/l. The 24-hour LC₅₀ for trout weighing ~47 g was 0.30 mg/l (Van Leeuwen et al., 1986a). Exposure of trout to thiram also resulted in significant changes in several blood parameters.

The 21-day LC₅₀ for thiram in the water flea, Daphnia magna, was 8 µg/l (Van Leeuwen et al., 1985b). The lowest tested concentration that resulted in a decrease in fecundity was 10 µg/l. The lowest tested concentration that resulted in a decrease in size of daphnids after 21 days was 1.8 µg/l. There were no significant effects on daphnids exposed to 1 µg/l of thiram over the 21-day study.

The 60-day LC₅₀ for embryolarval stages of rainbow trout, Salmo gairdneri, exposed to thiram was 1.1 µg/l (Van Leeuwen et al., 1986b). The 60-day EC₅₀ based on mortality and teratogenesis was 0.64 µg/l.
The lowest concentrations at which there were no observable effects based on mortality, total embryotoxicity, length and weight were 1.0, \( \leq 0.32 \), \( \leq 0.32 \) and 0.56 \( \mu g/L \), respectively. Exposure of juvenile rainbow trout to thiram for 21 days resulted in a concentration-related loss of glycogen in the liver at \( \geq 25 \) \( \mu g/L \) and was associated with reduced body weight gain. At 100 \( \mu g/L \), thiram induced a proliferation of bile duct epithelial cells both with and without formation of new ductules. Cell necrosis was observed occasionally, and hemorrhages were apparent in the brain and spinal cord at 5 \( \mu g/L \) (Van Leeuwen et al., 1986c). Thiram is not expected to bioaccumulate significantly in aquatic organisms based on an estimated BCF value of 90.8.

Motility and topophototaxis of Euglena gracilis were inhibited to 50% of control organisms within 30 minutes of exposure to \( 10^{-4} \) M solutions of tetramethythiuram disulfide (Diehn and Tollin, 1967). Cultures of the green alga, Scenedesmus acutus, exposed to 10 and 100 ppm tetramethythiuram disulfide were dead after 1 and 3 days, respectively. The NOEL appears to be \( < 0.5 \) ppm. Gangawane and Kulkarni (1979) reported a 25.4% reduction in growth for cultures of Nostoc sp. exposed to 500 ppm thiram and a 14.1% reduction in growth for cultures of Tolypothrix sp. exposed to 100 ppm thiram. Hutber et al. (1979) reported that growth of four species of blue-green algae, Aphanocapsa (strains 6308 and 6714), Anabaena variabilis and Nostoc, was reduced by 50% on exposure to 50, 100, 50 and 100 ppm thiram, respectively. The concentrations of thiram that inhibited growth completely were 100, \( > 100 \), 100 and \( > 100 \) ppm, respectively.

The minimal active dose of thiram required to produce reductions in the number of generations of the ciliate protozoan, Colpidium campylum, was 0.3 mg/L (Dive et al., 1980). The 24-hour IC\(_{50}\) for Chlorella vulgaris based
on ATP levels was >2 ppm thiram (Vasseur et al., 1982). Knie et al. (1983) reported an EC<sub>10</sub> of >6 mg/\text{L} for the alga, *Haematococcus pluvialis*, exposed to tetramethylthiuram disulfide. Growth rates of the ciliates, *Tetrahymena thermophila* and *Tetrahymena pyriformis* strains, were inhibited completely at 1.0 mg/\text{L} thiram for all but one strain at 28°C (Dive et al., 1984). Growth inhibition of amoebae exposed to thiram was achieved at concentrations ranging from 0.5-16 mg/\text{L}. Thiram at concentrations ranging from 0.25-1.0 mg/\text{L} induced a lengthening of the generation time in heat shock synchronized axenic cultures of *Tetrahymena pyriformis* (Grolliere and Dupy-Blanc, 1985).

The 72-hour IC<sub>50</sub> for growth of the green alga, *Chlorella vulgaris*, exposed to thiram as determined by optical density at 665 nm was ~5.5 mg/\text{L} (Jouany et al., 1985). The 96-hour EC<sub>50</sub>s for the average specific growth rate and effects on the time-lag until maximum population growth in *Chlorella pyrenoidosa* were 1.0 and 0.03 mg/\text{L}, respectively (Van Leeuwen et al., 1985a). The EC<sub>50</sub> for assimilation of radioactive bicarbonate by *C. pyrenoidosa* was 4.0 mg/\text{L}. The EC<sub>50</sub> for respiration of 14C by *C. pyrenoidosa* was >10.0 mg/\text{L}.

Growth of a chrysomonad was inhibited completely following exposure to 210 μM thiram. Growth of the ciliate, *Cyclidium* sp., was inhibited completely at ~180 μM thiram (Taylor and Pace, 1987). Growth of a chlorophyte, *Dunaliella tertiolecta*, was inhibited at 4 μM thiram after 7 days. Growth of five other phytoplankton species was inhibited from ~0.2-18.6% of controls by exposure to 4 μM thiram for 7 days. The 15-minute EC<sub>50</sub> value for *Photobacterium phosphoreum* exposed to thiram was 0.1 mg/\text{L} (Van Leeuwen et al., 1985a). The lowest effective concentration or minimum inhibiting concentration of thiram on the nitrification process of a mixed culture of *Nitrosomonas* and *Nitrobacter* after 3 hours was 18 mg/\text{L}.  

1x
The oral LD$_{50}$s for thiram in mallard ducks, *Anas platyrhynchos*, and ring-necked pheasants, *Phasianus colchicus*, were >2800 and 673, respectively (Tucker and Crabtree, 1970). Egberts et al. (1972) reported no statistically significant effects in Japanese quail, *Coturnix coturnix*, offered feed contaminated with 10 ppm thiram for 11 weeks. Birds fed 50 ppm contaminated feed demonstrated significant reductions in numbers of eggs laid and hatched and shell thickness of eggs. There were also significant reductions in the numbers of lymphocytes, granulocytes, and monocytes of blood from birds dosed with 50 ppm thiram-contaminated feed. Heath et al. (1972) reported a lack of mortality among Japanese quail, *C. coturnix japonica*, and pheasant, *P. colchicus*, fed the highest concentration of thiram tested (5000 ppm in feed). Mallard ducks, *Anas platyrhynchos*, fed mash containing 5000 ppm thiram had 20% mortality.

Lorgue et al. (1975) reported that thiram-contaminated feed (20 gc Thiran/10 kg) caused immediate (24 hours) blockage of egg laying in quail and regression of secondary sexual characteristics in males. Lorgue and Soyez (1976) reported that thiram completely inhibited egg laying by gray partridges exposed to 1.6 g/kg within 48 hours. The incidence of embryonic mortality was increased significantly at 4-fold lower doses. The LD$_{50}$ and LC$_{50}$ of thiram to Japanese quail, *C. coturnix japonica*, were 695 and >10,000 mg/kg, respectively (Gruen et al., 1982). Hadhazy and Glavits (1982) reported that 100 and 200 g thiram/100 kg feed caused imperfect egg shell calcification and production of eggs with abnormal size and form in pheasants.

Earthworms, *Eisenia foetida* exposed to thiram by immersion had mortality levels ranging from 5% seven days posttreatment, to 38% one hundred and one days posttreatment (Roark and Dale, 1979). Worms fed thiram-treated bermudagrass clippings had mortality levels ranging from 10% after 34 days
of treatment to 42% after 101 days. Mortality among worms reared in thiram-treated soil ranged from 21% after 10 days to 98.1% after 29 days and 99.9% after 52 days. The ALD of thiram to wild-trapped deer mice, *Peromyscus maniculatus*, was reported to be 1600 mg/kg (Schafer and Bowles, 1985).

Although specific quantitative data concerning the pharmacokinetics of thiram are limited, ACGIH (1986) stated (without providing documentation) that following absorption, thiram is widely distributed, and is predominantly excreted unchanged in the urine and feces. Rannug and Rannug (1984) stated that thiram and other disulfides have a tendency to participate in redox-reactions. Thiram is reduced by glutathione to dimethyldithiocarbamate, and it may also interact with SH-groups of proteins, which may result in the inhibition of a number of enzymes. Dalvi and Deoras (1986) reported a dose-related increase in the amount of carbon disulfide exhaled following treatment of rats with an intraperitoneal injection of thiram.

Data regarding the toxicity of thiram following inhalation exposure of animals were not located. Sivitiskaya (1974, summarized by Fishbein, 1976) reported opthalmologic changes in persons occupationally exposed to thiram. Exposure concentrations were not reported.

The most notable effect observed in animals following chronic oral exposure to thiram is ataxia and hind leg paralysis observed in rats fed thiram in the diet at $\geq$300 ppm (E.I. Du Pont de Nemours and Co., n.d.; Lee and Peters, 1976). Neurotoxic effects following exposure to thiram may result from the production of carbon disulfide. Thuranszky et al. (1982) found similar effects on the nervous system when rats were treated with a single oral dose of thiram or carbon disulfide.
Dietary treatment of animals with thiram has consistently resulted in decreased food intake and body weight gain. The study by Lowy et al. (1980), which found that body weight gain in thiram treated rats was below pair-fed controls, indicates that the effect on body weight is a result of thiram treatment rather than just a result of decreased food intake. The lowest dietary concentration of thiram resulting in decreased body weight gain in rats was 100 ppm (Lee et al., 1978). A study using mink and ferrets (Hornshaw et al., 1987) did not clearly identify levels resulting in changes in body weight because of the small numbers of animals used, and because of the high variability of body weight of the animals used in the study.

Thiram is an inhibitor of microsomal monoxygenases including aldehyde dehydrogenase and dopamine β-dehydrogenase. Combined exposure to thiram and ethanol has been shown to result in the accumulation of acetaldehyde (Garcia de Torres et al., 1983). Interactions between thiram and prometazine, meprobamate and trihexyphenidyl have also been reported (Fenyvesi et al., 1985). Oral carcinogenicity studies of thiram using rats (Lee et al., 1978; Takahashi et al., 1983; Lijinsky, 1984) and a limited carcinogenicity study using mice (BRL, 1968a) have not found a carcinogenic effect. Lijinsky (1984) found that simultaneous oral treatment of rats with thiram and sodium nitrite significantly increased nasal cavity and forestomach tumors. This effect probably was due to the in vivo formation of N-nitrosodimethylamine.

Mutagenicity studies of thiram have yielded mixed results, with numerous positive and negative studies available. Rannug and Rannug (1984) proposed that mutagenicity induced by thiram may result from the inhibition of enzymes that are involved in protecting against harmful oxygen species.
Oral teratogenicity studies using hamsters (Robens, 1969), mice (Roll, 1971; Matthiaschek, 1973; Short et al., 1976) and rats (Short et al., 1976) have reported an increased incidence of resorptions and malformations observed prenatally and reduced viability and growth, postnatally. In some instances, the findings were observed in the presence of maternal toxicity.

Oral studies concerning the effects of thiram on reproduction in rats (Short et al., 1976) indicate that at 132 mg/kg/day the 30% of the males who survived, failed to inseminate females and some exhibited testicular lesions. This dose also caused mortality. A dose of 30 mg/kg/day given to females reduced the number of implants/dam. Treatment at 96 mg/kg/day resulted in only 1 of the 15 female survivors to mate successfully. A cross-fostering experiment (Short et al., 1976), which found reduced survival of offspring from untreated dams placed with treated dams indicates that developing rats are still sensitive to thiram postnatally. Results of a reproductive study using mink and ferrets (Hornshaw et al., 1987) indicates that ferrets may be more sensitive than mink or rats to the reproductive effects of thiram; 0/12 female ferrets produced litters at a dose of 7 mg/kg/day.

Thiram was assigned to EPA group D: not classifiable as to human carcinogenicity. An RfD for subchronic and chronic oral exposure of 0.006 mg/kg/day was derived from the NOAEL for reproductive effects in female ferrets of 0.61 mg/kg/day in the study by Hornshaw et al. (1987). The verified oral RfD of 0.005 (U.S. EPA, 1987c) is based on an unpublished 2-year study in rats (E.I. Dupont de Nemours & Co. Inc., n.d.) derived from the NOEL of 5 mg/kg/day for weakness, atoxia, varying degrees of hind limb paralysis, and calcified masses in the basal gonglia and in the cerebellum.
Both RfDs are well below the boundary line for adverse effects when the available data are plotted in dose/duration-effect graphs. In addition, exposure to 2.1 mg/kg/day produced a decrease in the number of offspring/litter and in offspring body weights. In the adult animals, there was an increase in splenic weight at 2.1 and 7 mg/kg/day and a decrease in RBCs, hemoglobin and hematocrit at 7 mg/kg/day.

Freshwater criteria calculated for aquatic toxicity were a Final Acute Value of 20.4 μg/l, a Final Chronic Value of 0.0256 μg/l and a Final Acute-Chronic Ratio of 797.91. The Final Plant Value was estimated at 0.03 mg/l. Data were not sufficient for estimating saltwater criteria.

An RQ of 100 pounds was derived for chronic toxicity based on reproductive effects in female ferrets (Hornshaw et al., 1987). Data were not sufficient for derivation of a cancer-based RQ.
# TABLE OF CONTENTS

1. INTRODUCTION .................................................. 1
   1.1. STRUCTURE AND CAS NUMBER .......................... 1
   1.2. PHYSICAL AND CHEMICAL PROPERTIES ............... 1
   1.3. PRODUCTION DATA ........................................ 2
   1.4. USE DATA .................................................. 2
   1.5. SUMMARY .................................................. 3

2. ENVIRONMENTAL FATE AND TRANSPORT ..................... 4
   2.1. AIR ....................................................... 4
      2.1.1. Reaction with Hydroxyl Radicals .............. 4
      2.1.2. Reaction with Ozone .............................. 4
      2.1.3. Photolysis ......................................... 4
      2.1.4. Physical Removal Processes ................... 4
   2.2. WATER ................................................... 5
      2.2.1. Chemical Degradation ............................ 5
      2.2.2. Microbial Degradation ......................... 5
      2.2.3. Volatilization .................................... 5
      2.2.4. Adsorption ........................................ 5
   2.3. SOIL ..................................................... 6
      2.3.1. Chemical Degradation ............................ 6
      2.3.2. Volatilization .................................... 6
      2.3.3. Adsorption ........................................ 6
      2.3.4. Persistence ....................................... 6
   2.4. SUMMARY .................................................. 8

3. EXPOSURE ..................................................... 10

4. ENVIRONMENTAL TOXICOLOGY .................................. 11
   4.1. AQUATIC TOXICOLOGY .................................. 11
      4.1.1. Acute Toxic Effects on Fauna .................. 11
      4.1.2. Chronic Effects on Fauna ....................... 16
      4.1.3. Effects on Flora ................................ 18
      4.1.4. Effects on Bacteria ............................ 22
   4.2. TERRESTRIAL TOXICOLOGY .............................. 23
      4.2.1. Effects on Fauna ................................ 23
      4.2.2. Effects on Flora ................................ 25

xv
# Table of Contents (cont.)

4.3. **FIELD STUDIES** ........................................... 25
4.4. **AQUATIC RISK ASSESSMENT** .......................... 25
4.5. **SUMMARY** .................................................. 30

5. **PHARMACOKINETICS** ....................................... 36
   5.1. **ABSORPTION** ........................................... 36
   5.2. **DISTRIBUTION** ......................................... 36
   5.3. **METABOLISM** ........................................... 36
   5.4. **EXCRETION** ............................................. 38
   5.5. **SUMMARY** ............................................... 38

6. **EFFECTS** .................................................... 39
   6.1. **SYSTEMIC TOXICITY** .................................. 39
       6.1.1. Inhalation Exposure ............................... 39
       6.1.2. Oral Exposure ...................................... 39
       6.1.3. Other Relevant Information .................... 45
   6.2. **CARCINOGENICITY** .................................... 48
       6.2.1. Inhalation .......................................... 48
       6.2.2. Oral .................................................. 48
       6.2.3. Other Relevant Information .................... 50
   6.3. **MUTAGENICITY** ........................................ 50
   6.4. **TERATOGENICITY** ..................................... 54
   6.5. **OTHER REPRODUCTIVE EFFECTS** .................... 58
   6.6. **SUMMARY** ............................................... 61

7. **EXISTING GUIDELINES AND STANDARDS** .................. 64
   7.1. **HUMAN** ................................................. 64
   7.2. **AQUATIC** ............................................... 64

8. **RISK ASSESSMENT** .......................................... 65
   8.1. **CARCINOGENICITY** .................................... 65
       8.1.1. Inhalation .......................................... 65
       8.1.2. Oral .................................................. 65
       8.1.3. Other Routes ....................................... 66
       8.1.4. Weight of Evidence ............................... 66
       8.1.5. Quantitative Risk Estimates .................... 66
   8.2. **SYSTEMIC TOXICITY** .................................. 66
       8.2.1. Inhalation Exposure ............................... 66
       8.2.2. Oral Exposure ...................................... 67
**TABLE OF CONTENTS (cont.)**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. REPORTABLE QUANTITIES</td>
<td>75</td>
</tr>
<tr>
<td>9.1. BASED ON SYSTEMIC TOXICITY</td>
<td>75</td>
</tr>
<tr>
<td>9.2. BASED ON CARCINOGENICITY</td>
<td>81</td>
</tr>
<tr>
<td>10. REFERENCES</td>
<td>82</td>
</tr>
<tr>
<td>APPENDIX A: LITERATURE SEARCHED</td>
<td>102</td>
</tr>
<tr>
<td>APPENDIX B: SUMMARY TABLE FOR THIRAM</td>
<td>105</td>
</tr>
<tr>
<td>APPENDIX C: DOSE/DURATION RESPONSE GRAPH(S) FOR EXPOSURE TO THIRAM</td>
<td>106</td>
</tr>
<tr>
<td>No.</td>
<td>Title</td>
</tr>
<tr>
<td>-----</td>
<td>------------------------------------------------------------</td>
</tr>
<tr>
<td>6-1</td>
<td>Acute Toxicity of Thiram.</td>
</tr>
<tr>
<td>6-2</td>
<td>Mutagenicity and Genotoxicity Testing of Thiram</td>
</tr>
<tr>
<td>9-1</td>
<td>Toxicity Summary for Oral Exposure to Thiram</td>
</tr>
<tr>
<td>9-2</td>
<td>Composite Scores for Oral Exposure to Thiram</td>
</tr>
<tr>
<td>9-3</td>
<td>Minimum Effective Dose (MED) and Reportable Quantity (RQ)</td>
</tr>
<tr>
<td>No.</td>
<td>Title</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------------------------------------------------------</td>
</tr>
<tr>
<td>2-1</td>
<td>Degradation Pathways of Thiram and Ziram in Soil and in Microbial</td>
</tr>
<tr>
<td></td>
<td>Cultures</td>
</tr>
<tr>
<td>4-1</td>
<td>Organization Chart for Listing GMAVs, GMCVs and BCFs Required to</td>
</tr>
<tr>
<td></td>
<td>Derive Numerical Water Quality Criteria by the Method of U.S. EPA/</td>
</tr>
<tr>
<td></td>
<td>OWRS (1986) for the Protection of Freshwater Aquatic Life from</td>
</tr>
<tr>
<td></td>
<td>Exposure to Thiram</td>
</tr>
<tr>
<td>4-2</td>
<td>Example Computer Program in BASIC Language for Calculating the</td>
</tr>
<tr>
<td></td>
<td>Final Acute Value</td>
</tr>
<tr>
<td>4-3</td>
<td>Summary Chart for Data Required to Generate Criteria by the</td>
</tr>
<tr>
<td></td>
<td>Method of U.S. EPA/OWRS (1986) for Safe Levels of Thiram in</td>
</tr>
<tr>
<td></td>
<td>Aquatic Environments</td>
</tr>
<tr>
<td>5-1</td>
<td>Two-Step Reduction of Thiram to Dimethyldithiocarbamate Ion</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>AEL</td>
<td>Adverse effect level</td>
</tr>
<tr>
<td>ALD</td>
<td>Approximate lethal dose</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine 5'-triphosphate</td>
</tr>
<tr>
<td>BCF</td>
<td>Bioconcentration factor</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood urea nitrogen</td>
</tr>
<tr>
<td>CAS</td>
<td>Chemical Abstract Service</td>
</tr>
<tr>
<td>CHO</td>
<td>Chinese hamster ovary</td>
</tr>
<tr>
<td>CMC</td>
<td>Carboxymethyl cellulose</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CS</td>
<td>Composite score</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>EC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Concentration effective to 50% of recipients (and all other subscripted concentration levels)</td>
</tr>
<tr>
<td>FEL</td>
<td>Frank effect level</td>
</tr>
<tr>
<td>GMAV</td>
<td>Genus mean acute values</td>
</tr>
<tr>
<td>GMCV</td>
<td>Genus mean chronic values</td>
</tr>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Median inhibition concentration</td>
</tr>
<tr>
<td>K&lt;sub&gt;oc&lt;/sub&gt;</td>
<td>Soil sorption coefficient</td>
</tr>
<tr>
<td>K&lt;sub&gt;ow&lt;/sub&gt;</td>
<td>Octanol/water partition coefficient</td>
</tr>
<tr>
<td>LC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Concentration lethal to 50% of recipients (and all other subscripted dose levels)</td>
</tr>
<tr>
<td>LEL</td>
<td>Lowest effect level</td>
</tr>
<tr>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Dose lethal to 50% of recipients (and all other subscripted dose levels)</td>
</tr>
<tr>
<td>LOAEL</td>
<td>Lowest-observed-adverse-effect level</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>MED</td>
<td>Minimum effective dose</td>
</tr>
<tr>
<td>MPI</td>
<td>Maximum permissible intake</td>
</tr>
<tr>
<td>MTD</td>
<td>Maximum tolerated dose</td>
</tr>
<tr>
<td>NADP</td>
<td>Nicotinamide adenine dinucleotide</td>
</tr>
<tr>
<td>NOAEL</td>
<td>No-observed-adverse-effect level</td>
</tr>
<tr>
<td>NOEL</td>
<td>No-observed-effect level</td>
</tr>
<tr>
<td>PCV</td>
<td>Packed cell volume</td>
</tr>
<tr>
<td>PEL</td>
<td>Permissible exposure level</td>
</tr>
<tr>
<td>PNS</td>
<td>Peripheral nervous system</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cell cholinesterase</td>
</tr>
<tr>
<td>RfD</td>
<td>Reference dose</td>
</tr>
<tr>
<td>RQ</td>
<td>Reportable quantity</td>
</tr>
<tr>
<td>RV&lt;sub&gt;d&lt;/sub&gt;</td>
<td>Dose-rating value</td>
</tr>
<tr>
<td>RV&lt;sub&gt;e&lt;/sub&gt;</td>
<td>Effect-rating value</td>
</tr>
<tr>
<td>SGOT</td>
<td>Serum glutamic oxaloactic transaminase</td>
</tr>
<tr>
<td>SGPT</td>
<td>Serum glutamic pyruvic transaminase</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin-layer chromatography</td>
</tr>
<tr>
<td>TL&lt;sub&gt;m&lt;/sub&gt;</td>
<td>Median tolerance limit</td>
</tr>
<tr>
<td>TLV</td>
<td>Threshold limit value</td>
</tr>
<tr>
<td>TWA</td>
<td>Time-weighted average</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
</tbody>
</table>
1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Thiram is currently referred to by CAS as thioperoxydicarboxonic diamide, tetramethyl (SANSS, 1988). This compound is also known as bis(dimethylthiocarbamyl)disulfide, tetramethylthiuram disulfide, thiuram and TMTD (Hawley, 1981). Trade names for this compound include Arasan, Fernide, Fernasan, Pomarsol, Thianosan, AAPiro1 AAttack, Hexathir, Mercuram, Pomarsol forte, Chipco Thiram 75, Polyram-Ultra, Thiramad, Tripomol, Tuads, Tersan 75, Thylate, Vancide-TM and Vancide TM-95 (SANSS, 1988; Hartley and Kidd, 1983; SRI, 1987; Meister, 1988)). The structure, CAS Registry number, empirical formula and molecular weight of this compound are as follows:

\[
\begin{align*}
\text{CH}_3 & \quad \text{S} \quad \text{S} \quad \text{CH}_3 \\
\text{N-C-S-S-C-N} & \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

Molecular weight: 240.42

Empirical formula: C\(_{6}\)H\(_{12}\)N\(_2\)S\(_4\)

CAS Registry number: 137-26-8

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Thiram is a white crystalline solid at room temperature, with a characteristic odor (Hawley, 1981). It is soluble in water, benzene, chloroform and carbon disulfide, and insoluble in dilute alkali and aliphatic hydrocarbons (IARC, 1976). Selected physical and chemical properties are as follows:

Melting point: 155-156\(^\circ\)C
146\(^\circ\)C (commercial grade) Windholz, 1983

Boiling point: 129\(^\circ\)C (20 mm Hg) IARC, 1976
Water solubility: 30 mg/l (room temperature)  Worthing and Walker, 1983
Log $K_{ow}$: not available
Vapor pressure: <7.5x10^{-6} mm Hg (20°C)  Hartley and Kidd, 1983
Density: 1.29 g/cm³ (20°C)  Worthing and Walker, 1983

Chemically, thiram will be oxidized by strong oxidizing agents and will decompose in the presence of strong acids (HSDB, 1988).

1.3. PRODUCTION DATA

Thiram is believed to be produced commercially in the United States by passing chlorine gas through a solution of sodium dimethylthiocarbamate (IARC, 1976). It is manufactured in the United States by UCB Chemicals Corp., in Bucks, AL, and Goodyear Tire and Rubber in Akron, OH (SRI, 1987; USITC, 1987). During 1982, consumption of thiram in the United States was a minimum of 2.29 million pounds (HSDB, 1988).

1.4. USE DATA

According to IARC (1976), ~97% of the thiram consumed in the United States is used as a primary and secondary accelerator in compounding natural, isobutylene-isoprene, butadiene, styrene-butadiene, synthetic isoprene and nitrile-butadiene rubbers. Thiram renders low sulfur and sulfurless stock less heat-resistant, is non-discoloring and nonstaining, and is an excellent activator of guanidines, amines and thiazoles. Thiram is also used as a cure retarder for Neoprene G rubbers (IARC, 1976). Other applications include use as a fungicide (on seeds, fruits, nuts, vegetables and ornamental crops, and on paper, polyurethane foam and textiles), animal repellent, bacteriostat in soap and antiseptic sprays, anti-oxidant in polyolefin plastics, and peptizing agent in polysulphide elastomers (IARC, 1976).
1.5. SUMMARY

Thiram (137-26-8) is a white crystalline solid at room temperature (Hawley, 1981). It is insoluble in water but soluble in benzene, chloroform and carbon disulfide. Thiram is manufactured by UCB Chemicals Corp. in Bucks, AL, and Goodyear Tire and Rubber in Akron, OH (SRI, 1987; USITC, 1987). During 1982, a minimum of 2.29 million pounds of thiram was consumed in the United States (HSDB, 1988); ~97% of the thiram consumed in the United States is used as a rubber accelerator (IARC, 1976).
2. ENVIRONMENTAL FATE AND TRANSPORT

Limited experimental data regarding the environmental fate and transport of thiram were located in the available literature. Therefore, predictions concerning environmental fate and transport of this compound were based on theoretical calculations using physical properties or molecular structure.

2.1. AIR

It can be assumed from its vapor pressure of \( <7.5 \times 10^{-6} \text{ mm Hg at 20}\degree \text{C} \) (Hartley and Kidd, 1983) that thiram would exist mostly in the particulate form and partly in the vapor form in the atmosphere (Eisenreich et al., 1981).

2.1.1. Reaction with Hydroxyl Radicals. Using the method of Atkinson (1987), the rate constant for the reaction of thiram vapor with photochemically generated hydroxyl radicals in the atmosphere is estimated to be \( 3.23 \times 10^{-10} \text{ cm}^3/\text{molecule-sec at 25}\degree \text{C} \). Assuming an average ambient hydroxyl radical concentration of \( 5.0 \times 10^5 \text{ molecules/cm}^3 \) (Atkinson, 1985), the hydroxyl reaction half-life is estimated to be 71 minutes.

2.1.2. Reaction with Ozone. Thiram is not expected to be susceptible to reaction with ozone molecules in the atmosphere (U.S. EPA, 1987a).

2.1.3. Photolysis. At a concentration of 100 mg/l in methanol, thiram has been found to absorb UV light in the environmentally significant range (wavelengths >290 nm) (Gore et al., 1971). This suggests that thiram may be susceptible to direct photolysis in the atmosphere, although no data regarding the rate of this reaction are available in the literature.

2.1.4. Physical Removal Processes. Dry deposition may be a route of removal for particulate-phase thiram in the atmosphere.
2.2. WATER

2.2.1. Chemical Degradation. Thiram is reported to decompose in acidic media (Hartley and Kidd, 1983; Worthing and Walker, 1983). This information, as well as data pertaining to the persistence of thiram in soil, suggests that chemical processes such as hydrolysis in acidic medium will contribute to the decomposition of thiram in natural waters. Since thiram absorbs light in the environmentally significant region (>290 nm) (HSDB, 1988), it has the potential to undergo direct photolysis in surface waters when exposed to sunlight. Rate data that would permit estimation of half-lives for hydrolysis and photolysis are not available in the literature.

2.2.2. Microbial Degradation. Results of a study using the Japanese MITI test protocol indicate that thiram is resistant to biodegradation under aerobic conditions; <30% degradation was observed when 100 ppm thiram was incubated with 30 ppm activated sludge for 2 weeks (Sasaki, 1978; Kawasaki, 1980). Degradation of thiram to dimethylamine, carbon disulfide and hydrogen sulfide by ruminal microorganisms indicates that thiram may be susceptible to biodegradation under anaerobic conditions in the environment (Williams, 1977).

2.2.3. Volatilization. Henry's Law constant for thiram has been estimated to be $<7.9 \times 10^{-9}$ atm-m$^2$/mol based on a water solubility of 30 mg/L at room temperature and a vapor pressure of $<7.5 \times 10^{-6}$ mm Hg at 20°C. This value for Henry's Law constant suggests that volatilization from water surfaces would not be a significant fate process (Thomas, 1982).

2.2.4. Adsorption. A soil adsorption coefficient of 672 was estimated for thiram using the following regression equation (Lyman, 1982): $\log K_{oc} = -0.55 \log S + 3.64$. Based on this $K_{oc}$ value, thiram is expected to adsorb moderately to suspended solids and sediments in water.
2.3. SOIL

2.3.1. Chemical Degradation. It appears that the chemical decomposition of thiram in aerobic soil may be a significant process (Kluge, 1969a). Because of its ability to absorb light of wavelength >290 nm (HSDB, 1988), direct photolysis on soil surfaces is a potential loss process.

2.3.2. Volatilization. Moderate adsorption of thiram to soil and a relatively low value for Henry’s Law constant (<7.9x10^-8 atm-m^3/mol at 20-25°C) suggest that volatilization from moist soil surfaces would not be a significant fate process. The low vapor pressure of thiram suggests that volatilization from dry soil surfaces also would be insignificant.

2.3.3. Adsorption. Thiram has been found to be immobile in a black clay and a red sandy loam soil, but was more mobile in peat moss and particularly in loamy sand soil (Rajagopal et al., 1984). These observations are in agreement with an estimated K_{oc} value of 672, which indicates low mobility in soil. Helling et al. (1974) employed bioassay methods in combination with soil TLC to study the mobility of thiram in silty clay loam. The overall mean Rf value for this compound was determined to be 0.73, which indicates moderate mobility in this soil (Reinbold et al., 1979). These data indicate that in general thiram has low mobility in soil, although it may show moderate mobility in certain soils.

2.3.4. Persistence. It appears that thiram is degraded in soil by both biotic and abiotic mechanisms, with the rate of degradation depending on such variables as pH, soil type (humus content) and concentration of thiram (Munnecke and Mickail, 1967; Richardson, 1954; Shirkot and Gupta, 1985; Kluge, 1969a,b; Rajagopal et al., 1984). Thiram added to alluvial sandy loam at an initial concentration of 300 ppm underwent 16% degradation in autoclaved soil and 25% in nonautoclaved soil in 24 hours (Shirkot and
Gupta, 1985). In autoclaved and nonautoclaved alluvial sandy loam inoculated with *Pseudomonas aeruginosa*, thiram at an initial concentration of 300 ppm had a half-life of 8 days and underwent 90% degradation in 24 days (Shirkot and Gupta, 1985). At an initial concentration of 125 ppm, thiram had a half-life of 1 day when distributed evenly throughout a soil (45% moisture content) (Griffith and Matthews, 1969). In contrast, the same amount of thiram added to the soil in the form of a dressing on the surface of 0.7 mm glass beads was much more persistent, undergoing only about 10% degradation in 21 days (Griffith and Matthews, 1969). In a study by Chinn (1973), the persistence of thiram in loam soil was measured quantitatively using a method that incorporated some features of the cylinder-plate technique used for assaying antibiotics. Thiram was applied to loam soil at concentrations of 100 and 1000 ppm. Results showed that thiram at 100 ppm had a half-life of ~1 week, while at 1000 ppm it persisted longer than 32 weeks. It seems probable that thiram at 1000 ppm killed many of the soil microflora that are responsible for degradation of fungicides (Chinn, 1973).

In other studies, thiram added to sandy soil at concentrations of 100 and 200 ppm had a half-life of <2 days; at a concentration of 50 ppm, the half-life ranged between <2 days to ~7 days, and when added to greenhouse compost soil at a concentration of 50 ppm, thiram had a half-life of <1 day (Richardson, 1954). The addition of thiram to soil appeared to alter the microbiological balance of the soil, increasing the number of bacteria and decreasing the number of fungi over time (Richardson, 1954; Rajagopal et al., 1984). Thiram is reported to decompose faster in soils with greater humus content (Wendel, 1974). In soil with humus content ≤1.2%, an initial lag in the decomposition of thiram was observed (Kluge, 1969b). Thiram has been found to decompose faster in soil with a lower pH. In humus sandy soil at pH 3.5, thiram was largely decomposed after 4-5 weeks, while in the same
soil at pH 7.0, thiram decomposed after 14-15 weeks (Kluge, 1969a). The proposed degradation pathway for thiram in soil is shown in Figure 2-1 (Rajagopal et al., 1984).

2.4. SUMMARY

If released to the atmosphere, thiram is expected to exist partly in the vapor phase and partly in particulate form (Hartley and Kidd, 1983; Eisenreich et al., 1981). The dominant removal mechanism for thiram in the vapor phase appears to be reaction with photochemically generated hydroxyl radicals. The half-life for this reaction has been estimated to be 71 minutes (Atkinson, 1985; 1987). Dry deposition may be a significant route of removal for particulate-phase thiram. Because of its ability to absorb sunlight, direct photolysis is also a potential removal process for both vapor- and particulate-phase thiram. If released to water or soil, thiram is expected to decompose by chemical and microbial action to dimethyldithiocarbamate (Munnecke and Mickael, 1967; Richardson, 1954; Shirkot and Gupta, 1985; Kluge, 1969a,b; Rajagopal et al., 1984). Under acidic conditions, chemical processes should dominate. Under anaerobic conditions, thiram has been found to biodegrade to dimethylamine, carbon disulfide and hydrogen sulfide (Williams, 1977). Volatilization from water or soil surfaces is not expected to be an important fate process. This compound should adsorb moderately to suspended solids and sediments in water. In general, thiram is expected to have low mobility in soil, although potential exists for movement through some soils (Rajagopal et al., 1984; Helling et al., 1974; Reinbold et al., 1979). The half-life of thiram in soil has been found to vary from <1 day to >32 weeks, with the rate of degradation depending upon such variables as pH, humus content and initial concentration of the compound (Shirkot and Gupta, 1985; Griffith and Matthews, 1969; Chinn, 1973; Richardson, 1954; Kluge, 1969a).
FIGURE 2-1
Degradation Pathways of Thiram and Ziram in Soil and in Microbial Cultures

Source: Rajagopal et al., 1984
3. EXPOSURE

Pertinent data regarding human exposure to thiram were extremely limited. The U.S. EPA STORET data base contained no data regarding the detection of thiram in water, aquatic biota or sediment samples. Because thiram is used as a fungicide in fruit plants, it was analyzed for but not found in samples of sweet cherries and peaches grown domestically in Ontario, Canada, between 1983 and 1984. The detection limit for thiram in this study was 0.01 mg/kg (Frank et al., 1987).

Thiram is used as a primary and secondary accelerator in compounding rubber (IARC, 1976). In a study by Kruijs-de Vries et al. (1987), 6 of 8 haemodialysed patients developed subacute eczematous dermatitis in the area surrounding the rubber arteriovenous shunt in the forearm.

It is also possible that the dermatitis was caused by short and intermittent contact of the skin with rubber gloves used by the nursing personnel. Marks and Rainey (1984) conducted a prospective study of 100 surgical patients to identify causes of contact dermatitis. Patch testing was performed on 11 patients with post-operative dermatitis or a history of tape allergy. Two patients had reactions to the tests.

In two abstracts of Russian studies, workers exposed to unspecified concentrations of thiram exhibited neural and myocardial disorders, a thyroid volume increase, upper respiratory infections and hematological alterations (Cherpak et al., 1971; Kaskevich and Bezugly, 1973).

Although thiram was found at one superfund waste site, other data on environmental fate and human exposure pathways were not located in the available literature (U.S. EPA, 1987d).
4. ENVIRONMENTAL TOXICOLOGY

4.1. AQUATIC TOXICOLOGY

4.1.1. Acute Toxic Effects on Fauna. McKee and Wolf (1963) reported the results of a toxicity test in which fingerling channel catfish were exposed to thiram at 19°C. The 96-hour Tₐₘ was 0.79 mg/l.

Frear and Boyd (1967) assessed the acute toxicity of thiram to Daphnia magna. Daphnids were exposed singly in 100 ml solutions of thiram in 4-ounce bottles. The solubility of thiram in test solutions was enhanced by use of acetone as a carrier. LD₅₀ values were calculated from the results of 10 definitive assays. Investigators reported a 26-hour LD₅₀ of 1.3 ppm.

Voronkin and Loshakov (1973) reported a 48-hour LC₅₀ of 0.67 mg/l for Tubifex tubifex exposed to thiram.

Tooby et al. (1975) assessed the toxicity of thiram (80% active ingredient product) to harlequin fish, Rasbora heteromorpha, under flowthrough conditions. The dilution water had a hardness of 20 mg/l, a pH of 8.1 and a temperature of 20°C. Toxicity levels were calculated on the basis of commercial product and not on active ingredient. The 24-, 48- and 96-hour LC₅₀s were 0.02, 0.012 and 0.007 mg/l, respectively. The investigators estimated a 3-month LC₅₀ of 0.001 mg/l from an extrapolation of the results of acute studies.

Schneider (1979) reported 24-, 48- and 96-hour LC₅₀s of 0.138, 0.130 and 0.13 ppm for rainbow trout, Salmo gairdneri, exposed to solutions of thiram (99% active ingredient). The respective LC₅₀s for trout exposed to a thiram-containing product with 75% active ingredient were 0.50, 0.40 and 0.40 ppm. Exposure of bluegill sunfish, Lepomis macrochirus, to thiram (99% active ingredient) generated 24-, 48- and 96-hour LC₅₀s of 0.21, 0.093 and 0.045 ppm, respectively. The respective LC₅₀s for sunfish exposed to a
product containing 75% thiram were 0.71, 0.31 and 0.28 ppm. Tests were conducted under static conditions in 15% of reconstituted water at 12°C for trout and 18°C for sunfish.

Bluzat et al. (1981) assessed the acute toxicity of two commercial thiram-containing products (product A and product B) to the freshwater mollusc, *Lymnaea stagnalis*. Each product contained an 80% level of thiram but 20% levels of dissimilar inactive ingredients. Snails were exposed to aqueous suspensions of the products in groups of four in 800 ml of water at 230 ppm hardness and 20°C. The 48-, 72- and 96-hour LC\textsubscript{50}s based on active ingredient for product A were 35.7, 19.1 and 12 ppm, respectively, and 38, 19.1 and 8.9 ppm, respectively, for product B. The products were 2- to 4-fold more toxic when suspensions were prepared in acetone. The 96-hour LC\textsubscript{50}s for products A and B were 2.8 and 3.2 ppm, respectively.

Bluzat et al. (1982a) assessed the effects of short-term exposures (1 hour) of scud, *Gammarus pulex*, to a commercial product (probably product A as described above) containing 80% thiram. Thirty scud were exposed to nominal concentrations of thiram ranging from 1-50 ppm in 1% of water for 1 hour. Animals were rinsed and transferred to aerated freshwater (hardness=230 ppm, pH=7.5) for 10 days. All scud exposed to 50 ppm died within 5 days of treatment. Scud exposed to 10, 5, 2 and 1 ppm thiram experienced 95, 79, 48 and 25% mortality by the end of the 10-day observation period. The mortality level among control scud at the end of the 10-day observation period was 7.5%. Bluzat et al. (1982a) also assessed the dissipation of acute toxicity of aged thiram solutions to *G. pulex*. Groups of scud (n=130 and 190) were exposed for 96 hours to 0.7 ppm aqueous suspensions of thiram 1, 48 and 96 hours after preparation of the test solutions. Scud had 84.6, 91.5 and 50% mortality levels for 96-hour exposures to 1-, 48- and 96-hour aged solutions of 0.7 ppm thiram, respectively.
Bluzat et al. (1982b) assessed the acute toxicity of the two commercial thiram-containing products (product A and product B described above) to the freshwater scud, *Gammarus pulex*. Each product contained an 80% level of thiram but 20% levels of dissimilar inactive ingredients. Scud were exposed to aqueous suspensions of the products in groups of 10 in 800 ml of water at 230 ppm hardness and 20°C. The 24-, 48-, 72- and 96-hour LC$_{50}$s based on active ingredient for product A were 14.0, 1.21, 0.41 and 0.20 ppm, respectively, and 4.77, 0.48, 0.2 and 0.13 ppm, respectively, for product B. The toxicity of each product was only minimally influenced by the solvent used to prepare suspensions (water or acetone). The 96-hour LC$_{50}$s for products A and B in acetone were 0.22 and 0.06 ppm, respectively.

Bluzat and Seuge (1983) assessed the effects of exposure to thiram on *Gammarus pulex* by different routes of exposure (water and diet). Twenty scud were exposed to aqueous solutions of thiram at concentrations of 0.02, 0.025, 0.035, 0.05 and 0.08 ppm. Test solutions were renewed twice weekly. The approximate median lethal times for groups of scuds exposed to these solutions were 30, 8.5, 6.5, 4.5 and 5 days, respectively. Alternately, scud were offered either dried bean seeds soaked in, or pieces of moss rehydrated in, aqueous suspensions of thiram ranging from 50-10,000 ppm for 48 hours at 8°C. Observations were reported in terms of the duration of treatment over which 90 and 10% of the treated animals were expected to survive. Scud offered bean seeds treated with 3000 and 10,000 ppm thiram demonstrated 90% survival after 3-3.5 days and 10% survival after 29-36 days. Control animals survived 7.4-10 and 143-145 days, respectively. Scud offered mosses treated with 50-10,000 ppm thiram demonstrated 90% survival after 2.4-5.4 days and 10% survival after 9-27 days. Control animals survived 5.9-10 and 101-121 days, respectively.
Seuge et al. (1983) assessed the acute toxicity of an aqueous suspension of thiram in a flatworm, *Dugesia gonocephala*, an isopod, *Asellus aquaticus*, and an amphibian, *Xenopus laevis*, at two stages of development (47 and 53). Organisms were exposed to nominal concentrations of thiram in 800 ml of water at 230 ppm hardness and 20°C. The 24-, 48-, 72- and 96-hour LC50s for *D. gonocephala* were 0.53, 0.26, 0.088 and 0.048 ppm, respectively. The 24-, 48-, 72- and 96-hour LC50s for *A. aquaticus* were 1,882, 688, 161, and 61 ppm, respectively. The 24-, 48-, 72- and 96-hour LC50s for *X. laevis* were 0.017, 0.014, 0.013 and 0.013 ppm, respectively, for stage 47 and 0.025, 0.022, 0.021 and 0.021 ppm, respectively, for stage 53. The investigators noted that the slopes of the response curves were much steeper for *X. laevis* than for either of the other organisms tested.

Seuge and Bluzat (1983) assessed the acute toxicity of fresh and aged aqueous suspensions of thiram to larvae of the mayfly, *Cloeon dipterum*. Organisms were exposed to nominal concentrations of thiram in 800 ml of water at 230 ppm hardness and 20°C. Tests with larvae were begun within 2 hours of collection from the field. The 24-, 48-, 72- and 96-hour LC50s for larvae exposed to freshly prepared solutions of thiram were 1.92, 1.3, 1.08 and 1.01 mg/l, respectively. Tests with larvae that had been held in the laboratory for 4 days before testing demonstrated a significantly greater sensitivity (~2-fold) to thiram than larvae used immediately upon collection. The toxicity of aged solutions of thiram to larvae of *C. dipterum* was assessed by exposing larvae to solutions that had been prepared 1, 7 and 36 hours before initiation of exposure. The levels of mortality after 24 hours were 50.4, 16.7 and 3.3%, respectively. The levels of mortality after 48 hours were 67.3, 26.6 and 8.6%, respectively. The levels of mortality after 72 hours were 73.6, 46.7 and 22%, respectively.
The levels of mortality after 96 hours were 79.5, 64.7 and 45.3%, respectively.

Knief et al. (1983) reported an EC$_{50}$ of 0.06 µg/l for Daphnia magna exposed to thiram. The respective EC$_{0}$ and EC$_{100}$ concentrations were 0.05 and 0.8 µg/l.

Jouany et al. (1985) assessed the toxicity of thiram to the water flea, Daphnia magna, carp, Cyprinus carpio, and zebrafish, Brachydanio rerio. Daphnids were exposed to 0, 0.1 and 1 mg/l thiram in crystallizing dishes containing 500 ml of test solution for 24 hours. None of the daphnids exposed to 1 mg/l survived, and mortality among those exposed to 0.1 mg/l was 50%. The toxicity of thiram to carp, Cyprinus carpio, and zebrafish, Brachydanio rerio, was assessed under static conditions in a synthetic dilution water. There was no mortality among fish of either species exposed to 0.1 mg/l after 24 hours. Zebrafish had 100% mortality at 1.0 mg/l, while carp had no mortality at 1.0 mg/l after 24 hours.

Jouany et al. (1985) also assessed the toxicity of thiram to zebrafish by passage of thiram through a simple food chain. Exponentially growing cultures of algae were incubated with 0.1 mg/l thiram for 48 hours. Cells were centrifuged, washed and offered to daphnids that were then offered to zebrafish. Fish were each fed 20 daphnids/day. Mortality among zebrafish rose 0% at 4 days to 100% at 8 days after initiation of the experiment. Mortality among control fish was ~40% after 8 days.

Van Leeuwen et al. (1985a) assessed the acute toxicity of thiram to guppies, Poecilia reticulata, and water fleas, D. magna, in static renewal assays using standard protocols. The 96- and 48-hour LC$_{50}$s for guppies and daphnids exposed to thiram were 0.27 and 0.21 mg/l, respectively.
Van Leeuwen et al. (1986a) assessed the acute toxicity of thiram (>98% purity) to rainbow trout, *Salmo gairdneri*. Fish (average weight of 34.0 g and average length of 15.3 cm), were acclimatized to laboratory conditions for 5-7 days in a 400 l tank at 15°C. Diluent water used in the toxicity tests was reconstituted with a pH of 7.8 and a hardness of 50 mg/l. Fish were fasted for 24 hours before being exposed to thiram in 10 l tanks. The 24-hour LC50 (and 95% confidence limits) was 0.26 mg/l (0.24-0.32). For fish weighing ~47 g, the 24-hour LC50 (and 95% confidence limits) was 0.30 mg/l (0.18-0.50).

Van Leeuwen et al. (1986a) also assessed the sublethal effects of acute exposure of rainbow trout, *S. gairdneri*, to thiram (>98% purity). Ten fish were exposed to 0.18 mg/l of thiram for 24 hours under the conditions described above for the lethality assays. Fish were anaesthetized at the end of the 24-hour exposure period. Tissue samples were analyzed for a variety of parameters. Exposure of trout to thiram resulted in significant declines in blood glucose levels and liver protein bound SH content. Investigators also noted significant increases in liver LDH activity, percent lipid content of liver, nonprotein bound SH content in liver, G-6-PDH activity in blood, and blood osmolarity. The investigators concluded that thiram should be regarded as a cytotoxic chemical.

4.1.2. Chronic Effects on Fauna.

4.1.2.1. TOXICITY — Van Leeuwen et al. (1985b) assessed the chronic effects of thiram (98% purity) on survival, reproduction and growth of the water flea, *Daphnia magna*, in a 21-day study. Daphnids were exposed to thiram in 500 ml of solution in 800 ml vessels. Test solutions were renewed 3 times a week from freshly prepared stock solutions of thiram.
Test concentrations were not verified by analysis. The test was conducted at 20°C in a temperature controlled room with a photoperiod of 12 hours. Diluent water had a hardness of 225 mg/l and a pH of 8.1. Daphnids starting at <24 hours old were fed daily with 3x10⁶ cells/l of the green algae, *Chlorella pyrenoidosa*. Investigators reported a 21-day LC₅₀ of 8 µg/l. The lowest tested concentration that resulted in a decrease in fecundity was 10 µg/l. The lowest tested concentration that resulted in a decrease in size of daphnids after 21 days was 1.8 µg/l. There were no significant effects on daphnids exposed to 1 µg/l of thiram over the 21-day study.

Van Leeuwen et al. (1986b) assessed the chronic toxicity of thiram to embryolarval stages of rainbow trout, *Salmo gairdneri*. Eggs within 3 hours of fertilization were exposed to 10⁻¹ volumes of a series of thiram concentrations in all-glass aquaria. The test temperature was 10°C. Diluent water was reconstituted with a hardness of 50 mg/l and a pH of 7.7. Test solutions were renewed 3 times weekly and were aerated continuously. Thiram stock solutions were prepared freshly at each renewal. Test concentrations were not measured, and eggs were kept in the dark until embryogenesis, after which a photoperiod of 12:12 hours was imposed. Larvae were not fed during the study. The 60-day LC₅₀ (and 95% confidence limits) for embryolarval stages of rainbow trout exposed to thiram was 1.1 µg/l (1.1-1.2). The 60-day EC₅₀ (and 95% confidence limits) based on mortality and teratogenesis was 0.64 µg/l (0.57-0.73). The most pronounced teratogenic lesions observed included severe spinal and vertebral abnormalities, scoliosis, lordosis, kyphosis and dwarfed structures of the trunk. The lowest concentrations at which there were no observable effects based on mortality, total embryotoxicity, length and weight were 1.0, <0.32, <0.32 and 0.56 µg/l, respectively.
Van Leeuwen et al. (1986c) assessed the effects of exposure of juvenile rainbow trout to thiram. Trout ~5 cm in length were exposed to thiram in reconstituted water with a hardness of 50 mg/l and a pH of 7.7 for 21 days. Exposure of trout to thiram resulted in a concentration-related loss of glycogen in the liver at ≥25 μg/l and was associated with reduced body weight gain. At 100 μg/l, thiram induced a proliferation of bile duct epithelial cells both with and without formation of new ductules. Cell necrosis was observed occasionally, and hemorrhages were apparent in the brain and spinal cord at 5 μg/l. The investigators concluded that the teratogenic action of the dithiocarbamates is confined to the notochord at concentrations likely to be encountered in the environment.

4.1.2.2. BIOACCUMULATION/BIOCONCENTRATION -- No measured steady-state BCF value for thiram was found in the literature. Based on the regression equation, log BCF = 2.791 - 0.564 log S (Lyman et al., 1982) and a water solubility of 30 mg/l (see Section 1.2.), a BCF of 90.8 is estimated for this compound. This value suggests that thiram will not bioaccumulate significantly in aquatic organisms.

4.1.3. Effects on Flora.

4.1.3.1. TOXICITY -- Diehn and Tollin (1967) assessed the effects of thiram on motility and topophototaxis of *Euglena gracilis*. Phototactic responses were determined in a phototaxisigraph using white light of 140 erg/cm² second. Motility of *E. gracilis* was determined by microscopic observation at low levels of illumination. The investigators reported that motility and topophototaxis were inhibited to 50% of control organisms within 30 minutes of exposure to 10⁻⁴ M solutions of tetramethylthiuram disulfide.
Krishnakumari (1977) assessed the toxicity of tetramethylthiuram disulfide to the green alga, *Scenedesmus acutus*. Cultures were maintained at a temperature of 28±1°C, a light intensity of 8500 lux and a pH of 7-8. Growth of cultures was measured daily by optical density. Assays were continued for 5 days. Cultures exposed to 10 and 100 ppm tetramethylthiuram disulfide were dead after 1 and 3 days, respectively. Cultures exposed to 0.5, 1, 5 and 10 ppm demonstrated 90.9, 90.9, 75 and 59% growth compared with controls after 1 day. Cultures exposed to 0.5, 1 and 5 ppm demonstrated 83.1, 80.3 and 56.3% growth compared with controls after 3 days. Cultures exposed to 0.5, 1 and 5 ppm demonstrated 82.0, 77.7 and 42.8% growth compared with controls. The NOEL for tetramethylthiuram disulfide in *S. acutus* appears to be <0.5 ppm.

Gangawane and Kulkarni (1979) assessed the effect of thiram on growth of the blue-green algae, *Nostoc* sp. and *Tolypothrix* sp. Cultures of these algal species were exposed to thiram in test tubes in 10 mL of medium at 1500 lux and 25°C for 8 hours. Growth of algae was determined by the optical density of acetone-soluble pigments. The investigators reported a 25.4% reduction in growth for cultures of *Nostoc* sp. exposed to 500 ppm thiram and a 14.7% reduction in growth for cultures of *Tolypothrix* sp. exposed to 100 ppm thiram.

Hutber et al. (1979) assessed the effect of thiram on growth of four species of blue-green algae, *Aphanocapsa* (strains 6308 and 6714), *Anabaena variabilis* and *Nostoc*. Cultures were maintained at 30°C at 9000 lux illumination intensity. Thiram was added to the cultures during the exponential growth phase. Exposure of cultures to various concentrations of thiram continued for 48 hours. The concentrations that reduced the exponential
growth rate of these algae by 50% were 50, 100, 50 and 100 ppm, respectively; the concentrations that inhibited growth completely were 100, >100, 100 and >100 ppm, respectively.

Dive et al. (1980) assessed the toxicity of thiram to the ciliate protozoan, *Colpidium campylum*. Protozoan cultures were cultivated monoxenically on *Escherichia coli*. Solutions (0.25 ml) of thiram with acetone as a carrier were added to 50 ml of culture medium. Protozoa were counted with a Coulter counter after 43 hours of incubation at 20°C. The minimal active dose of thiram required to produce reductions in the number of generations of *C. campylum* was 0.3 mg/l.

Vasseur et al. (1982) assessed the toxicity of thiram to the alga, *Chlorella vulgaris*, by monitoring the effect on ATP levels. Cultures were swirled at a rate of 150 oscillations/minute and maintained at 20°C under 1500 lux intensity light. The 24-hour IC$_{50}$ for *C. vulgaris* based on ATP levels was >2 ppm thiram.

Knie et al. (1983) reported an EC$_{10}$ of >6 mg/l for the alga, *Haematococcus pluvialis*, exposed to tetramethylthiuram disulfide.

Dive et al. (1984) assessed the effects of thiram on growth of various strains of the ciliates, *Tetrahymena thermophila* and *Tetrahymena pyriformis*, and various species of amoebae. Ciliates were exposed to thiram in sterile cotton plugged glass tubes containing 10 ml of medium. Tests were performed in an automatic biophotometer. Optical density of cultures was monitored every 30 minutes for 3 days. Experiments were conducted at 28, 37 and 39°C. The effects of thiram on amoebae growth was achieved by exposing amoebae to thiram-contaminated agar plates spread with bacteria or yeast. A drop of amoebae cyst suspension was placed in the center of the plate.
Growth of amoebae was monitored by observation of the extension of lysis of the prey. Growth rates of ciliate strains were inhibited completely at 1.0 mg/l thiram for all but one strain cultured at 28°C. At 0.5 mg/l, growth rates were relatively unaffected, except for a single strain. Effects of thiram on growth of amoebae were highly variable and species- and strain-dependent. Growth inhibition ranged from 0.5-16 mg/l. Complete inhibition of growth commenced at 8 mg/l for one species but was >32 mg/l for several strains of another species.

Grollier and Dupy-Blanc (1985) reported that thiram induced a lengthening of the generation time in heat shock synchronized axenic cultures of Tetrahymena pyriformis. The effect was observed for concentrations of thiram ranging from 0.25-1.0 mg/l applied at the end of the 6th heat shock treatment and at various intervals (<90 minutes) after completion of heat shock treatments.

Jouany et al. (1985) assessed the toxicity of thiram to the green alga, Chlorella vulgaris. Algal cultures were incubated at 20°C under 1500 lux and a 16:8 photoperiod on a gyratory shaker at 150 rpm. Thiram was added to exponentially growing cultures with cell concentrations of 15x10^6 cells/ml. The 72-hour IC_{50} for growth of algal cultures as determined by optical density at 665 nm was 5.5 mg/l.

Van Leeuwen et al. (1985a) assessed the toxicity of thiram to algae, Chlorella pyrenoidosa. Algal bioassays were conducted at 20°C with an initial cell density of ~10^6 cells/l in 200 ml Erlenmeyer flasks held on a mechanical shaker. Cells were counted with a Coulter counter. The 96-hour EC_{50} for two measures of algal density, the average specific growth rate and effects on the time-lag until maximum population growth, were 1.0 and 0.03 mg/l, respectively. Van Leeuwen et al. (1985a) also
assessed the effects of thiram on photosynthesis and respiration in C. pyrenoidosa. Effects of thiram on photosynthesis was assessed by incubating algae with NaH¹⁴CO₃ in the presence of thiram for 4 hours and determining the bicarbonate uptake by liquid scintillation. Effects of thiram on respiration were assessed by incubating ¹⁴C-labeled algae in the dark for 16 hours before determining the radioactivity remaining in the cells by liquid scintillation. The EC₅₀ for assimilation of radioactive bicarbonate by algae was 4.0 mg/l. The EC₅₀ for respiration of ¹⁴C by algae was >10.0 mg/l.

Taylor and Pace (1987) assessed the effect of thiram on growth of cultures of a chrysomonad and a ciliate, Cyclidium sp. Log-phase cultures of the chrysomonad and ciliate were exposed to thiram for 24 and 48 hours, respectively, in darkness at 22°C. Culture flasks were neither agitated nor aerated. Growth of the chrysomonad was inhibited completely following exposure to 210 μM thiram. Growth of the ciliate was inhibited completely at ~80 and ~1800 μM, but was inhibited 60% of control levels at ~560 μM thiram. Taylor and Pace (1987) also reported that 4 μM thiram did not inhibit growth of a chlorophyte, Dunaliella tertiolecta, after 7 days. Growth of five other phytoplankton species were inhibited from ~0.2-18.6% of controls by exposure to 4 μM thiram for 7 days.

4.1.3.2. BIOCONCENTRATION -- Pertinent data regarding the bioconcentration potential of thiram in aquatic flora were not located in the available literature cited in Appendix A.

4.1.4. Effects on Bacteria. Van Leeuwen et al. (1985a) assessed the toxicity of thiram to luminescent bacteria, Photobacterium phosphoreum, and nitrifying bacteria, Nitrosomonas and Nitrobacter. The EC₅₀ value for P. phosphoreum exposed to thiram, defined as the concentration of thiram that
produced a 50% reduction in bacterial luminescence after 15 minutes, was 0.1 mg/l. The effects of exposure to thiram on the nitrification process of a mixed culture of *Nitrosomonas* and *Nitrobacter* were monitored by using a pH-indicator mixture that assessed the conversion of ammonia by nitrite to nitrate. The lowest effective concentration or minimum inhibiting concentration of thiram on the nitrification process after 3 hours was 18 mg/l.

### 4.2. TERRESTRIAL TOXICOLOGY

#### 4.2.1. Effects on Fauna

Tucker and Crabtree (1970) reported the results of studies assessing the acute oral toxicity of thiram to 3- to 4-month-old pen-reared mallard ducks, *Anas platyrhynchos*, and ring-necked pheasants, *Phasianus colchicus*. Birds were dosed by inserting gelatin capsules containing thiram through glass tubing to the level of the crop, proventriculus or stomach. Birds were fasted for 16-20 hours before dosing. Two to seven animals were employed at each of four dosage levels. Birds were observed for 14 days posttreatment. The authors reported oral LD₅₀ s of >2800 and 673 (95% confidence limits of 485-932) mg/kg for ducks and pheasants, respectively.

Egberts et al. (1972) examined the oral chronic toxicity of thiram to Japanese quail, *Coturnix coturnix*. Four groups of quail consisting of five hens and two cocks each were exposed to thiram in their diet (turkey starter) at concentrations of 2, 10 and 50 ppm (mg/kg) for 11 weeks. Females were housed separately but mated with one of the males each 2.5 days. There were no statistically significant effects in birds offered feed contaminated with 10 ppm thiram. Birds fed 50 ppm contaminated feed demonstrated significant reductions in numbers of eggs laid and hatched and shell thickness of eggs. Investigators also demonstrated that there were significant reductions in the numbers of lymphocytes, granulocytes and monocytes of blood from birds dosed with 50 ppm thiram-contaminated feed.
Heath et al. (1972) assessed the oral acute toxicity of thiram to Japanese quail, C. coturnix japonica, pheasant, P. colchicus, and mallard ducks, A. platyrhynchos. All test birds were incubator-hatched progeny of breeding colonies. Thiram was dissolved in a carrier and added to the diet by mixing with commercial mash in a ratio of 2 parts of solution to 98 parts of feed by weight. Birds were offered thiram-contaminated mash for 5 days and monitored for 3 days after termination of treatments. The investigators reported a lack of mortality among quail and pheasants fed the highest concentration tested (5000 ppm in feed). Mallard ducks experienced 20% mortality among birds fed mash containing 5000 ppm thiram.

Lorgue et al. (1975) also examined the oral acute toxicity of thiram to quail. These investigators reported that thiram-contaminated feed (20 g Thirban/10 kg) caused immediate (24 hours) blockage of egg laying and regression of secondary sexual characteristics in males. These effects were reversible on withdrawal of contaminated feed from diet. Lorgue and Soyez (1976) assessed the oral toxicity of thiram to gray partridges. Thiram at 1.6 g/kg completely inhibited egg laying within 48 hours. The incidence of embryonic mortality was increased significantly at 4-fold lower doses.

Gruen et al. (1982) assessed the acute toxicity of thiram to Japanese quail C., coturnix japonica. The investigators reported an LD₅₀ of 695 and an LC₅₀ of 695 and >10,000 mg/kg, respectively. Hadhazy and Glavits (1982) reported that 100 and 200 g thiram/100 kg feed caused imperfect egg shell calcification and production of eggs with abnormal size and form in pheasants. Apparently, disturbances were due to oviduct inflammation, but were reversible 2-3 weeks after cessation of dosing.

Schafer and Bowles (1985) reported the results of studies assessing the ALD of thiram to wild-trapped deer mice, Peromyscus maniculatus. The ALD
was obtained with a single level at each treatment that was 50% higher than the preceding treatment. Thiram was administered by gavage with a carrier. Mice were monitored for mortality for 3 days. Investigators reported an ALD of 1600 mg/kg; deer mice ingested an average of +200 mg thiram/kg bw/day over the 3-day test period.

Roark and Dale (1979) assessed the toxicity of thiram to earthworms, Eisenia fetida. Worms were exposed to thiram by immersion in a 2.0% solution for 1 minute, as a component of their diet (bermudagrass feed treated with a 0.1% aqueous solution), and mixed with the worms' culture soil (0.426 g thiram in 4719 cm³ of soil). Worms exposed to thiram by immersion experienced mortality levels ranging from 5%, 7 days posttreatment, to 38%, 101 days posttreatment. Worms fed thiram-treated bermudagrass clippings experienced mortality levels ranging from 10% after 34 days of treatment to 42% after 101 days. Mortality among worms reared in thiram-treated soil ranged from 21% after 10 days to 98.1% after 29 days and 99.9% after 52 days.

4.2.2. Effects on Flora. Ingham (1985) reviewed the effects of thiram-containing products on soil bacteria and fungi in a wide variety of test systems. The author listed inhibitory and stimulatory effects, as well as the presence of tolerant populations of soil microflora.

4.3. FIELD STUDIES

Pertinent data regarding the effects of thiram on flora and fauna in the field were not located in the available literature cited in Appendix A.

4.4. AQUATIC RISK ASSESSMENT

Aquatic toxicity data for tetramethylthiuram disulfide (thiram) were sufficient to calculate a Final Acute Value, Final Chronic Value, Final Acute-Chronic Ratio and Final Plant Value. The lack of appropriately
conducted bioconcentration/bioaccumulation studies prevented the estimation of a Final Residue Value.

The Final Acute Value was calculated from GMAVs for flatworms, Dugesia gonocephala (0.038 mg/L), bluegill sunfish, Lepomis macrochirus (0.045 mg/L), scud, Gammarus pulex (0.104 mg/L), and rainbow trout, Salmo gairdneri (0.13 mg/L), listed in Figure 4-1 using the computer program appearing in Figure 4-2. The Final Acute Value obtained in this manner was 20.4 µg/L (Figure 4-3).

The Final Chronic Value was calculated from the ratio of the Final Acute Value and the Final Acute-Chronic Ratio. The Final Acute-Chronic Ratio was calculated from the geometric mean of the ratio of results from acute and chronic studies listed in Figure 4-1 with rainbow trout, Salmo gairdneri (0.13/0.00032=406.25), and the water flea, Daphnia magna (0.21/0.000134=1567.16). The Final Acute-Chronic Ratio obtained from the geometric mean of 406.25 and 1567.16 was 797.91 (see Figure 4-3). The Final Chronic Value obtained from the ratio of the Final Acute Value and the Final Acute-Chronic Ratio (20.4/797.91) was 0.0256 µg/L (see Figure 4-3).

The Final Plant Value was obtained from the lowest EC_{50} obtained from an acceptable study with freshwater algae. The Final Plant Value obtained in this manner was 0.03 mg/L for a study with Chlorella pyrenoidosa (see Figures 4-1 and 4-3).

The Criterion Maximum Concentration as described in U.S. EPA/OWRS (1986) is equal to 1/2 the Final Acute Value (20.4/2). The Criterion Continuous Concentration as described in U.S. EPA/OWRS (1986) is equal to the lowest of the Final Chronic Value, the Final Plant Value and the Final Residue Value.
<table>
<thead>
<tr>
<th>Family</th>
<th>TEST TYPE</th>
<th>GMAV*</th>
<th>GMCV*</th>
<th>BCF*</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 Chordate (Salmonid-fish)</td>
<td>0.13*</td>
<td>&lt;0.00032'</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>#2 Chordate (warmwater fish)</td>
<td>0.045*</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>#3 Chordate (fish or amphibian)</td>
<td>0.27*</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>#4 Crustacean (planktonic)</td>
<td>0.21*</td>
<td>0.000134*</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>#5 Crustacean (benthic)</td>
<td>0.104'</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>#6 Insectan</td>
<td>0.81*</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>#7 non-Arthropod/-Chordate</td>
<td>0.038*</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>#8 New Insectan or phylum representative</td>
<td>0.67'</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>#9 algae</td>
<td>XXXXXXXXXXXX</td>
<td>XXXXXXXXXXXX</td>
<td>0.03'</td>
<td>NA</td>
</tr>
<tr>
<td>#10 Vascular plant</td>
<td>XXXXXXXXXXXX</td>
<td>XXXXXXXXXXXX</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*NA=not available *96-hr LC₅₀ in ppm for rainbow trout Salmo gairdneri *96-hr LC₅₀ in ppm for bluegill sunfish Lepomis macrochirus *96-hr LC₅₀ in mg/L for guppies Pogonias reticulata *48-hr LC₅₀ in mg/L for the water flea Daphnia magna *96-hr LC₅₀ in mg/L for scud Gammarus pulex *96-hr LC₅₀ for the mayfly Cloeon dipterum *96-hr LC₅₀ for the flatworm Dugesia monosperma *48-hr LC₅₀ in mg/L for the worm Tubifex tubifex *60-day NOEC in mg/L for rainbow trout S. gairdneri *21-day NOEC in mg/L for the water flea D. magna *96-hr EC₅₀ in mg/L for the algae Chlorella pyrenoidosa

FIGURE 4-1

Organization Chart for Listing GMAVs, GMCVs and BCFs Required to Derive Numerical Water Quality Criteria by the Method of U.S. EPA/OWRS (1986) for the Protection of Freshwater Aquatic Life from Exposure to Thiram
10 REM THIS PROGRAM CALCULATES THE FAV WHEN THERE ARE LESS THAN
20 REM 59 MAVS IN THE DATA SET
30 X=0
40 X2=0
50 Y=0
60 Y2=0
70 PRINT "HOW MANY MAVS ARE IN THE DATA SET?"
80 INPUT N
90 PRINT "WHAT ARE THE FOUR LOWEST MAVS?"
100 FOR R=1 TO 4
110 INPUT V
120 X=X+LOG(V)
130 X2=X2+(LOG(V))*(LOG(V))
140 P=P/N-1
150 Y2=Y2+P
160 Y=Y+SQR(P)
170 NEXT R
180 S=SQR((X2-X*X/4)/(Y2-Y*Y/4))
190 L=(X-S*Y)/4
200 A=S+SQR(.05)*L
210 F=EXP(A)
220 PRINT "FAV = "#F
230 END

FIGURE 4-2
Example Computer Program in BASIC Language for Calculating the
Final Acute Value

Source: U.S. EPA/OWRS, 1986
<table>
<thead>
<tr>
<th></th>
<th>FAV*</th>
<th>FCV*</th>
<th>FACR*</th>
<th>FPV*</th>
<th>FRV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freshwater</td>
<td>20.4</td>
<td>0.0256</td>
<td>797.91</td>
<td>30 ug/L</td>
<td>ID</td>
</tr>
<tr>
<td>Saltwater</td>
<td>ID</td>
<td>ID</td>
<td>ID</td>
<td>ID</td>
<td>ID</td>
</tr>
</tbody>
</table>

*Minimum data requirements for generation of a Final Acute Value (FAV) include the results of at least one acceptable test with organisms in each of eight taxonomic families.

*Minimum data requirements for generation of a Final Chronic Value (FCV) include the results of at least one acceptable test with organisms in each of three taxonomic families with at least one fish and one invertebrate. A freshwater criterion must include at least one species that is freshwater while the remaining may be marine. A saltwater criterion must include at least one species that is marine while the remaining may be freshwater.

*Minimum data requirements for generation of a Final Acute-Chronic Ratio (FACR) include satisfying the minimum data requirements for the FAV and FCV.

*The Final Plant Value (FPV) is obtained by selecting the lowest plant value from a test with either an algae or vascular plant in which the concentrations of test material were measured.

*The Final Residue Value (FRV) is obtained by selecting the lowest of the available residue values.

*ID=Insufficient data for calculation of a criterion.

FIGURE 4-3

Summary Chart for Data Required to Generate Criteria by the Method of U.S. EPA/OWRS (1986) for Safe Levels of Thiram in Aquatic Environments
The procedures described in U.S. EPA/OWRS (1986) indicate that, except possibly where a locally important species is very sensitive, freshwater aquatic organisms and their uses should not be affected unacceptably if the 4-day average concentration of tetramethylthiuram disulfide (thiram) does not exceed the Criterion Continuous Concentration of $\leq 0.0256 \ \mu g/\ell$ more than once every 3 years on the average, and if the 1-hour average concentration does not exceed the Criterion Maximum Concentration of 10.2 $\mu g/\ell$ more than once every 3 years on the average.

The lack of pertinent data regarding the effects of exposure of marine fauna and flora to tetramethylthiuram disulfide (thiram) prevented the development of a saltwater criterion.

4.5. SUMMARY

The 96-hour TL$_m$ of thiram in fingerling channel catfish was reported as 0.79 mg/\ell (McKee and Wolf, 1963). The 26-hour LD$_{50}$ of thiram to Daphnia magna was 1.3 ppm (Frear and Boyd, 1967). The 48-hour LC$_{50}$ of thiram to Tubifex tubifex was 0.67 mg/\ell (Voronkin and Loshakov, 1973). Tooby et al. (1975) reported a 96-hour LC$_{50}$ of 0.007 mg/\ell (based on concentration of product) for harlequin fish, Rasbora heteromorpha, exposed to a thiram-containing product with 80% active ingredient under flowthrough conditions. Tooby et al. (1975) estimated a 3-month LC$_{50}$ of 0.001 mg/\ell from an extrapolation of the acute test results.

Schneider (1979) reported 96-hour LC$_{50}$s of 0.13 and 0.4 ppm for rainbow trout, Salmo gairdneri, exposed to solutions of thiram (99 and 75% active ingredient, respectively). Exposure of bluegill sunfish, Lepomis macrochirus, to thiram (99 and 75% active ingredient) generated 96-hour LC$_{50}$s of 0.045 and 0.28 ppm, respectively. The 96-hour LC$_{50}$s (based on active ingredients) for two products each containing an 80% level of thiram
but 20% levels of dissimilar inactive ingredients to the freshwater mollusc, Lymnaea stagnalis, were 12 and 8.9 ppm for products A and B, respectively, in aqueous solutions (Bluzat et al., 1981). The 96-hour LC$_{50}$s for acetone suspensions of products A and B were 2.8 and 3.2 ppm, respectively.

Exposure of scud, Gammarus pulex, to 10, 5, 2 and 1 ppm of a commercial product containing 80% thiram resulted in 95, 79, 48 and 25% mortality after 10 days (Bluzat et al., 1982a). Groups of scud (n=130 and 190) exposed to 0.7 ppm aqueous suspensions of thiram 1, 48 and 96 hours after preparation of the test solutions experienced 84.6, 91.5 and 50% mortality levels, respectively, after 96 hours of treatment. The 96-hour LC$_{50}$s for two commercial thiram-containing products (80% active ingredient) to G. pulex were 0.20 ppm and 0.13 ppm for products A and B, respectively, in aqueous solutions (Bluzat et al., 1982b). The 96-hour LC$_{50}$s for products A and B in acetone were 0.22 and 0.06 ppm, respectively. The approximate median lethal times for G. pulex exposed to 0.02, 0.025, 0.035, 0.05 and 0.08 ppm solutions of thiram were 30, 8.5, 6.5, 4.5 and 5 days, respectively (Bluzat and Seuge, 1983). Scud offered bean seeds treated with 3000 and 10,000 ppm thiram demonstrated 90% survival after 3-3.5 days and 10% survival after 29-36 days. Scud offered mosses treated with 50-10,000 ppm thiram demonstrated 90% survival after 2.4-5.4 days and 10% survival after 9-27 days.

The 96-hour LC$_{50}$s for the flatworm, Dugesia gonocephala, the isopod, Asellus aquaticus, and the amphibian, Xenopus laevis, at two stages of development (47 and 53) were 0.048, 61, 0.013 and 0.021 ppm, respectively (Seuge et al., 1983). The 96-hour LC$_{50}$ for mayfly larvae, Cloeon dipterum, exposed to freshly prepared solutions of thiram was 1.01 mg/l. Solutions of thiram aged for 1, 7 and 36 hours produced mortality levels among mayfly larvae of 79.5, 64.7 and 45.3%, respectively, after 96 hours of exposure (Seuge and Bluzat, 1983).
The respective EC$_0$, EC$_{50}$ and EC$_{100}$ for *Daphnia magna* exposed to tetramethylthiuram disulfide were 0.05, 0.06 and 0.8 µg/l, respectively (Knle et al., 1983). Jouany et al. (1985) reported 0% mortality for the water flea, *Daphnia magna*, carp, *Cypinus carpio*, and zebrafish, *Brachydanio rerio*, exposed to <0.1, 1.0 and 0.1 mg/l after 24 hours. Zebrafish fed thiram-contaminated daphnids experienced a linear increase in mortality from 0-100% between 4 and 8 days after the initiation of the experiment. The 96- and 48-hour LC$_{50}$s for guppies, *Poecilia reticulata*, and daphnids, *Daphnia magna*, exposed to thiram were 0.27 and 0.21 µg/l, respectively (Van Leeuwen et al., 1985a). The 24-hour LC$_{50}$ of thiram (>98% purity) to rainbow trout, *Salmo gairdneri*, weighing 34.0 g was 0.26 µg/l. The 24-hour LC$_{50}$ for trout weighing ~47 g was 0.30 µg/l (Van Leeuwen et al., 1986a). Exposure of trout to thiram also resulted in significant changes in several blood parameters.

The 21-day LC$_{50}$ for thiram in the water flea, *Daphnia magna*, was 8 µg/l (Van Leeuwen et al., 1985b). The lowest tested concentration that resulted in a decrease in fecundity was 10 µg/l. The lowest tested concentration that resulted in a decrease in size of daphnids after 21 days was 1.8 µg/l. There were no significant effects on daphnids exposed to 1 µg/l of thiram over the 21-day study.

The 60-day LC$_{50}$ for embryolarval stages of rainbow trout, *Salmo gairdneri*, exposed to thiram was 1.1 µg/l (Van Leeuwen et al., 1986b). The 60-day EC$_{50}$ based on mortality and teratogenesis was 0.64 µg/l. The lowest concentrations at which there were no observable effects based on mortality, total embryotoxicity, length and weight were 1.0, <0.32, <0.32 and 0.56 µg/l, respectively. Exposure of juvenile rainbow trout to thiram for 21 days resulted in a concentration-related loss of glycogen in the liver at ≥25 µg/l and was associated with reduced body weight gain.
At 100 μg/l, thiram induced a proliferation of bile duct epithelial cells both with and without formation of new ductules. Cell necrosis was observed occasionally, and hemorrhages were apparent in the brain and spinal cord at 5 μg/l (Van Leeuwen et al., 1986c). Thiram is not expected to bioaccumulate significantly in aquatic organisms based on an estimated BCF value of 90.8.

Motility and topophototaxis of *Euglena gracilis* were inhibited to 50% of control organisms within 30 minutes of exposure to 10⁻⁶ M solutions of tetramethylthiuram disulfide (Diehn and Tollein, 1967). Cultures of the green alga, *Scenedesmus acutus*, exposed to 10 and 100 ppm tetramethylthiuram disulfide were dead after 1 and 3 days, respectively. The NOEL appears to be <0.5 ppm. Gangawane and Kulkarni (1979) reported a 25.4% reduction in growth for cultures of *Nostoc* sp. exposed to 500 ppm thiram and a 14.1% reduction in growth for cultures of *Tolypothrix* sp. exposed to 100 ppm thiram. Hutber et al. (1979) reported that growth of four species of blue-green algae, *Aphanocapsa* (strains 6308 and 6714), *Anabaena variabilis* and *Nostoc*, was reduced by 50% on exposure to 50, 100, 50 and 100 ppm thiram, respectively. The concentrations of thiram that inhibited growth completely were 100, >100, 100 and >100 ppm, respectively.

The minimal active dose of thiram required to produce reductions in the number of generations of the ciliate protozoan, *Colpidium campyllum*, was 0.3 mg/l (Dive et al., 1980). The 24-hour IC₅₀ for *Chlorella vulgaris* based on ATP levels was >2 ppm thiram (Vasseur et al., 1982). Knie et al. (1983) reported an EC₁₀ of >6 mg/l for the alga, *Haematococcus pluvialis*, exposed to tetramethylthiuram disulfide. Growth rates of the ciliates, *Tetrahymena thermophila* and *Tetrahymena pyriformis* strains, were inhibited completely at 1.0 mg/l thiram for all but one strain at 28°C (Dive et al., 1980).
Growth inhibition of amoebae exposed to thiram was achieved at concentrations ranging from 0.5-16 mg/l. Thiram at concentrations ranging from 0.25-1.0 mg/l induced a lengthening of the generation time in heat shock synchronized axenic cultures of Tetrahymena pyriformis (Grolliere and Dupy-Blanc, 1985).

The 72-hour IC$_{50}$ for growth of the green alga, Chlorella vulgaris, exposed to thiram as determined by optical density at 665 nm was ~5.5 mg/l (Jouany et al., 1985). The 96-hour EC$_{50}$s for the average specific growth rate and effects on the time-lag until maximum population growth in Chlorella pyrenoidosa were 1.0 and 0.03 mg/l, respectively (Van Leeuwen et al., 1985a). The EC$_{50}$ for assimilation of radioactive bicarbonate by C. pyrenoidosa was 4.0 mg/l. The EC$_{50}$ for respiration of $^{14}$C by C. pyrenoidosa was >10.0 mg/l.

Growth of a chrysomonad was inhibited completely following exposure to 210 μM thiram. Growth of the ciliate, Cyclidium sp., was inhibited completely at ~180 μM thiram (Taylor and Pace, 1987). Growth of a chlorophyte, Dunaliella tertiolecta, was inhibited at 4 μM thiram after 7 days. Growth of five other phytoplankton species was inhibited from ~0.2-18.6% of controls by exposure to 4 μM thiram for 7 days. The 15-minute EC$_{50}$ value for Photobacterium phosphoreum exposed to thiram was 0.1 mg/l (Van Leeuwen et al., 1985a). The lowest effective concentration or minimum inhibiting concentration of thiram on the nitrification process of a mixed culture of Nitrosomonas and Nitrobacter after 3 hours was 18 mg/l.

The oral LD$_{50}$s for thiram in mallard ducks, Anas platyrhynchos, and ring-necked pheasants, Phasianus colchicus, were >2800 and 673, respectively (Tucker and Crabtree, 1970). Egberts et al. (1972) reported no statistically significant effects in Japanese quail, Coturnix coturnix, offered feed
contaminated with 10 ppm thiram for 11 weeks. Birds fed 50 ppm contaminated feed demonstrated significant reductions in numbers of eggs laid and hatched and shell thickness of eggs. There were also significant reductions in the numbers of lymphocytes, granulocytes and monocytes of blood from birds dosed with 50 ppm thiram-contaminated feed. Heath et al. (1972) reported a lack of mortality among Japanese quail, *C. coturnix japonica*, and pheasant, *P. colchicus*, fed the highest concentration of thiram tested (5000 ppm in feed). Mallard ducks, *Anas platyrhynchos*, fed mash containing 5000 ppm thiram had 20% mortality.

Lorgue et al. (1975) reported that thiram-contaminated feed (20 gc Thirban/10 kg) caused immediate (24 hours) blockage of egg laying in quail and regression of secondary sexual characteristics in males. Lorgue and Soyez (1976) reported that thiram completely inhibited egg laying by gray partridges exposed to 1.6 g/kg within 48 hours. The incidence of embryonic mortality was increased significantly at 4-fold lower doses. The LD<sub>50</sub> and LC<sub>50</sub> of thiram to Japanese quail, *C. coturnix japonica*, were 695 and >10,000 mg/kg, respectively (Gruen et al., 1982). Hadhazy and Glavits (1982) reported that 100 and 200 g thiram/100 kg feed caused imperfect egg shell calcification and production of eggs with abnormal size and form in pheasants.

Earthworms, *Eisenia fetida* exposed to thiram by immersion had mortality levels ranging from 5%, 7 days posttreatment, to 38%, 101 days posttreatment (Roark and Dale, 1979). Worms fed thiram-treated bermudagrass clippings had mortality levels ranging from 10% after 34 days of treatment to 42% after 101 days. Mortality among worms reared in thiram-treated soil ranged from 21% after 10 days to 98.1% after 29 days and 99.9% after 52 days. The ALD of thiram to wild-trapped deer mice, *Peromyscus maniculatus*, was reported to be 1600 mg/kg (Schafer and Bowles, 1985).
5. PHARMACOKINETICS

5.1. ABSORPTION

Pertinent data regarding the absorption of thiram were not located in the available literature cited in Appendix A.

5.2. DISTRIBUTION

ACGIH (1986) stated that after absorption (respiratory, dermal, gastrointestinal), thiram is widely distributed, with much of the dose excreted unchanged in the urine and feces. Supporting data were not provided.

5.3. METABOLISM

In a general discussion of the reactions of the disulfide analogs of dialkyldithiocarbamates including thiram, Rannug and Rannug (1984) stated that these compounds have a tendency to participate in redox-reactions. For example, thiram is reduced by glutathione to dimethylthiocarbamate in two steps as illustrated in Figure 5-1. Thiram may also interact with SH-groups of proteins, which could result in the inhibition of a number of enzymes.

Dalvi and Deoras (1986) studied the metabolism of thiram to carbon disulfide in male Sprague-Dawley rats treated by intraperitoneal injection. Rats were treated with thiram in corn oil at doses of 15, 30 or 60 mg/kg, and expired air was collected and analyzed for carbon disulfide for 5 hours after dosing. The results indicated a dose-related increase in the proportion of the dose exhaled as carbon disulfide, with 0.510, 2.334 and 5.435 μmol carbon disulfide/g of thiram (0.012, 0.056 and 0.13% of administered dose) exhaled at doses of 15, 30 and 60 mg/kg, respectively. Carbon disulfide was detected beginning 1.5-2 hours after treatment. Pretreatment of rats with intraperitoneal injections of phenobarbital to induce microsomal enzyme activity resulted in a nonsignificant increase in the amount of carbon disulfide exhaled from a 60 mg/kg intraperitoneal dose of thiram.
FIGURE 5-1
Two-Step Reduction of Thiram to Dimethyldithiocarbamate Ion

Source: Rannug and Rannug, 1984
Pretreatment with SKF 525-A to inhibit microsomal enzyme activity resulted in a significant (p<0.05) decrease in the amount of carbon disulfide exhaled. According to the investigators, these results suggest the involvement of liver microsomal enzymes in the metabolism of thiram. Dalvi and Deoras (1986) noted that Merlevede and Peters (1965) detected carbon disulfide in expired air following oral administration of thiram to humans.

5.4. EXCRETION

Without providing documentation, ACGIH (1986) stated that thiram is "mainly excreted unchanged in urine and feces." Dalvi and Deoras (1986) reported a dose-related increase in the amount of carbon disulfide exhaled following the treatment of rats with an intraperitoneal injection of thiram (15-30 mg/kg). Other routes of excretion were not studied.

5.5. SUMMARY

Although specific quantitative data concerning the pharmacokinetics of thiram are limited, ACGIH (1986) stated (without providing documentation) that following absorption, thiram is widely distributed, and is predominantly excreted unchanged in the urine and feces. Rannug and Rannug (1984) stated that thiram and other disulfides have a tendency to participate in redox-reactions. Thiram is reduced by glutathione to dimethyldithiocarbamate, and it may also interact with SH-groups of proteins, which may result in the inhibition of a number of enzymes. Dalvi and Deoras (1986) reported a dose-related increase in the amount of carbon disulfide exhaled following treatment of rats with an intraperitoneal injection of thiram.
6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposure.

6.1.1.1. SUBCHRONIC -- Pertinent data regarding the toxicity of thiram following chronic inhalation exposure were not located in the available literature cited in Appendix A.

6.1.1.2. CHRONIC -- Fishbein (1976) summarized a report by Sivitskaya (1974) concerning ophthalmologic changes in 50 workers (20-58 years old) with prolonged occupational contact (not otherwise specified) with thiram. The predominant route of exposure and exposure concentrations were not stated. The initial symptoms reported were lacrimation and photophobia, which disappeared after prolonged interruption of contact with thiram. Additional symptoms reported were chronic conjunctivitis, reduced visual acuity, delayed dark adaption, reduced corneal sensitivity, change in the diameter of the retinal vessels and increased tonometric and retinal artery pressure.

6.1.2. Oral Exposure.

6.1.2.1. SUBCHRONIC -- In a 13-week study, Lee et al. (1978) provided groups of 20 young male CD rats with practical grade thiram in the diet at 0, 0.05, 0.1 or 0.25%. Variables evaluated included general appearance and behavior, food intake, body weights, comprehensive hematology and blood chemistry analyses, organ weights and comprehensive histopathological examinations. According to the investigators, these diets provided thiram doses of 0, 30, 58 or 132 mg/kg/day. Body weight gain was 81, 64 and 22% of controls in low-, middle- and high-dose rats. Statistical analysis of body weight gain data was not performed. Food intake was also reduced in a dose-related manner in all treated groups compared with controls. One rat
treated at 58 mg/kg/day and five at 132 mg/kg/day died. At 132 mg/kg/day, SGOT and SGPT were mildly elevated, while a mild elevation of BUN was noted in rats treated at 58 mg/kg/day. No changes in hematological parameters were reported. The only histological effect observed was mild tubular degeneration of the testes with atypical spermatids in the epididymis in rats treated at 132 mg/kg/day. In another report of this study, Short et al. (1976) stated that rough hair coats and alopecia were observed at 58 and 132 mg/kg/day. In contrast to the report by Lee et al. (1978), Short et al. (1976) stated that 70% of the rats died at 132 mg/kg/day.

In a study by Lowy et al. (1979, 1980), groups of six young (0.080 kg) male Wistar rats were fed diets containing thiram (90% pure) at 0, 225, 300, 450, 600, 900 or 1200 ppm for 29 days. Similar groups of rats were maintained as pair-fed controls. Based on food intake and body weight data provided by the investigators (Lowy et al., 1980), the rats were treated with thiram at estimated doses of 0, 33.6, 41.9, 54.7, 71.9, 106.7 or 143.4 mg/kg/day. The results indicated that body weight gain was significantly reduced (Fisher-Snedecor F test) compared with pair-fed controls at 300 ppm (41.9 mg/kg/day) on study days 16 and 19, and was consistently reduced compared with pair-fed controls at ≥450 ppm (≥54.7 mg/kg/day). Organ weight measurements indicated a dose-related decrease in the weights of epididymal fat pads, and perirenal fat pads that were significantly different from pair-fed controls at all doses. Dose-related decreases in the weights of the kidneys (significant at ≥900 ppm), testes (significant at ≥900 ppm) and seminal vesicles (significant at ≥450 ppm) were also noted. Organ weight data were applied to a model designed to estimate the lowest dosage that would result in a statistically significant effect, and conventionally derived levels of significance (p values) were not provided. Histological
examinations and hematological analyses were not performed. The use of pair-fed controls in this study provides evidence that decreased body weight gain is a result of thiram treatment rather than just a result of decreased food intake.

In a 28-day study, Hornshaw et al. (1987) fed groups of two male and two female standard dark mink (5-6 months old) and groups of five male and five female agouti-colored ferrets (6-7 months old) thiram (analytical grade) in the diet. Mink were fed at dietary levels of 0, 45 or 82 ppm thiram. Additional groups of five mink/sex were fed at 147 and 265 ppm, but these groups were terminated after 2 weeks because the minks avoided the diets. Ferrets were fed at 0, 8, 20, 50, 125 and 312 ppm. Based on body weight and food intake data provided by the authors, mink were treated at doses of 0, 8.6 or 12.6 mg/kg/day for males, and 0, 6.6 or 9.5 mg/kg/day for females, and ferrets were treated at doses of 0, 1.1, 2.8, 5.6, 14.8 or 27.5 mg/kg/day for males and 0, 1.6, 3.3, 8.6, 16.5 or 44.8 mg/kg/day for females. No treatment-related deaths were reported in mink, and no changes in organ weights or gross lesions were observed at necropsy (histological examinations were not performed). Effects observed in mink at 82 ppm included a reduction in food consumption, loss of body weight and bloody feces. Hematocrit values for mink treated at 45 and 82 ppm were significantly (p<0.01) below control values. In ferrets, all animals treated at 312 ppm died between days 11 and 16. Signs of toxicity observed in these animals included bloody feces, inanition, listlessness, incoordination and occasional convulsions accompanied by intense vocalization. Changes in body weight were significantly different from controls in male ferrets at ≥20 ppm (p<0.05) and in females at ≥125 ppm (p<0.01). At necropsy, spleen weights were increased in females fed at 125 ppm. No gross lesions were observed.
RBC counts and hemoglobin values were significantly (p<0.01) reduced in ferrets compared with controls at 50 and 125 ppm, and hematocrit was also significantly reduced (p<0.05) at 50 ppm. The investigators stated that based on this study, a dietary NOEL for mink was not found, while a level of 8 ppm was a dietary NOEL for ferrets. This study is difficult to interpret because body weights of mink and ferrets were highly variable, thiram treatment decreased food intake and group sizes were small.

6.1.2.2. CHRONIC -- Lee and Peters (1976) reported neurotoxicity and behavioral effects of thiram in CD rats. Groups of 24 rats/sex were fed diets containing practical grade thiram at 0, 0.01, 0.04 or 0.1% for 80 weeks. The diets were adjusted during the study to maintain thiram doses at about 0, 5.3, 20.4 and 52 mg/kg/day for males and 0, 6.1, 25.5 and 66.9 mg/kg/day for females. The rats were observed for overt signs of neurobehavioral toxicity and given experimental behavioral tests (hind leg walking gait, jump/climb ability, open field test). Among high-dose female rats, eight developed hind limb ataxia or paralysis. These rats became very emaciated near the end of the study. Histological examinations of the gastrocnemius muscle, sciatic nerve and spinal cord of two ataxic rats revealed demyelination and degeneration of the sciatic nerve, and degeneration of the lumbar region of the spinal cord. Analysis of the hind leg walking gait of female rats indicated a significant (p<0.05) difference in stride width and the angle between the hind feet in rats treated at ≥25.5 mg/kg/day and controls. Nonataxic high-dose female rats required significantly (p<0.01) more shocks and cleared a lower height in the jump/climb ability test compared with control, low- and mid-dose rats. In the open-field test, mid-dose males and high-dose males and females (including five ataxic females) were hyperactive.
In a second part of this study, groups of 24 female rats were fed diets containing thiram that provided dosages of 0 or 65.8 mg/kg/day for 36 weeks (Lee and Peters, 1976). Impaired nerve conduction, peripheral neuropathy, ataxia and paralysis were observed in 4/24. When picked up by the tail, 9 treated rats exhibited hindfoot clasping.

Lee et al. (1978) reported additional effects observed in the 80-week rat study described above. Alopecia was observed among ataxic and nonataxic high-dose rats and in a few mid-dose rats. It is not clear if hair loss occurred only in females or in both sexes. Body weight gain was reduced compared with controls at all doses in males and in high- and mid-dose females. Blood and clinical analyses completed on four rats/sex/group were similar to controls. At necropsy, results of organ weight measurements showed increased relative thyroid and testes weight in high-dose males, and increased relative liver, kidney, thyroid, ovary and brain weights in high-dose females, with relative spleen weights increased in both high- and mid-dose females. Statistical analyses and actual values for blood and clinical chemistry studies and organ weights were not provided. Histopathological examinations revealed a dose-related increase in the incidence and severity of fatty infiltration of the pancreas in male rats, with 1/17, 3/13, 11/15 (p=0.0001, Fisher Exact test run at Syracuse Research Corporation) and 14/16 control, low-, middle- and high-dose rats affected. Fatty infiltration of the pancreas was found in only 1/11 high-dose female rats. Squamous metaplasia of the thyroid was observed in 4/16 and 3/11 high-dose male and female rats, compared with 1/17 male and 0/18 female control rats. Specific lesions of the central and peripheral nervous systems were not observed in nonataxic, ataxic or paralyzed rats, with the exception of the lesions reported in two ataxic rats (Lee and Peters, 1976).
U.S. EPA (1987a) cited a 2-year industry study (E.I. Du Pont de Nemours & Co., n.d.) in which groups of 24 rats (strain and sex not specified) were fed thiram (purity not provided) in the diet at 0, 100, 300, 1000 or 2500 ppm. Observations and tests reported included body weight, mortality, clinical signs, neurological examination and microscopic examination of tissues. Weakness, ataxia, varying degrees of hind limb paralysis, and calcified masses in the basal ganglia and cerebellum were observed at 300, 1000 and 2500 ppm. Additional information concerning this study was not provided.

Abstracts briefly describe 2-year Japanese studies using rats and dogs. Maita et al. (1980) fed diets containing thiram at 0, 3, 30 or 300 ppm to groups of 64 JCL Wistar SPF rats of both sexes. Examinations included urinalysis, hematology, blood biochemistry, ophthalmoscopy, organ weights and histopathology. Interim kills of eight rats/sex/group were performed at 13, 26 and 52 weeks. Effects were restricted to the 300 ppm level and included reduced food consumption and growth, reduced erythrocyte count in females during the first year of the study, and reduced muscle mass and an increased incidence of muscle lesions (not specified), compared with controls. The investigators concluded that 30 ppm, equivalent to 1.15 mg/kg/day for males and 1.39 mg/kg/day for females, was a NOEL.

Saito et al. (1980) treated groups of four beagle dogs/sex with thiram in gelatin capsules at dosages of 0, 0.4, 4 or 40 mg/kg/day. Examinations included hematology, blood biochemistry, urinalysis and ophthalmoscopy at 0, 4, 13, 26, 39, 52, 78 and 104 weeks, and organ weights and histopathology at termination. All dogs at 40 mg/kg/day died within 6-29 weeks. Other effects observed at this dosage included vomiting, salivation, convulsions, ocular changes, a marked decrease in erythrocyte counts, and altered blood
biochemistry including elevated SGOT and SGPT. Some dogs at 4 mg/kg/day exhibited vomiting, salivation and clonic convulsions. A slight to moderate reduction in erythrocyte count was observed during the first 13 weeks of exposure, but not thereafter. At termination, the liver exhibited hepatocellular atrophy and granuloma formation with an increase in brown pigmentation. No effects were reported at 0.4 mg/kg/day.

6.1.3. Other Relevant Information. Acute toxicity data for thiram are summarized in Table 6-1, which indicates that oral LD\textsubscript{50} values have varied between investigators, with 2300 mg/kg in female NMRI mice (Matthiaschik, 1973) reported as the highest value, and 190 mg/kg in female CD rats (Lee et al., 1978) reported as the lowest value. Studies in which male and female rats or mice were studied separately appear to indicate little gender-related difference in sensitivity.

Thuranszky et al. (1982) studied the effect of thiram or carbon disulfide on the nervous system of male Wistar rats treated with a single oral dose. Endpoints examined were the "orientation of hypermotility" (measured using an LKB ANIMEX activity meter), analysis of dopamine and the formation of norepinephrine and epinephrine from 3H-tyrosine (rats were pretreated with an intraperitoneal injection of 3H-tyrosine). The results indicated that thiram (240 mg/kg) or carbon disulfide treatment (152 mg/kg) significantly reduced the "orientation of hypermotility" (not otherwise specified), compared with untreated controls. The effect was comparable to meprobamat, a tranquilizer. Both thiram (60 mg/kg) and carbon disulfide (152 mg/kg) resulted in an increase in dopamine levels and a decrease in norepinephrine and epinephrine formation. The investigators suggested that the effects were consistent with a proposed mechanism of inhibition of
<table>
<thead>
<tr>
<th>Species/Strain</th>
<th>Sex</th>
<th>Route</th>
<th>LD$_{50}$ (mg/kg)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats/Sherman</td>
<td>M</td>
<td>oral</td>
<td>640</td>
<td>Gaines, 1969</td>
</tr>
<tr>
<td>Rat/CD</td>
<td>M</td>
<td>oral</td>
<td>400</td>
<td>Lee et al., 1978</td>
</tr>
<tr>
<td>Rats/Sherman</td>
<td>F</td>
<td>oral</td>
<td>620</td>
<td>Gaines, 1969</td>
</tr>
<tr>
<td>Rat/CD$-$</td>
<td>F</td>
<td>oral</td>
<td>190</td>
<td>Lee et al., 1978</td>
</tr>
<tr>
<td>Mice/CD-1</td>
<td>M</td>
<td>oral</td>
<td>400</td>
<td>Lee et al., 1978</td>
</tr>
<tr>
<td>Mice/CD-1</td>
<td>F</td>
<td>oral</td>
<td>380</td>
<td>Lee et al., 1978</td>
</tr>
<tr>
<td>Mice/NMRZ</td>
<td>F</td>
<td>oral</td>
<td>2300</td>
<td>Matthiaschek, 1973</td>
</tr>
<tr>
<td>Rats/Wistar</td>
<td>M,F</td>
<td>i.p.</td>
<td>248</td>
<td>Poitou et al., 1978</td>
</tr>
<tr>
<td>Rats/Sherman</td>
<td>M,F</td>
<td>dermal</td>
<td>&gt;2000</td>
<td>Gaines, 1969</td>
</tr>
</tbody>
</table>

i.p. = intraperitoneal
dopamine-β-hydroxylase activity and suggested that carbon disulfide may be responsible for at least some of the nervous system effects observed following thiram treatment.

Dalvi and Deoras (1986) treated male Sprague-Dawley rats with an intraperitoneal injection of thiram in corn oil (60 mg/kg) and examined the effect on hepatic microsomal enzymes 5 and 24 hours after treatment. Elevated serum sorbitol dehydrogenase levels and SGOT levels were observed at 5 and 24 hours, with significant \( p < 0.05 \) increases found 24 hours after treatment. Liver cytochrome P-450 activity and benzphetamine N-demethylase activity were significantly \( p < 0.05 \) decreased at 24 hours, but not at 5 hours after dosing.

Thiram, similar in structure to Antabuse, is a potent inhibitor of microsomal monoxygenases including aldehyde dehydrogenase and dopamine β-dehydrogenase (ACGIH, 1986). Combined exposure to thiram and ethanol can result in the accumulation of acetaldehyde. In a study by García de Torres et al. (1983), treatment of female Wistar rats with two oral doses of thiram at 16 or 256 \( \mu \text{mol/kg} \) (3.8 or 61.5 mg/kg) followed by an intraperitoneal injection of ethanol (2 g/kg) resulted in a significant increase in the blood acetaldehyde level for \( \leq 240 \) minutes after ethanol treatment. The increase in blood acetaldehyde was still detectable in rats pretreated with thiram (16 \( \mu \text{mol/kg} \) 48 hours before treatment with ethanol.

Fenyvesi et al. (1985) reported that combined oral treatment of female Wistar rats with thiram (10 mg/kg) and the drugs promethazine or meprobamate (dose not specified) resulted in a potentiation of the CNS effects of the drugs. Treatment with thiram and trihexyphenidyl resulted in an additive effect.
6.2. CARCINOGENICITY

6.2.1. Inhalation. Pertinent data regarding the carcinogenicity of thiram following inhalation exposure were not located in the available literature cited in Appendix A.

6.2.2. Oral. In a carcinogenicity study sponsored by BRL (1968a), groups of 18 (C57BL/6xC3H/Anf)F1 mice/sex and 18 (C57/BL/6xAKR)F1 mice/sex were treated orally with commercial thiram (purity not reported). Gavage treatment at a dose of 10 mg/kg/day in gelatin was initiated when the mice were 7 days old. At 4 weeks of age, the mice were provided with diets containing thiram at 26 ppm. The IARC (1976) review of this study stated that treatment was an MTD for infant and young mice, but may not have been an MTD for adults. The number of mice surviving to 78 weeks of age, when the experiment was ended, was 16 male and 18 female (C57BL/6xC3H/Anf)F1 mice and 18 male and 15 female (C57/BL/6xAKR)F1 mice. Tumor incidences were not significantly greater in thiram treated mice compared with 79-90 necropsied negative control mice of each sex and strain, which had been treated with gelatin or had been left untreated.

In an 80-week study, Lee et al. (1978) did not observe increased tumor incidences in CD rats treated with thiram in the diet at concentrations that provided doses of 0, 5.3, 20.4 and 52 mg/kg/day for males and 6.1, 25.5 and 66.9 mg/kg/day for females. Additional details of this study are presented in Section 6.1.1.2.

Takahashi et al. (1983) examined the potential carcinogenicity of thiram in F344 rats treated for 2 years. Groups of 50 rats/sex were fed diets containing thiram (99.76% pure) at 0, 0.05 or 0.1% (0, 500 or 1000 ppm). Body weights of the high-dose rats were slightly depressed. No effects on mortality, gross pathology or histopathology were observed. Treated male
and female rats exhibited a significantly lower incidence of leukemia than controls and historical controls. Although not significant, incidences of pituitary chromophore tumors in females and thyroid C-cell adenomas in males were also reduced. The investigators speculated that thiram, a known inhibitor of hepatic microsomal monooxygenases, may alter metabolism or the endocrine state of the animal to inhibit spontaneous tumor development.

In a study that examined the carcinogenicity of simultaneous treatment with thiram and sodium nitrite, Lijinsky (1984) fed 24 male and 24 female F344 rats a diet containing thiram at 500 ppm and sodium nitrite at 2000 ppm for 130 weeks. Additional groups of rats were fed the basal diet, basal diet containing thiram (500 ppm) or basal diet containing sodium nitrite (2000 ppm). The study began at thiram concentrations of 750 ppm, but because of decreased food intake the concentration was lowered to 500 ppm after 3 weeks of treatment. Lijinsky (1984) noted that the only biological effect observed was the production of copious amounts of urine by rats treated with thiram and nitrite. No explanation of this effect was available, and the kidneys did not appear to be adversely affected. Only the survival of thiram and nitrite treated rats was affected, with deaths from treatment-related tumors. Tumors incidences that were increased in thiram and nitrite treated rats compared with controls were nasal cavity tumors (18/24 treated males, 0/24 untreated control males; 15/24 treated females, 0/24 untreated control females) and forestomach tumors (5/24 treated males, 0/24 untreated control males; 5/24 treated females, 0/24 untreated control females). Increased tumor incidences were not observed in rats treated with only thiram or nitrite. Lijinsky (1984) noted that "although this study was not large enough to state categorically that thiram is noncarcinogenic in rats, we feel that a maximally tolerated dose was achieved, and that, therefore, the carcinogenic effect of thiram in rats, if any, must be very weak."
The carcinogenic effect of simultaneous treatment with thiram and nitrite may be the result of the formation of N-nitrosodimethylamine. IARC (1976) stated that Elespuru and Lijinsky (1973) and Sen et al. (1974) found that thiram reacts with nitrite at the acid pH in the stomach of guinea pigs, resulting in the formation of N-nitrosodimethylamine.

6.2.3. Other Relevant Information. BRL (1968a) treated groups of 18 (C57BL/6xC3H/Anf)F1 mice/sex and 18 (C57/BL/6xAKR)F1 mice/sex with a single subcutaneous injection of commercial thiram in gelatin at a dose of 46.4 mg/kg. The mice were treated at 28 days of age and observed until 78 weeks of age. Tumor incidences were not increased compared with 141-161 untreated or vehicle treated controls. IARC (1976) noted that "a single subcutaneous injection may not be an adequate basis for discounting carcinogenicity."

Goodyear Tire & Rubber Co. (1982) reported that thiram did not increase the frequency of transformation in BALB/3T3 cells in vitro. The concentration range tested, 2.8-13.8 pg/mL, resulted in 12 to ~90% survival. In preliminary tests, no cells survived at concentrations >25 pg/mL.

6.3. MUTAGENICITY

Mutagenicity data for thiram are summarized in Table 6-2. Thiram has been tested in numerous systems with inconsistent results. Thiram has generally tested positive in at least one strain of Salmonella typhimurium (TA100) without metabolic activation, but the available studies do not clearly indicate if S-9 increases or decreases the mutagenic activity of thiram. Mixed results have been reported for several assays in Chinese hamster V79 cells, sex-linked recessive lethals in Drosophila melanogaster and micronucleus tests in mice. Tests reporting positive results for thiram include mutation in CHO cells and Aspergillus nidulans, DNA damage in Escherichia coli, prophage lambda induction in E. coli and increases in the
<table>
<thead>
<tr>
<th>Assay</th>
<th>Indicator Organism</th>
<th>Purity</th>
<th>Application</th>
<th>Concentration/ Dose</th>
<th>Activating System</th>
<th>Response</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reverse mutation</td>
<td>Salmonella typhimurium TA1535, TA90, TA1538, TA1537, TA100</td>
<td>NR</td>
<td>plate incorporation</td>
<td>0.1-32 μg/plate</td>
<td>+ S-9</td>
<td>+ TA100</td>
<td>None</td>
<td>Goodyear Tire &amp; Rubber Co., 1979</td>
</tr>
<tr>
<td></td>
<td>S. typhimurium</td>
<td>98%</td>
<td>plate incorporation or pre-incubation</td>
<td>59-200 μg/plate</td>
<td>+ S-9</td>
<td>+ TA1538, TA90</td>
<td>Mutagenic activity in TA1535 and TA100 disappeared following a 20-minute pre-incubation period with S-9, L-cystein, or glutathione. Pre-incubation with L-cysteine glutathione (not S-9) reduced mutagenicity to TA1538 and TA90.</td>
<td>Zdzienicka et al., 1979</td>
</tr>
<tr>
<td></td>
<td>TA1535, TA100, TA1538, TA90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-/+ TA1535, TA98</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>S. typhimurium</td>
<td>NR</td>
<td>plate incorporation</td>
<td>5-5000 μg/plate</td>
<td>+ S-9</td>
<td>+ TA100; weakly + TA1535 - TA1537, TA1538 TA98</td>
<td>The response was dose-related in TA1535.</td>
<td>Moriya et al., 1978, 1983</td>
</tr>
<tr>
<td></td>
<td>TA1535, TA1537, TA1538, TA90, TA100</td>
<td>technical and purified</td>
<td>plate incorporation</td>
<td>0.5-25 μg/plate</td>
<td>+ S-9 TA100 none for strains</td>
<td>+/+ TA100 weakly + TA1537, TA1538</td>
<td>S-9 induced a slight increase in activity in TA100.</td>
<td>Hedenstedt et al., 1979</td>
</tr>
<tr>
<td></td>
<td>S. typhimurium</td>
<td>purified</td>
<td>plate incorporation</td>
<td>5-50 μg/plate</td>
<td>+ S-9 and NADP</td>
<td>+/ without S-9 in all strains except TA1530 + with S-9 and NADP (only TA100 tested)</td>
<td>Incubation in oxygen-rich atmosphere increased the number of mutations. Glutathione added with S-9 and NADP greatly reduced the mutagenicity of thiram.</td>
<td>Rannug and Rannug, 1984</td>
</tr>
<tr>
<td></td>
<td>TA1535, TA1537, TA90, TA100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Escherichia coli</td>
<td>NR</td>
<td>plate incorporation</td>
<td>5-5000 μg/plate</td>
<td>+ S-9</td>
<td>-</td>
<td>Number of revertants increased weakly but did not show a dose-response relationship.</td>
<td>Moriya et al., 1983</td>
</tr>
<tr>
<td></td>
<td>MP2 her</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repair test</td>
<td>S. typhimurium</td>
<td>98%</td>
<td>spot test</td>
<td>50 or 100 μg/plate</td>
<td>+ S-9</td>
<td>-</td>
<td>Difference in zones of killing between the two strains only without S-9 suggests that thiram causes damage that is not repaired in the TA1978 (rev^) strain</td>
<td>Zdzienicka et al., 1981</td>
</tr>
<tr>
<td></td>
<td>TA1538 his D3052</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>sfaVrR, TA1978</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>his D3052rfa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td>Indicator Organism</td>
<td>Purity</td>
<td>Application</td>
<td>Concentration/Dose</td>
<td>Activating System</td>
<td>Response</td>
<td>Comment</td>
<td>Reference</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------</td>
<td>--------</td>
<td>---------------------------</td>
<td>--------------------</td>
<td>-------------------</td>
<td>----------</td>
<td>-------------------------------------------------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>DNA damage</td>
<td>E. coli M3110(Pol A⁺) p3070(Pol A⁻)</td>
<td>NR</td>
<td>pre-incubation</td>
<td>0.5-5000 µg/tube</td>
<td>S-9</td>
<td>+/+</td>
<td>More effective without S-9 than in the presence of S-9.</td>
<td>Goodyear Tire &amp; Rubber Co., 1981</td>
</tr>
<tr>
<td>Prophage λ induction</td>
<td>E. coli GYS027, GYS4018</td>
<td>98%</td>
<td>added to cultures</td>
<td>up to 10⁶ ng/assay</td>
<td>S-9</td>
<td>+</td>
<td>Only a slight increase in prophage λ induction in the presence of S-9.</td>
<td>Zdzientcka et al., 1981</td>
</tr>
<tr>
<td>Gene mutation</td>
<td>Aspergillus niger A</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>S-9</td>
<td>-/+</td>
<td>None</td>
<td>Szymczyk, 1981</td>
</tr>
<tr>
<td>forward mutation</td>
<td>A. nidulans 35</td>
<td>98%</td>
<td>plate and liquid tests</td>
<td>0.5-4 µg/plate or 0.01-2.5 µg/ml</td>
<td>S-9</td>
<td>-/+</td>
<td>None</td>
<td>Zdzientcka et al., 1981</td>
</tr>
<tr>
<td>Chromosome mis-segregation</td>
<td>A. nidulans</td>
<td>commercial preparation</td>
<td>added to cultures</td>
<td>20-40 ppm</td>
<td>none</td>
<td>+</td>
<td>Survival was 17-25% over the range of concentration studied.</td>
<td>Upshall and Johnson, 1981</td>
</tr>
<tr>
<td>Reverse mutation</td>
<td>CHO cells</td>
<td>NR</td>
<td>added to cultures</td>
<td>0.05 or 0.1 µg/ml</td>
<td>none</td>
<td>+</td>
<td>Thiram was very toxic to cells with only -2% of cells surviving at 0.1 µg/ml.</td>
<td>Goodyear Tire &amp; Rubber Co., 1980a</td>
</tr>
<tr>
<td>Point mutation</td>
<td>Chinese hamster V79 cells</td>
<td>technical grade 80%</td>
<td>added to cultures</td>
<td>0.01-20.0 µg/ml</td>
<td>none</td>
<td>+ at concentrations that were cytotoxic</td>
<td>Paschke and Bakitova, 1985</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chinese hamster V79 cells</td>
<td>technical</td>
<td>added to cultures</td>
<td>0.2-1.6 µg/ml</td>
<td>S-9</td>
<td>=</td>
<td>Survival low at &gt;10 µg/ml</td>
<td>Paschke and Bakitova, 1985</td>
</tr>
<tr>
<td>Anaphase-telephase test</td>
<td>CHO</td>
<td>commercial formulation</td>
<td>added to cultures</td>
<td>100 µg/ml</td>
<td>none</td>
<td>=</td>
<td>Frequency of cells with chromatid bridges or multi-polar mitoses was not increased in thiaram-treated cells. Frequency of cells in anaphase decreased, and the frequency of cells in telophase increased.</td>
<td>Dulout et al., 1982</td>
</tr>
<tr>
<td>Sister chromatid exchange</td>
<td>Chinese hamster ovary cells</td>
<td>technical</td>
<td>added to cultures</td>
<td>10⁻⁷ to 10⁻³ M</td>
<td>S-9</td>
<td>=</td>
<td>Toxic at ≥5x10⁻⁸ M without S-9; S-9 decreased toxicity</td>
<td>Donner et al., 1983</td>
</tr>
<tr>
<td>Assay</td>
<td>Indicator Organism</td>
<td>Purity</td>
<td>Application</td>
<td>Concentration/ Dose</td>
<td>Activating System</td>
<td>Response</td>
<td>Comment</td>
<td>Reference</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------------</td>
<td>-----------</td>
<td>----------------------------------</td>
<td>---------------------</td>
<td>-------------------</td>
<td>-----------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Unscheduled DNA synth</td>
<td>thymus cells from Mistar rats</td>
<td>90.8%</td>
<td>added to cultures</td>
<td>0.1-10 μg/ml/mt</td>
<td>none</td>
<td>-</td>
<td>None</td>
<td>Rocchi et al., 1980</td>
</tr>
<tr>
<td></td>
<td>human lymphocytes</td>
<td>90.8%</td>
<td>added to cultures</td>
<td>1 μg/ml/mt</td>
<td>none</td>
<td>-</td>
<td>None</td>
<td>Rocchi et al., 1980</td>
</tr>
<tr>
<td>Sex-linked recessive lethal</td>
<td>Drosophila melanogaster</td>
<td>NR</td>
<td>male flies were fed the compound</td>
<td>100-10,000 μg/ml food solution</td>
<td>NA</td>
<td>reproduction and mutagenicity</td>
<td>Test was not sensitive to &lt;10-fold increase in mutagenicity.</td>
<td>Goodyear Tire &amp; Rubber Co., 1980b</td>
</tr>
<tr>
<td></td>
<td>D. melanogaster</td>
<td>technical</td>
<td>male flies were fed thiram</td>
<td>0.04-4.0 mg/ml</td>
<td>NA</td>
<td>+</td>
<td>None</td>
<td>Donner et al., 1983</td>
</tr>
<tr>
<td>Micronucleus</td>
<td>bone marrow erythrocytes of Chinese hamsters</td>
<td>technical</td>
<td>thiram given to hamsters by gavage</td>
<td>100, 200, 500 μg/kg</td>
<td>NA</td>
<td>-</td>
<td>Thiram decreased the ratio of polychromatic to nonpolychromatic erythrocytes (indicates that thiram is cytotoxic).</td>
<td>Donner et al., 1983</td>
</tr>
<tr>
<td></td>
<td>male Balb/c mice</td>
<td>commercial formulation</td>
<td>two intraperitoneal injections at 24-hour intervals</td>
<td>100, 500 or 1000 mg/kg</td>
<td>NA</td>
<td>+ at &gt;500 mg/kg</td>
<td>Mice were killed 6 hours after second injection; 2/5 mice died following treatment with thiram at 1000 mg/kg.</td>
<td>Dulout et al., 1982</td>
</tr>
<tr>
<td></td>
<td>male and female (CBAxC57BL/6J) F1 grade, 80% mice</td>
<td>technical</td>
<td>intraperitoneal injection</td>
<td>100 mg/kg</td>
<td>NA</td>
<td>+ at all sampling times (maximum at 24 hours)</td>
<td>Bone marrow was examined 24, 36 and 48 hours after treatment with thiram.</td>
<td>Paschin and Bakitova, 1985</td>
</tr>
<tr>
<td>Chromosomal aberrations, sperm-head morphology</td>
<td>sperm of treated Swiss albino mice</td>
<td>NR</td>
<td>gavage dose in 5% gum acacia</td>
<td>total of 80, 200 or 320 in 3 doses, 24 hours apart</td>
<td>NA</td>
<td>+ numerical chromosome aberrations, + abnormal sperm</td>
<td>Mice were killed 60 days after the last dose.</td>
<td>Prasad et al., 1987</td>
</tr>
<tr>
<td>Sperm-head abnormalities</td>
<td>male (CF1xC57BL/6J) F1 mice</td>
<td>98%</td>
<td>single dose or 5 consecutive, daily intraperitoneal injections</td>
<td>0-100 mg/kg</td>
<td>NA</td>
<td>- at 1 week after treatment + at 5 weeks after treatment</td>
<td>Results indicate that thiram treatment caused effects on late spermatogonia or early primary spermatocytes, but no effect on spermatids.</td>
<td>Zdzienicka et al., 1982</td>
</tr>
</tbody>
</table>

NA = Not applicable; NR = not reported
number of abnormal sperm and chromosomal aberrations in treated mice. Tests reporting negative results for thiram include mutation in E. coli, sister chromatid exchange and the anaphase-telophase test in CHO cells, and unscheduled DNA synthesis in thymus cells from rats and human lymphocytes.

Rannug and Rannug (1984) proposed that mutagenicity induced by thiram may result from the inhibition of enzymes involved in protecting against harmful oxygen species. Thiram may react with sulfhydryl groups in enzymes, or may react to form dithiocarbamate metal chelate complexes, decreasing the activity of enzyme systems requiring metal ions. Experiments by Rannug and Rannug (1984) that found increased mutagenicity in S. typhimurium strain TA100 in the presence of increased oxygen, copper sulfate and menadione, which results in the formation of large amounts of singlet oxygen and \( \text{H}_2\text{O}_2 \) inside the cell, support this hypothesis.

6.4. TERATOGENICITY

Robens (1969) studied the teratogenicity of thiram in Syrian golden hamsters. Groups of four to eight pregnant hamsters were treated by gavage with thiram in DMSO or CMC at doses of 0 (vehicle control), 31, 63, 125, 250 or 500 mg/kg (DMSO) or 0 (vehicle control), 125, 250, 300 or 500 mg/kg CMC) on gestation day 7 or 8. Dams were sacrificed on gestation day 15, and the viability of fetuses was studied by placing them in an incubator for 6 hours. Maternal mortality occurred in hamsters at doses \( \geq 125 \) mg/kg, and at 500 mg/kg in hamsters treated with thiram in DMSO and CMC, respectively. Litters were resorbed completely from one or more hamsters at \( \geq 125 \) mg/kg thiram in DMSO and \( \geq 300 \) mg/kg thiram in CMC. There was a dose-related decrease in the number of live fetuses/litter and an increase in percent fetal deaths for thiram in DMSO and in CMC groups. In addition, there was a dose-related decrease in fetal weight for thiram in DMSO groups. At 500
mg/kg/day thiram in either vehicle, there was 100% fetal death. It is not clear how many fetuses were examined for visceral and skeletal effects. The investigator stated that "the percentage of fetuses showing terata would probably be larger if all of the fetuses had been stained and examined for bone anomalies." It was difficult to assess the teratogenic effects of thiram in DMSO because DMSO is teratogenic. Robens (1969) considered that the teratogenic effect of DMSO and thiram was additive or slightly more than additive. The most common abnormalities in thiram-treated and DMSO-control hamsters were exencephaly and fused ribs. In addition, a few fetuses in the thiram in DMSO group were found to have heart defects, predominantly of the great vessels. Fused ribs were the most common anomaly observed in fetuses from hamsters treated with thiram in CMC. Although the effects of thiram in CMC on the number of fetuses/litter, fetal mortality, average fetal body weight and the number of fetuses with terata appeared to be dose-related, statistical analyses were not performed. The investigator concluded, however, that thiram in CMC was teratogenic at ≥250 mg/kg.

An abstract of a study by Roll (1971) reported that thiram was teratogenic to NMRI and SW mice. The mice were treated between gestation day 6 and 17 and "during other stages of gestation." There was a dose-related increase in resorptions and "impaired fetal development". Mice were most susceptible when treated on gestation day 12 and 13. NMRI mice were more susceptible than SW mice to the development of cleft palate. The "teratogenically ineffective dose" was estimated to be ~250 mg/kg.

Matthiaschk (1973) reported increased resorptions and a dose-related incidence of malformations in fetuses from NMRI mice treated orally with thiram at 10, 20 or 30 mg/animal/day on gestation days 5-15. Simultaneous oral treatment with thiram and intraperitoneal injection with L-cysteine at
2.5 or 5 mg/mouse on gestation days 5-15 reduced the severity of malformations but not the number of malformations. Oral treatment with thiram (30 mg/kg) on gestation days 12-13 increased the number of malformations compared with treatment on gestation days 5-15. Simultaneous treatment with thiram and L-cysteine at 10 mg/kg (days of treatment unspecified) reduced the number of malformations.

Short et al. (1976) treated groups of 10-32 pregnant CD rats by gavage with thiram (practical grade) in CMC at doses of 0, 40, 90, 136 or 164 mg/kg/day on gestation days 6-15, or at 200 mg/kg/day on gestation day 6 or 7-12. For calculation of doses, "the thiram preparation was considered to be pure and no corrections were made for inactive ingredients." Rats were sacrificed on gestation day 20; 50% of the fetuses were examined for soft tissue anomalies; and the remaining fetuses were examined for skeletal anomalies. At 200 mg/kg/day, only 6/18 rats survived. Body weight gain and food consumption were significantly depressed in all treated groups. Treatment resulted in a significant decrease in the number of fetuses/dam and a corresponding increase in resorptions at levels ≥136 mg/kg/day. Fetal body weight was significantly reduced at all doses. The investigators reported higher incidences of hydrocephalus, domed cranium split or lobed antra and decreased ossification in rats treated at 136 mg/kg compared with controls, although statistical analysis of these data was not performed. Incidences at other doses were not reported.

Short et al. (1976) also completed a teratogenicity study in which groups of 18-19 pregnant Swiss-Webster mice were treated by gavage with thiram (practical grade) in CMC at doses of 0, 100 or 300 mg/kg/day on gestation days 6-14. Mice were sacrificed on gestation day 18. Half of the fetuses were examined for soft tissue anomalies and half were examined for
skeletal anomalies. At 300 mg/kg, 4/18 mice died. No effects on body weight gain of dams, litter size, incidence of resorptions or fetal body weights were observed. An increased incidence of hydrocephalus, hydro-nephrosis, collapsed cranium, malaligned sternebrae, eye and cardiovascular defects was observed at 300 mg/kg. Short et al. (1976) concluded that rats were more sensitive than mice to the developmental toxic effects of thiram.

Short et al. (1976) also conducted a study regarding the effects of peri- and postnatal thiram (practical grade) treatment in rats. In this study, groups of 10-20 pregnant rats were provided with diets containing 0, 0.03 or 0.1% thiram from day 16 of gestation to postpartum day 21. Practical grade thiram doses were 0, 17 and 26 mg/kg/day before birth and 0, 51 and 115 mg/kg/day after birth. A control group of food-restricted rats was also maintained. Directly after birth, pups of six thiram-treated dams/group were exchanged with control pups in a cross-fostering experiment. Food consumption and body weights of dams were reduced in both treatment groups, although at the low dose, body weights returned to normal by the end of the experiment. Body weights of food-restricted rats were depressed throughout lactation. Survival of pups from dams treated at 0.03% thiram was not affected. However, pup body weights were significantly decreased throughout the period of lactation. At 0.1% thiram, there was a significant decrease in pup body weights on days 0 and 4 and in survivors on day 4 (viability index); there were no survivors at weaning. In the cross-fostering experiment, survival and body weights of offspring from untreated dams placed with treated dams (0.1%) were significantly reduced; in contrast, survival of prenatally exposed pups (0.1%) nursed by untreated dams was normal, and body weights, which were initially significantly depressed, reached control values by day 21.
In a BRL (1968b) study, eight pregnant BL6 mice and seven pregnant AKR mice were treated by subcutaneous injection with thiram in DMSO on gestation days 6-14 (BL6) or 6-15 (AKR). BL6 mice were treated at 10 mg/kg/day and AKR mice were treated at 115 mg/kg/day. Maternal weight gain was significantly (p<0.05) decreased in AKR mice. A number of abnormalities were reported in BL6 mice, but the abnormalities were similar in type to those observed in DMSO-treated controls. Because only one dose was studied in a small number of mice, no conclusions can be made from this study.

6.5. OTHER REPRODUCTIVE EFFECTS

Fishbein (1976) summarized a study by Davydova (1973) concerning the reproductive function of female albino rats exposed to thiram by inhalation. Female rats (number unspecified) were exposed to thiram (purity not specified) at concentrations of 3.8±0.058 mg/m³, 6 hours/day, 5 days/week for 4.5 months. No information concerning controls was provided. Effects noted included an extension of the estrous cycle at the expense of the resting phase during the beginning of the study (the estrous cycle returned to normal by the end of the study), reduced rate of conception, reduced fertility and reduced body weights of fetuses. No additional information regarding this study was reported in Fishbein (1976).

Short et al. (1976) studied the effects of thiram on reproduction in male and female CD rats. In the study on male reproduction, groups of 20 male rats were fed thiram in the diet at 0, 0.05, 0.1 or 0.25% for 13 weeks before mating with untreated controls (see Section 6.1.2.1.). Based on food intake and body weight data, the investigators indicated that the rats consumed 0, 30, 58 or 132 mg practical grade thiram/kg/day. On gestation day 13, half of the females were sacrificed, while the remaining were allowed to deliver; the pups were examined at birth and on postpartum days 4
and 21. Thiram at 30 and 58 mg/kg/day had no effect on the ability of males to fertilize females. Male animals in the 58 and 132 mg/kg/day groups exhibited loss of hair and had rough coats; 70% of males in the latter group died. At 132 mg/kg/day, males failed to inseminate females. Testicular lesions (hypoplasia, tubular degeneration, and atypical spermatids in the epididymis) were observed in <50% of the rats with impaired breeding performance.

In the reproductive study in female rats (Short et al., 1976), groups of 20 virgin females were provided with thiram in the diet at 0, 0.04 or 0.2% (0, 30 or 96 mg practical grade thiram/kg/day) for at least 14 days before mating with untreated males. After mating, all female rats were fed the control diet. On gestation day 13, half of the females were sacrificed, while the remaining females were allowed to deliver; the pups were examined at birth and on postpartum days 4 and 21. Body weights of female rats treated with thiram at 30 or 96 mg/kg/day were 94 and 74% of the control value after 2 weeks of treatment. At 30 mg/kg/day, significant reductions in the number of implants/dam (11.9 vs. 14.4 in controls) and pups/dam (10.8 vs. 12.9 in controls) were observed. Treatment at 96 mg/kg/day prolonged the diestrous phase of the estrous cycle. Only 1/20 rats at 96 mg/kg/day was mated successfully, with 5/20 dead after 4.5 weeks of treatment. The effect of 96 mg/kg/day thiram treatment on estrous cycle was reversible; 9/9 rats became pregnant within 9 days of being transferred to the control diet. The number of implants (9.5) and embryos (8.5) was reduced in this group, although no effect on fertility index, gestation index or the ratio of viable embryos to implants was noted.

Hornshaw et al. (1987) completed reproductive studies where mink were fed thiram for 20 weeks and ferrets were fed thiram for 24 weeks in the
diet. Groups of 4 male and 12 female mink were fed thiram in the diet at 0, 2.5, 10 or 40 ppm, and similar groups of ferrets were fed at 0, 4, 16 or 64 ppm. Based on food intake and body weight data during 8 weeks before the breeding season, dosages for male mink were estimated at 0, 0.5, 1.4 and 6.1 mg/kg/day, for female mink at 0, 0.4, 1.5 or 5.7 mg/kg/day, for male ferrets at 0, 0.6, 2.7 or 10 mg/kg/day and for female ferrets at 0, 0.61, 2.1 or 7.0 mg/kg/day. The animals were treated until the kits were weaned. After weaning, four adult males and four adult females from each group were necropsied, organ weights (brain, liver, spleen, kidney, heart and lung) were recorded and hematologic parameters were determined.

Body weight changes, reported for the first 8 weeks of the study, are difficult to interpret because female ferrets and, to a lesser extent, mink tend to reduce food consumption and lose body weight as they approach estrus. The only body weight changes that were significantly different compared with controls were in male mink at 40 ppm and female ferrets (which lost less weight than controls) at 64 ppm. The investigators suggested that in ferrets at 64 ppm the normal pre-estrus pattern may have been disrupted; only 7/12 females were in estrus (vulvar swelling) after 8 weeks of treatment. Thiram treatment did not result in signs of intoxication or deaths in either species. Gross lesions were not observed at necropsy, and no birth defects were observed. The only significant effect on reproduction in mink was a decrease in average birth weight at 40 ppm. At 40 ppm, only 7/12 female mink whelped compared with 10/12 controls, and 6/9 and 11/11 at 2.5 and 10.0 ppm, respectively. In ferrets, no females at 64 ppm whelped, compared with 12/12 controls, and 9/12 and 8/12 at 4 and 16 ppm, respectively. At 16 ppm, the number of ferrets/litter was reduced (10.6/litter, controls; 8.2/litter, 16 ppm); ferret litter weights were significantly
reduced at birth, 3 and 6 weeks; and average kit body weights were reduced at 3 weeks. For both mink and ferrets, the investigators stated that kit survival was dose-related. Kit survival was 85.0, 80.0, 73.6 and 72.2% for control, low-, middle- and high-dose mink, and 94.1, 89.2 and 81.5% for control, low- and middle-dose ferrets kits surviving for 6 weeks. At necropsy, spleen weights of adults were increased significantly compared with controls at 40 ppm in mink, and at 16 and 64 ppm in ferrets. RBC counts, hemoglobin concentration and hematocrit were reduced significantly at 40 ppm in mink and 64 ppm in ferrets.

6.6. SUMMARY

Data regarding the toxicity of thiram following inhalation exposure of animals were not located. Svitiskaya (1974, summarized by Fishbein, 1976) reported ophthalmologic changes in persons occupationally exposed to thiram. Exposure concentrations were not reported.

The most notable effect observed in animals following chronic oral exposure to thiram is ataxia and hind leg paralysis observed in rats fed thiram in the diet at \( \geq 300 \) ppm (E.I. Du Pont de Nemours and Co., n.d.; Lee and Peters, 1976). Neurotoxic effects following exposure to thiram may result from the production of carbon disulfide. Thuranszky et al. (1982) found similar effects on the nervous system when rats were treated with a single oral dose of thiram or carbon disulfide.

Dietary treatment of animals with thiram has consistently resulted in decreased food intake and body weight gain. The study by Lowy et al. (1980), which found that body weight gain in thiram treated rats was below pair-fed controls, indicates that the effect on body weight is a result of thiram treatment rather than just a result of decreased food intake. The lowest dietary concentration of thiram resulting in decreased body weight gain in rats was 100 ppm (Lee et al., 1978). A study using mink and ferrets...
(Hornshaw et al., 1987) did not clearly identify levels resulting in changes in body weight because of the small numbers of animals used, and because of the high variability of body weight of the animals used in the study.

Thiram is an inhibitor of microsomal monoxygenases including aldehyde dehydrogenase and dopamine β-dehydrogenase. Combined exposure to thiram and ethanol has been shown to result in the accumulation of acetaldehyde (Garcia de Torres et al., 1983). Interactions between thiram and prometazine, meprobamate and trihexyphenidyl have also been reported (Fenyvesi et al., 1985). Oral carcinogenicity studies of thiram in rats (Lee et al., 1978; Takahashi et al., 1983; Lijinsky, 1984) and a limited carcinogenicity study in mice (BRL, 1968a) have not found a carcinogenic effect. Lijinsky (1984) found that simultaneous oral treatment of rats with thiram and sodium nitrite significantly increased nasal cavity and forestomach tumors. This effect probably was due to the \textit{in vivo} formation of \textit{N}-nitrosodimethylamine.

Mutagenicity studies of thiram have yielded mixed results, with numerous positive and negative studies available. Rannug and Rannug (1984) proposed that mutagenicity induced by thiram may result from the inhibition of enzymes that are involved in protecting against harmful oxygen species.

Oral teratogenicity studies in hamsters (Robens, 1969), mice (Roll, 1971; Matthiaschk, 1973; Short et al., 1976) and rats (Short et al., 1976) have reported an increased incidence of resorptions and malformations observed prenatally and reduced viability and growth, postnatally. In some instances, the findings were observed in the presence of maternal toxicity.

Oral studies concerning the effects of thiram on reproduction in rats (Short et al., 1976) indicate that at 132 mg/kg/day the 30% of the males who survived failed to inseminate females and exhibited testicular lesions. A dose of 30 mg/kg/day given to females reduced the number of implants/dam.
Treatment at 96 mg/kg/day resulted in only 1 of the 15 female-survivors to mate successfully. A cross-fostering experiment (Short et al., 1976), which found reduced survival of offspring from untreated dams placed with treated dams indicates that developing rats are still sensitive to thiram post-natally. Results of a reproductive study using mink and ferrets (Hornshaw et al., 1987) indicates that ferrets may be more sensitive than mink or rats to the reproductive effects of thiram; 0/12 female ferrets produced litters at a dose of 7 mg/kg/day. In addition, exposure to 2.1 mg/kg/day produced a decrease in the number of offspring/litter and in offspring body weights. In the adult animals, there was an increase in splenic weight at 2.1 and 7 mg/kg/day and a decrease in RBCs, hemoglobin and hematocrit at 7 mg/kg/day.
7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The OSHA (1985) PEL for thiram is 5 mg/m³. The ACGIH (1987) TLV-TWA was recently lowered from 5 to 1 mg/m³, based on the probability that clinical symptoms in exposed workers occurred at concentrations >1.0 mg/m³.

Tolerances for thiram on raw agricultural products are 7 ppm in or on apples, celery, peaches, strawberries, tomatoes and bananas (not more than 1 ppb shall be in the pulp after the peel is removed and discarded), and 0.5 ppm in or on onions (U.S. EPA, 1986a).

U.S. EPA (1984a) determined that data were insufficient for identification of a NOEL; therefore, an MPI could not be calculated. The verified oral RFD for thiram is 0.005 mg/kg/day (U.S. EPA, 1987c); the derivation is discussed in Section 8.2.2.2. The RQ for thiram is 10 pounds, based on aquatic toxicity data (U.S. EPA, 1988).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic life from exposure to tetramethylthiuram disulfide (thiram) were not located in the available literature cited in Appendix A.
8. RISK ASSESSMENT

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential business information (CBI), which this document could not address, are not in existence. From examination of the bibliographies of the CBI data, however, it was determined that CBI data that would alter the approach to risk assessment or the risk assessment values presented herein do not exist.

8.1. CARCINOGENICITY

8.1.1. Inhalation. Pertinent data regarding the carcinogenicity of thiram following inhalation exposure were not located in the available literature cited in Appendix A.

8.1.2. Oral. In a BRL (1968a) study, thiram tested negative for carcinogenicity in (C57BL/6xC3H/Anf)F1 mice and in (C57/BL/6xAKR)F1 mice. This study is limited; only one dose level was used, and it is not clear if the mice received an MTD throughout the study.

Additional oral chronic studies in rats (Lee et al., 1978; Takahashi et al., 1983; Lijinsky, 1984) also reported negative results for carcinogenicity. The study by Takahashi et al. (1983) reported significantly lower incidences of leukemia in thiram treated rats (0, 500 or 1000 ppm in the diet) compared with controls. The investigators speculated that thiram, a known inhibitor of hepatic microsomal monooxygenases, may alter metabolism to inhibit tumor development or may inhibit microsomal activation of other chemical carcinogens. Lijinsky (1984) found that thiram was not carcinogenic when given to rats in the diet at 500 ppm, but that thiram (500 ppm) and nitrite (2000 ppm) in the diet significantly increased the number of
nasal cavity tumors and the number of forestomach tumors. The carcinogenicity of thiram and nitrite treatment may be the result of in vivo formation of N-nitro-sodimethylamine, a potent carcinogen.

8.1.3. Other Routes. BRL (1968a) reported negative results in a carcinogenicity study in which 28-day-old mice were given a single subcutaneous injection of thiram (46.4 mg/kg) and observed until 78 weeks of age. IARC (1976) noted that "a single subcutaneous injection may not be an adequate basis for discounting carcinogenicity."

8.1.4. Weight of Evidence. No data were available regarding the carcinogenicity of thiram in humans. The available data indicate no evidence of a carcinogenic effect in mice or rats treated with thiram, but the animal data base is inadequate. According to U.S. EPA (1986b) guidelines, thiram can be placed in EPA group D: not classifiable as to human carcinogenicity.

8.1.5. Quantitative Risk Estimates. The lack of inhalation carcinogenicity data and the lack of positive oral carcinogenicity data preclude the derivation of carcinogenic potency factors for thiram.

8.2. SYSTEMIC TOXICITY

8.2.1. Inhalation Exposure. Fishbein (1976) summarized a study by Sivitskaya (1974) that reported ophthalmologic changes in workers with prolonged occupational contact with thiram. Because estimates of exposure levels were not provided, this information is not useful for risk assessment.

The only inhalation study in animals was a reproductive study using rats (Davydova, 1973) summarized by Fishbein (1976). In this study, effects on reproduction (extension of the estrous cycle, reduced rate of conception, reduced fertility and underweight fetuses) were observed in rats exposed to thiram at a concentration of 3.8±0.058 mg/m³, 6 hours/day, 5 days/week for 4.5 months. This study was reported inadequately for proper evaluation and is therefore not suitable for risk assessment.
The lack of inhalation data useful for risk assessment precludes the derivation of subchronic and chronic inhalation RfDs.

8.2.2. Oral Exposure.

8.2.2.1. LESS THAN LIFETIME EXPOSURES (SUBCHRONIC) -- Lowy et al. (1980) fed groups of six young male Wistar rats thiram in the diet at concentrations that provided doses of 0, 33.6, 41.9, 54.7, 71.9, 106.7 or 143.4 mg/kg/day for 29 days. Similar groups of pair-fed rats were maintained as controls. Body weight gain was consistently different from pair-fed controls at ≥54.7 mg/kg/day. Organ weight measurements indicated a dose-related decrease in the weights of epididymal fat pads and perirenal fat pads that was significant at all doses. Histological examinations were not completed. Because only one sex and small numbers of rats were used, and because hematology and histopathology were not evaluated, this study is not sufficient for risk assessment. The use of pair-fed controls in this study provides evidence that decreased body weight gain is a result of thiram treatment, rather than just a result of decreased food intake.

Lee et al. (1978) provided groups of 20 young male rats with thiram in the diet at concentrations that provided doses of 30, 58 or 132 mg/kg/day for 13 weeks. Food intake was decreased and body weight gain was 81, 64 and 22% of controls at 30, 58 or 132 mg/kg/day, respectively. At 132 mg/kg/day, 18% of the rats died (Short et al., 1976). SGOT and SGPT were mildly elevated and mild tubular degeneration of the testes was noted. Mild elevation of BUN was reported at 58 mg/kg/day. The lowest dose used in this study can be considered a LOAEL, which resulted in decreased body weight gain. This study is limited by the use of only male rats.

Teratogenicity studies using hamsters (Robens, 1969), mice (Roll, 1971; Matthiasch, 1973; Short et al., 1976; BRL, 1968b) and rats (Short et al.,
1976) have reported an increased incidence of resorptions and malformations observed prenatally and reduced viability and growth, postnatally. In some instances, the findings were observed in the presence of maternal toxicity. The studies by Robens (1969) and BRL (1968b) are confounded by the use of DMSO, a teratogen, as the vehicle. In reproductive studies, Short et al. (1976) found that reproduction was affected in male rats mated with untreated females at an oral dose of 132 mg/kg/day (13 weeks), a dose that also resulted in deaths, and in female rats mated to untreated males at 30 and 96 mg/kg/day (96 mg/kg/day also resulted in deaths). In a cross-fostering experiment (Short et al., 1976), survival and body weights of offspring from untreated rats placed with treated rats (0.1% in the diet, 115 mg/kg/day) were reduced. This experiment indicates that developing rats exposed to thiram postnatally are still susceptible to the developmental effects.

Hornshaw et al. (1987) fed groups of 2 male and 2 female mink and 5 male and 5 female ferrets thiram in the diet for 28 days at concentrations that provided doses of 0, 8.6 or 12.6 mg/kg/day for male mink, 0, 6.6 or 9.5 mg/kg/day for female mink, 0, 1.1, 2.8, 5.6, 14.8 or 27.5 mg/kg/day for male ferrets, and 0, 1.6, 3.3, 8.6, 16.5 or 44.8 mg/kg/day for female ferrets. The only effects noted in mink were significantly decreased hematocrit values at both doses and a reduction in food consumption, loss of body weight and bloody feces at the high dose (12.6 mg/kg/day males, 9.5 mg/kg/day females). All high-dose male (27.5 mg/kg/day) and female (44.8 mg/kg/day) ferrets died between days 11 and 16. Signs of toxicity observed in these animals included bloody feces, inanition, listlessness, incoordination and occasional convulsions accompanied by intense vocalizations. Changes in body weights were significantly different in male ferrets at ≥2.8
mg/kg/day and in females at ≥16.5 mg/kg/day. At necropsy, spleen weights were increased in female ferrets at 16.5 mg/kg/day, and RBC counts and hemoglobin counts were significantly reduced at 5.6 and 14.8 mg/kg/day in males, and 8.6 and 16.5 mg/kg/day in females.

Hornshaw et al. (1987) also completed reproductive studies where groups of 4 male and 12 female mink (20 weeks) and similar numbers of ferrets (24 weeks) were fed thiram in the diet at concentrations 0, 2.5, 10 and 40 ppm for mink and 0, 4, 16 or 64 ppm for ferrets. Based on food intake and body weight data for the first 8 weeks of the study, the diets provided doses of 0, 0.5, 1.4 or 6.1 mg/kg/day in male mink, 0, 0.4, 1.5 or 5.7 mg/kg/day in female mink, 0, 0.6, 2.7 or 10 mg/kg/day in male ferrets and 0, 0.6, 2.1 or 7.0 mg/kg/day in female ferrets. The accuracy of these dose estimates is unclear; female ferrets and to a lesser extent female mink tend to reduce feed consumption and lose body weight as they approach estrus, so actual doses during gestation and weaning may have been higher. The animals were treated until the kits were weaned. The investigators suggested that in female ferrets at 7 mg/kg/day, the normal pre-estrus pattern may have been disrupted; only 7/12 females were in estrus (vulvar swelling) after 8 weeks of treatment.

Thiram treatment did not result in signs of intoxication or deaths in either species. Gross lesions were not observed at necropsy, and no birth defects were observed. The only significant effect on reproduction in mink was a decrease in average birth weight at the high dose. In ferrets, no females at 7 mg/kg/day whelped, compared with 12/12 controls and 9/12 and 8/12 at the low and middle dose, respectively. At the middle dose, (2.1 mg/kg/day in females), the number of offspring/litter was reduced and ferret litter weights were reduced significantly at birth, 3 and 6 weeks, and
average kit body weights were reduced at 3 weeks. For both mink and ferret, the investigators stated that kit survival was dose-related; 85.0, 80.0, 73.6 and 72.2% survived in control, low-, middle- and high-dose mink kits, and 94.1, 89.2 and 81.5% control, low- and middle-dose ferret kits surviving for 6 weeks. Kit survival data are not considered in the identification of a LOAEL and NOAEL for reproduction because the data reported cannot be statistically analyzed. This study appears to identify a reproductive FEL for ferrets of ~7 mg/kg/day, a LOAEL of 2.1 mg/kg/day and a NOAEL of 0.61 mg/kg/day.

It appears that the ferret is the species most sensitive to thiram and that the critical effect in this species involves impaired female reproduction. In the reproduction study by Hornshaw et al. (1987), 2.1 mg/kg/day was a LOAEL and 0.61 mg/kg/day was a NOAEL for reproductive effects. An RfD for subchronic oral exposure to thiram can be derived by application of an uncertainty factor of 100: 10 for extrapolation from animals to humans and 10 to provide additional protection for unusually sensitive humans, to the reproduction NOAEL in ferrets of 0.61 mg/kg/day (Hornshaw et al., 1987). The RfD is 0.006 mg/kg/day. Confidence in the data base is medium because the chronic, developmental and reproductive toxicity of thiram have been investigated in a wide range of experimental species, although no multi-generation study has been reported. Confidence in the key study is low because group sizes were small, histopathological examinations were not performed, and because variable food intake and body weight data made reliable estimation of dosage levels difficult. Data obtained from other species, however, suggest that the NOAEL for reproduction in ferrets is below dosages in other species associated with CNS signs, hematologic effects and histopathologic lesions. Confidence in the RfD is medium.
8.2.2.2. CHRONIC EXPOSURE -- The verified oral RfD (U.S. EPA, 1987c) is based on an unpublished study in rats (E.I. Du Pont de Nemours & Co., Inc., n.d.) in which groups of 24 rats (strain and sex unspecified) were fed diets containing thiram at 0, 100, 300, 1000 or 2500 ppm for 2 years. Weakness, ataxia, varying degrees of hind limb paralysis and calcified masses in the basal ganglia and in the cerebellum were noted at ≥300 ppm. The 300 ppm level [a dose of 15 mg/kg/day, calculated assuming a rat food consumption factor of 0.05 (U.S. EPA, 1986c)] was considered a LOAEL and the 100 ppm level (5 mg/kg/day) was considered a NOEL. An uncertainty factor of 1000, 10 for interspecies extrapolation, 10 for intraspecies extrapolation, and an additional uncertainty factor to account for the severity of the effect and the questionable quality of the database, was used to calculate an RfD of 0.005 mg/kg/day. Confidence in the RfD was considered low, based on low to medium confidence in the study and low confidence in the data base.

U.S. EPA (1987b) cited the Lee and Peters (1976) 80-week study using rats and indicated that the dose of 6.1 mg/kg/day (female rats) is a NOEL and 25.5 mg/kg/day is a LEL resulting in alopecia. The Lee et al. (1978) study, which reported additional effects in the study described by Lee and Peters (1976), is not cited.

In the 80-week study reported by Lee and Peters (1976) and Lee et al. (1978), groups of 24 CD rats/sex were fed diets containing practical grade thiram that provided doses of 0, 5.3, 20.4 or 52 mg/kg/day to males, and 6.1, 25.5 and 66.9 mg/kg/day to females. Hind limb ataxia or paralysis was observed in 8/24 high-dose female rats (Lee and Peters, 1976). Histological examinations of nervous tissue of two ataxic rats revealed demyelination and degeneration of the sciatic nerve, and degeneration of the spinal cord (Lee and Peters, 1976).
This is in conflict with Lee et al. (1978), who stated that specific lesions of the central and peripheral nervous systems were not observed in nonataxic, ataxic or paralyzed rats. Additional nervous system effects noted were changes in hind leg walking gait in females treated at \( \geq 25.5 \) mg/kg/day, and hyperactivity in males at \( \geq 20.4 \) mg/kg/day and females at 66.9 mg/kg/day (five ataxic females were also hyperactive). Effects reported in Lee et al. (1978) included alopecia in middle- and high-dose rats and decreased body weight compared with controls at all doses in males, and in middle- and high-dose females. Body weight, presented in growth curves, was consistently below controls in low-dose males. Statistical analyses of body weight data were not presented. Results of organ weight measurements showed increased relative thyroid and testes weight in high-dose males and increased relative liver, kidney, thyroid, ovary and brain weights in high-dose females, with relative spleen weights increased in both high- and middle-dose females. Statistical analyses and actual organ weight data were not provided. Histopathological examinations revealed a dose-related increase in the incidence and severity of fatty infiltration of the pancreas in male rats, with 1/17, 3/13, 11/15 and 14/16 control, low-, middle- and high-dose rats affected. Fatty infiltration of the pancreas was found in only 1/11 high-dose female rats. Squamous metaplasia of the thyroid was observed in 4/16 and 3/11 high-dose male and female rats compared with 1/17 male and 0/18 female control rats. Based on decreased body weight gain, in low-dose males, the 5.3 mg/kg/day dose can be considered an effect level. Although it is not clear whether decreased body weight gain should be considered an adverse effect, it is an effect observed consistently in thiram treated animals, and the subchronic study by Lowy et al. (1979, 1980)
in which body weight was decreased in thiram treated rats compared with pair-fed controls indicated that thiram itself contributes to the effect on body weight.

In addition, it is known that thiram is an inhibitor of aldehyde dehydrogenase, a biochemical effect that is significant to humans because of the widespread use of ethanol. In the study by Garcia de Torres et al. (1983), two gavage doses of thiram at 3.8 mg/kg given to female rats followed by an intraperitoneal injection of ethanol (2 g/kg) significantly increased blood acetaldehyde levels for up to 240 minutes after treatment. The increases in blood acetaldehyde were also detectable when ethanol was administered 48 hours after thiram treatment. Although this study is acute, it suggests that exposure to thiram may potentiate the action of ethanol.

Minimal toxicity data are available in dogs. U.S. EPA (1987c) mentioned a 1-year dog study in which 200 ppm (5 mg/kg/day) was considered a NOEL. Saito et al. (1980), however, reported CNS signs and liver lesions where dogs were treated for 2 years with thiram in gelatin capsules at 4 mg/kg/day. In addition, there was a transient reduction in erythrocyte count at that dosage. All dogs treated at 40 mg/kg/day died. There were no effects at 0.4 mg/kg/day.

No single chronic study with thiram clearly defines a NOAEL and LOAEL for the critical effect in the most sensitive species. The NOAEL of 0.61 mg/kg/day for reproductive effects in the ferret (Hornshaw et al., 1987) appears to be the most defensible basis for the RfD, because it is below any LOAEL for chronic toxicity in rats and dogs. Application of an uncertainty factor of 100 (see Section 8.2.2.1.) results in an RfD for chronic oral exposure of 0.006 mg/kg/day, the same as the RfD for subchronic oral exposure. Confidence in the RfD is medium (see Section 8.2.2.1.).
A significant feature of the graphs is that the boundary line for adverse effects is nearly without slope at human equivalent durations beyond about 0.0025 lifespan. This feature is consistent with the observation that there is little difference between the subchronic and chronic toxicity of thiram, and with the fact that the subchronic and chronic oral RfD values are identical.

No one species, effect, or study figures prominently in defining the boundary line for adverse effects, as can be seen by identifying the FELs and LOAELs on or near the line. The LOAEL for the major inflection (at 0.0025 lifespan) is for inhibited metabolism in rats treated with thiram at 3.8 mg/kg/day for 2 days (Garc'ía de Torres et al., 1983). The FEL located slightly above the line at 0.013 lifespan is for teratogenicity where NMRI mice were treated at 10 mg/kg/day for 2 days, as reported in an abstract (Matthiaschik, 1973). The LOAEL slightly above the line at 0.022 lifespan is for reduced body weight in male ferrets fed a diet that provided 2.8 mg/kg/day for 28 days. At 0.12 lifespan, the LOAEL on the line is for reproduction in ferrets fed a diet that provided 2.1 mg/kg/day for 24 weeks (Hornshaw et al., 1987). The LOAEL slightly above the line at 0.76 lifespan is for reduced body weight in male rats fed a diet that provided 5.3 mg/kg/day for 80 weeks.

The region of contradiction is not unduly large and is restricted to the region between 0.0011 and 0.12 lifespan. This region probably reflects differences in study quality and protocol rather than differences in species sensitivity. The regions of ambiguity are also relatively small, reflecting the rather extensive nature of the data base as well as general agreement between studies. The subchronic and chronic RfD value, 0.006 mg/kg/day or 0.4 mg/day for a 70 kg human, is well below the boundary for no adverse effects.
9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

The toxicity of thiram was discussed in Chapter 6. Data suitable for the derivation of an RQ are summarized in Table 9-1. In the study using mink and ferrets (Hornshaw et al., 1987), ferrets appeared to be more sensitive than mink; therefore, only data concerning ferrets are presented in Table 9-1. In the 28-day study, male ferrets treated at a dose of 27.5 mg/kg/day died following 11-16 days of treatment. Death within such a short period of time is considered an acute effect and is not scored for CS determination. Altered body weights were observed in males at >20 ppm (2.8 mg/kg/day) and reduced erythrocyte counts and hematocrits were observed in both sexes at >50 ppm (5.6-8.6 mg/kg/day). Only the effect on body weight is entered in Table 9-1, because this effect and the hematologic effects would both be assigned an RNe of 4. Although this study was extremely short in duration, no uncertainty factor is applied to expand to chronic exposure because data in other species do not show differences in subchronic and chronic toxicity. In the reproductive study, no offspring were produced by ferrets treated at 7 mg/kg/day, and reduced litter and kit weights were reported at 2.1 mg/kg/day.

In an 80-week study (Lee and Peters, 1976; Lee et al., 1978), subtle nervous system effects (altered gait) were noted in female rats treated at >25.5 mg/kg/day, while body weights were decreased in males at 5.3 mg/kg/day. E.I. Du Pont de Nemours & Co. (n.d.) reported ataxia, hind limb paralysis and calcified masses in the basal ganglia and cerebellum of rats treated with thiram in the diet at doses of 15 mg/kg/day for 2 years. Incidence data were not provided. Maita et al. (1980) reported reduced muscle weight and the presence of histopathologic lesions in the muscles of
## Toxicity Summary for Oral Exposure to Thiram

<table>
<thead>
<tr>
<th>Species/Strain</th>
<th>Sex</th>
<th>No. at Start</th>
<th>Average Weight (kg)</th>
<th>Vehicle/Physical State</th>
<th>Purity</th>
<th>Exposure</th>
<th>Transformed Animal Dose (mg/kg/day)</th>
<th>Transformed Human Dose (mg/kg/day)</th>
<th>Response</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrets/Agouti-colored</td>
<td>M</td>
<td>5</td>
<td>1.79</td>
<td>suspended in water, added to the diet</td>
<td>analytical</td>
<td>312 ppm in the diet for 11-16 days</td>
<td>27.5\textsuperscript{b}</td>
<td>8.1</td>
<td>Death of all ferrets</td>
<td>Hornshaw et al., 1987</td>
</tr>
<tr>
<td>Ferrets/Agouti-colored</td>
<td>M</td>
<td>5</td>
<td>2.065\textsuperscript{c}</td>
<td>suspended in water, added to the diet</td>
<td>analytical</td>
<td>20 ppm in diet for 20 days</td>
<td>2.8\textsuperscript{b}</td>
<td>0.87</td>
<td>Reduced body weight gain</td>
<td>Hornshaw et al., 1987</td>
</tr>
<tr>
<td>Rats/CD</td>
<td>F</td>
<td>24</td>
<td>0.35\textsuperscript{c}</td>
<td>added to the diet</td>
<td>practical grade</td>
<td>0.04% in the diet for 80 weeks</td>
<td>25.5\textsuperscript{d}</td>
<td>4.4</td>
<td>Altered gait, alopecia</td>
<td>Lee and Peters, 1976</td>
</tr>
<tr>
<td>Rats/CD</td>
<td>M</td>
<td>24</td>
<td>0.625\textsuperscript{c}</td>
<td>added to the diet</td>
<td>practical grade</td>
<td>0.01% in the diet for 80 weeks</td>
<td>5.3\textsuperscript{d}</td>
<td>1.1</td>
<td>Decreased body weight</td>
<td>Lee et al., 1978</td>
</tr>
<tr>
<td>Rats/NR</td>
<td>NR</td>
<td>24</td>
<td>0.35\textsuperscript{e}</td>
<td>added to the diet</td>
<td>NR</td>
<td>300 ppm in the diet for 80 weeks</td>
<td>15\textsuperscript{f}</td>
<td>2.6</td>
<td>Weakness, ataxia, hind limb paralysis, calcified masses in the basal ganglia and cerebellum, incidence data not provided</td>
<td>E.I. du Pont de Nemours &amp; Co., n.d.</td>
</tr>
<tr>
<td>Rats/Mistar</td>
<td>M,F</td>
<td>64</td>
<td>0.35\textsuperscript{e}</td>
<td>diet</td>
<td>NR</td>
<td>300 ppm in diet for 104 weeks</td>
<td>15</td>
<td>2.6</td>
<td>Reduced muscle (M. triceps surae) weight and histopathologic lesions</td>
<td>Malta et al., 1980</td>
</tr>
<tr>
<td>Dogs/Beagle</td>
<td>M,F</td>
<td>4/sex</td>
<td>12.7\textsuperscript{e}</td>
<td>capsule</td>
<td>NR</td>
<td>40 mg/kg/day for 2 years</td>
<td>40</td>
<td>23</td>
<td>Mortality</td>
<td>Salto et al., 1980</td>
</tr>
<tr>
<td>Dogs/Beagle</td>
<td>M,F</td>
<td>4/sex</td>
<td>12.7\textsuperscript{e}</td>
<td>capsule</td>
<td>NR</td>
<td>4 mg/kg/day for 2 years</td>
<td>4</td>
<td>2</td>
<td>CNS signs; liver lesions</td>
<td>Salto et al., 1980</td>
</tr>
<tr>
<td>Rats/CD</td>
<td>F</td>
<td>17</td>
<td>0.35\textsuperscript{e}</td>
<td>carboxymethyl cellulose</td>
<td>practical grade</td>
<td>136 mg (practical grade)/kg by gavage on gestation days 6-15</td>
<td>136</td>
<td>23.3</td>
<td>Reduction in the number of mated rats, decrease in the number fetuses/litter, higher incidence of hydrocephalus, decreased ossification, body weight and food intake of dams decreased</td>
<td>Short et al., 1976</td>
</tr>
<tr>
<td>Rats/CD</td>
<td>F</td>
<td>20</td>
<td>0.35\textsuperscript{e}</td>
<td>added to the diet</td>
<td>practical grade</td>
<td>0.04 in the diet up to 4.5 weeks</td>
<td>30\textsuperscript{d}</td>
<td>5.1</td>
<td>Reduced number of implants and offspring/litter</td>
<td>Short et al., 1976</td>
</tr>
<tr>
<td>Species/Strain</td>
<td>Sex</td>
<td>No. at Start</td>
<td>Average Weight (kg)</td>
<td>Vehicle/Physical State</td>
<td>Purity</td>
<td>Exposure</td>
<td>Transformed Animal Dose (mg/kg/day)</td>
<td>Transformed Human Dose (mg/kg/day)</td>
<td>Response</td>
<td>Reference</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----</td>
<td>--------------</td>
<td>---------------------</td>
<td>------------------------</td>
<td>---------</td>
<td>----------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------------------</td>
<td>-------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Ferrets/Agouti-colored</td>
<td>F</td>
<td>12</td>
<td>0.870</td>
<td>suspended in water, added to the diet</td>
<td>analytical</td>
<td>16 ppm in the diet for 24 weeks (reproduction study)</td>
<td>2.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.49</td>
<td>Reduced litter weight; reduced kit body weights</td>
<td>Hornshaw et al., 1987</td>
</tr>
<tr>
<td>Rats/CD</td>
<td>F</td>
<td>10-32</td>
<td>0.35&lt;sup&gt;e&lt;/sup&gt;</td>
<td>carboxymethyl cellulose practical grade</td>
<td>40 mg/kg/day gavage on gestation days 6-15</td>
<td>40</td>
<td>6.8</td>
<td>Decreased fetal body weight</td>
<td>Short et al., 1976</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Estimated by multiplying transformed animal dose by the cube root of the ratio of the animal to human reference (70 kg) body weight

<sup>b</sup>Estimated from body weight and food intake data provided by investigators

<sup>e</sup>Estimated from data provided by investigators

<sup>d</sup>Dosage estimated by investigators

<sup>f</sup>Reference body weight (U.S. EPA, 1986c)

<sup>f</sup>Estimated by using reference food factors

NR = Not reported
rats at 300 ppm in the diet (15 mg/kg/day) for 2 years. In a 2-year study in dogs treated with thiram in gelatin capsules, 40 mg/kg/day resulted in the death of all dogs by 29 weeks, and 4 mg/kg/day was associated with CNS effects and liver lesions.

Short et al. (1976) reported maternal and teratogenic effects in rats treated by gavage at 136 mg (practical grade thiram)/kg/day on gestation days 6-15. The only effect reported at 40 mg/kg/day was reduced fetal body weight. In a rat reproduction study (Short et al., 1976), a dosage of 96 mg/kg/day precluded reproduction and 30 mg/kg/day was associated with reduced number of implants and offspring/litter.

The derivations of CS and RQ values are presented in Table 9-2. CSs were not calculated from studies in which deaths occurred shortly after the study began (Hornshaw et al., 1987; Short et al., 1976). As indicated in Table 9-2, the highest CS is calculated from the ferret study in which reduced litter and kit body weights were reported at a human equivalent dose of 0.49 mg/kg/day. The CS of 25.6 corresponds to an RQ of 100 (Table 9-3). That reproduction in ferrets is the critical effect in the most sensitive species is supported by the fact that the highest CS was calculated for this effect.

U.S. EPA (1987b) derived an RQ of 100 for thiram based on an inhalation study of reproductive effects in rats (Davydova, 1973). In this study (summarized by Fishbein, 1976), reproductive effects (extension of the estrous cycle, reduced fertility, underweight fetuses) were observed in rats exposed to thiram at a concentration of 3.8±0.058 mg/m³ 6 hours/day, 5 days/week for 4.5 months. A CS of 35.4 was calculated from this study based on an RV_d of 4.4 and an RV_e of 9. Although the CS calculated from the
<table>
<thead>
<tr>
<th>Species</th>
<th>Animal Dose (mg/kg/day)</th>
<th>Chronic Human MED (mg/day)</th>
<th>RV₀</th>
<th>RVₑ</th>
<th>CS</th>
<th>RQ</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferret</td>
<td>2.8</td>
<td>60.9</td>
<td>2.8</td>
<td>4</td>
<td>11.2</td>
<td>1000</td>
<td>Hornshaw et al., 1987</td>
</tr>
<tr>
<td>Rat</td>
<td>25.5</td>
<td>308</td>
<td>1.8</td>
<td>7</td>
<td>12.6</td>
<td>1000</td>
<td>Lee and Peters, 1976</td>
</tr>
<tr>
<td></td>
<td>1.1</td>
<td>77</td>
<td>2.7</td>
<td>4</td>
<td>10.8</td>
<td>1000</td>
<td>Lee et al., 1978</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>182</td>
<td>2.1</td>
<td>9</td>
<td>18.9</td>
<td>1000</td>
<td>E.I. Du Pont de Nemours &amp; Co., n.d.</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>182</td>
<td>2.1</td>
<td>7</td>
<td>14.7</td>
<td>1000</td>
<td>Malta et al., 1980</td>
</tr>
<tr>
<td>Dog</td>
<td>40</td>
<td>1610</td>
<td>1</td>
<td>10</td>
<td>10</td>
<td>1000</td>
<td>Saito et al., 1980</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>140</td>
<td>2.3</td>
<td>7</td>
<td>16.1</td>
<td>1000</td>
<td>Saito et al., 1980</td>
</tr>
<tr>
<td>Rat</td>
<td>136</td>
<td>1631</td>
<td>1</td>
<td>9</td>
<td>9</td>
<td>1000</td>
<td>Short et al., 1976</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>476</td>
<td>1.5</td>
<td>8</td>
<td>12</td>
<td>1000</td>
<td>Short et al., 1976</td>
</tr>
<tr>
<td>Ferret</td>
<td>2.1</td>
<td>34.3</td>
<td>3.2</td>
<td>8</td>
<td>25.6</td>
<td>100</td>
<td>Hornshaw et al., 1987</td>
</tr>
<tr>
<td>Rat</td>
<td>30</td>
<td>357</td>
<td>1.7</td>
<td>8</td>
<td>13.6</td>
<td>1000</td>
<td>Short et al., 1976</td>
</tr>
</tbody>
</table>

*Human equivalent dosage (from Table 9-1) multiplied by 70 kg to express MED in terms of kg/day for 70 kg human
**TABLE 9-3**

Thiram

**Minimum Effective Dose (MED) and Reportable Quantity (RQ)**

<table>
<thead>
<tr>
<th>Route:</th>
<th>oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose*:</td>
<td>34.3 mg/day</td>
</tr>
<tr>
<td>Effect:</td>
<td>reproductive; reduced litter size and reduced litter and kit body weights</td>
</tr>
<tr>
<td>Reference:</td>
<td>Hornshaw et al., 1987</td>
</tr>
<tr>
<td>RVd:</td>
<td>3.2</td>
</tr>
<tr>
<td>RVe:</td>
<td>8</td>
</tr>
<tr>
<td>Composite Score:</td>
<td>25.6</td>
</tr>
<tr>
<td>RQ:</td>
<td>100</td>
</tr>
</tbody>
</table>

*Equivalent human dose*
Davydova (1973) study is larger than the CS calculated from the Hornshaw et al. (1987) study, the Hornshaw et al. (1987) study is a more appropriate basis for the RQ because only limited information concerning the Davydova (1973) study was available in the review by Fishbein (1976).

9.2. BASED ON CARCINOGENICITY

Thiram has tested negative in a limited oral study using mice (BRL, 1968a) and in oral carcinogenicity studies using rats (Lee et al., 1978; Takahashi et al., 1983). Lijinsky (1984) found that oral treatment of rats with thiram did not result in a carcinogenic effect, while treatment with thiram and nitrite in the diet increased the incidence of nasal cavity and forestomach tumors. Data regarding the carcinogenicity of thiram to humans were not located.

Based on the negative animal data and the lack of human carcinogenicity data, thiram can be classified in EPA group D - not classifiable as to human carcinogenicity. EPA group D compounds cannot be given a hazard ranking; therefore, an RQ based on carcinogenicity cannot be assigned.
10. REFERENCES


0133d -82- 08/24/89
Bluzat, R., O. Jonot and J. Seuge. 1982a. Acute toxicity of thiram in
gammarus-pulex effect of a 1-hour contamination and degradation of an

Bluzat, R., O. Jonot and J. Seuge. 1982b. Acute toxicity of a fungicide,
thiram (dithiocarbamate) in the freshwater amphipod crustacean Gammarus

BRL (Bionetics Research Labs). 1969a. Evaluation of Carcinogenic, Terato-
genic, and Mutagenic Activities of Selected Pesticides and Industrial Chemi-
cals. Volume I. Carcinogenic Study. Prepared for National Cancer Insti-

BRL (Bionetics Research Labs). 1969b. Evaluation of Carcinogenic, Terato-
genic, and Mutagenic Activities of Selected Pesticides and Industrial Chemi-
cals. Volume II. Teratogenic Study in Mice and Rats. Prepared for National

Cherpak, V.V., B. Bezugly and L.M. Kaskevich. 1971. Sanitary and hygenic
characteristics of working conditions and the state of health in persons
working with tetramethylthiram disulfide (TMTD). Vrach. Delo. 10:
136-139. (English Abst).

Chinn, S.H.F. 1973. Effect of eight fungicides on microbial activities in


0133d  -84-  08/24/89


Lowy, R., G. Griffaton, L. Brigant, B. Ardouin and F. Dupuy. 1979. The dietary no-effect level of a dithiocarbamate fungicide, thiram, as evaluated from the measurement data on rats. II. The various sensitivities of the various parameters. Toxicology. 14(1): 39-53.


Roll, R. 1971. Teratologic studies with thiram (TMD) on two strains of mice. Arch. Toxicol. 27(3): 173-86. (Taken from TOXIB/71/206703)


This HEED is based on data identified by computerized literature searches of the following:

CHEMLINE
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
TOXLINE
TOXLIT
TOXLIT 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register
CAS ONLINE (Chemistry and Aquatic)
HSDB
SCISEARCH
Federal Research in Progress

These searches were conducted in May, 1988, and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.


In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:


### Summary Table for Thiram

<table>
<thead>
<tr>
<th>Species</th>
<th>Exposure</th>
<th>Effect</th>
<th>RfD or qₜ*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhalation Exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subchronic</td>
<td>ID</td>
<td>ID</td>
<td>ID</td>
<td>NA</td>
</tr>
<tr>
<td>Chronic</td>
<td>ID</td>
<td>ID</td>
<td>ID</td>
<td>NA</td>
</tr>
<tr>
<td>Carcinogenicity</td>
<td>ID</td>
<td>ID</td>
<td>ID</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Oral Exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subchronic</td>
<td>ferret</td>
<td>0.61 mg/kg/day for 24 weeks</td>
<td>NOAEL for impaired reproduction</td>
<td>0.006 mg/kg/day</td>
</tr>
<tr>
<td>Chronic</td>
<td>ferret</td>
<td>0.61 mg/kg/day for 24 weeks</td>
<td>NOAEL for impaired reproduction</td>
<td>0.006 mg/kg/day</td>
</tr>
<tr>
<td>Carcinogenicity</td>
<td>ID</td>
<td>ID</td>
<td>ID</td>
<td>NA</td>
</tr>
</tbody>
</table>

### REPORTABLE QUANTITIES

- Based on chronic toxicity: 100 pounds  
  Hornshaw et al., 1987
- Based on carcinogenicity: ID  
  NA

ID = Insufficient data
APPENDIX C

DOSE/DURATION RESPONSE GRAPH(S) FOR EXPOSURE TO THIRAM

C.1. DISCUSSION

Dose/duration-response graphs for oral exposure to thiram generated by the method of Crockett et al. (1985) using the computer software by Durkin and Meylan (1988) under contract to ECAO-Cincinnati are presented in Figures C-1 and C-2. Data used to generate this (these) graph(s) are presented in Section C.2. In the generation of this (these) figure(s) all responses are classified as adverse (FEL, AEL or LOAEL) or nonadverse (NOEL or NOAEL) for plotting. If data are available for inhalation exposure: The ordinate expresses concentration in either of two ways. In figure(s) (--), the experimental concentration expressed as mg/m^3 was multiplied by the time parameters of the exposure protocol (e.g., hours/day and days/week) and is presented as expanded experimental concentration [expanded exp conc (mg/m^3)]. In figure(s) (--), the expanded experimental concentration was multiplied by the cube root of the ratio of the animal:human body weight to estimate an equivalent human or scaled concentration [scaled conc (mg/m^3)] (U.S. EPA, 1980; Mantel and Schneiderman, 1975).

The boundary for adverse effects (solid line) is drawn by identifying the lowest-adverse-effect dose or concentration at the shortest duration of exposure at which an adverse effect occurred. From this point an infinite line is extended upward parallel to the dose axis. The starting point is then connected to the lowest-adverse-effect dose or concentration at the next longer duration of exposure that has an adverse-effect dose or concentration equal to or lower than the previous one. This process is continued to the lowest-adverse-effect dose or concentration. From this point a line is extended to the right parallel to the duration axis. The region of adverse effects lies above the adverse effects boundary.
FIGURE C-2

Dose/Duration - Effect Graph for Oral Exposure to Thiram: Censored Data Method
Using the envelope method, the boundary for no adverse effects (dashed line) is drawn by identifying the highest no-adverse-effects dose or concentration. From this point a line parallel to the duration axis is extended to the dose or concentration axis. The starting point is then connected to the next highest or equal no-adverse-effect dose or concentration at a longer duration of exposure. When this process can no longer be continued, a line is dropped parallel to the dose or concentration axis to the duration axis. The region of no adverse effects lies below the no-adverse-effects boundary. At both ends of the graph between the adverse-effects and no-adverse-effects boundaries are regions of ambiguity. The area (if any) resulting from intersection of the adverse-effects and no-adverse-effects boundaries is defined as the region of contradiction.

In the censored data method, all no-adverse-effect points located in the region of contradiction are dropped from consideration and the no-adverse-effect boundary is redrawn so that it does not intersect the adverse-effects boundary and no region of contradiction is generated. This method results in the most conservative definition of the no-adverse-effects region.

C.2. DATA USED TO GENERATE DOSE/DURATION-RESPONSE GRAPHS

Chemical Name: Thiram
CAS Number: 137-26-8
Document Title: Health and Environmental Effects Document on Thiram
Document Number: SRC-TR-88-133
Document Date: 12/22/88
Document Type: HEED
RECORD #1:
Species: Rats
Sex: Male
Effect: FEL
Route: Gavage
Dose: 400.000
Duration Exposure: 1.0 days
Duration Observation: 1.0 days
Number Exposed: NR
Number Responses: NR
Type of Effect: DEATH
Site of Effect: BODY
Severity Effect: 9
Comment: LD50
Citation: Lee et al., 1978

---

RECORD #2:
Species: Rats
Sex: Female
Effect: FEL
Route: Gavage
Dose: 190.000
Duration Exposure: 1.0 days
Duration Observation: 1.0 days
Number Exposed: NR
Number Responses: NR
Type of Effect: DEATH
Site of Effect: BODY
Severity Effect: 9
Comment: LD50
Citation: Lee et al., 1978

---

RECORD #3:
Species: Rats
Sex: Male
Effect: FEL
Route: Gavage
Dose: 640.000
Duration Exposure: 1.0 days
Duration Observation: 1.0 days
Number Exposed: NR
Number Responses: NR
Type of Effect: DEATH
Site of Effect: BODY
Severity Effect: 9
Comment: LD50
Citation: Gaines, 1969

---

0133d -110- 08/23/89
RECORD #4: Species: Rats  Dose: 620.000
Sex: Female  Duration Exposure: 1.0 days
Effect: FEL  Duration Observation: 1.0 days
Route: Gavage

Number Exposed: NR
Number Responses: NR
Type of Effect: DEATH
Site of Effect: BODY
Severity Effect: 9

Comment: LD50
Citation: Gaines, 1969

RECORD #5: Species: Mice  Dose: 400.000
Sex: Male  Duration Exposure: 1.0 days
Effect: FEL  Duration Observation: 1.0 days
Route: Gavage

Number Exposed: NR
Number Responses: NR
Type of Effect: DEATH
Site of Effect: BODY
Severity Effect: 9

Comment: LD50
Citation: Lee et al., 1978

RECORD #6: Species: Mice  Dose: 380.000
Sex: Female  Duration Exposure: 1.0 days
Effect: FEL  Duration Observation: 1.0 days
Route: Gavage

Number Exposed: NR
Number Responses: NR
Type of Effect: DEATH
Site of Effect: BODY
Severity Effect: 9

Comment: LD50
Citation: Lee et al., 1978

0133d -111- 08/23/89
RECORD #7:  Species: Mice  Dose: 2300.000  
Sex: NS  Duration Exposure: 1.0 days  
Effect: FEL  Duration Observation: 1.0 days  
Route: Oral (NOS)  
Number Exposed: NR  
Number Responses: NR  
Type of Effect: DEATH  
Site of Effect: BODY  
Severity Effect: 9  
Comment: LD50; abstract  
Citation: Matthiaschk, 1973

RECORD #8:  Species: Rats  Dose: 3.800  
Sex: Female  Duration Exposure: 2.0 days  
Effect: LOAEL  Duration Observation: 2.0 days  
Route: Oral (NOS)  
Number Exposed: NR  
Number Responses: NR  
Type of Effect: ENZYM  
Site of Effect: NS  
Severity Effect: 2  
Comment: Altered metabolism of ethanol  
Citation: Garcia de Torres et al., 1983

RECORD #9:  Species: Rats  Dose: 132.000  
Sex: Male  Duration Exposure: 13.0 weeks  
Effect: FEL  Duration Observation: 13.0 weeks  
Route: Food  
Number Exposed: 20  NR  20  20  
Number Responses: 14  NR  NR  NR  
Type of Effect: DEATH  
Site of Effect: BODY  
Severity Effect: 9  5  2  5  
Comment: 2500 ppm in diet; food intake also reduced  
Citation: Lee et al., 1978; Short et al., 1976
RECORD #10: Species: Rats  Dose: 58.000
Sex: Male  Duration Exposure: 13.0 weeks
Effect: AE  Duration Observation: 13.0 weeks
Route: Food

Number Exposed: 20 20
Number Responses: NR NR
Type of Effect: WGTDC ENZYM
Site of Effect: BODY KIDNY
Severity Effect: 5 2

Comment: 1000 ppm in diet
Citation: Lee et al., 1978; Short et al., 1976

RECORD #11: Species: Rats  Dose: 30.000
Sex: Male  Duration Exposure: 13.0 weeks
Effect: LOAEL  Duration Observation: 13.0 weeks
Route: Food

Number Exposed: 20
Number Responses: NR
Type of Effect: WGTDC
Site of Effect: BODY
Severity Effect: 5

Comment: 500 ppm in diet
Citation: Lee et al., 1978; Short et al., 1976

RECORD #12: Species: Rats  Dose: 41.900
Sex: Male  Duration Exposure: 29.0 days
Effect: AE  Duration Observation: 29.0 days
Route: Food

Number Exposed: 6
Number Responses: NR
Type of Effect: WGTDC
Site of Effect: BODY
Severity Effect: 5

Comment: 300 ppm in diet; controls were pair-fed
Citation: Lowy et al., 1979, 1980
RECORD #13:  
Species: Rats  
Sex: Male  
Effect: LOAEL  
Route: Food  
Dose: 33.600  
Duration Exposure: 29.0 days  
Duration Observation: 29.0 days  
Number Exposed: 6  
Number Responses: NR  
Type of Effect: WGTDC  
Site of Effect: BODY  
Severity Effect: 4  
Comment: 225 ppm in diet; controls were pair-fed  
Citation: Lowy et al., 1979, 1980

RECORD #14:  
Species: Rats  
Sex: Female  
Effect: FEL  
Route: Food  
Dose: 66.900  
Duration Exposure: 80.0 weeks  
Duration Observation: 80.0 weeks  
Number Exposed: 24  
Number Responses: NR  
Type of Effect: FUNP  
Site of Effect: PNS  
Severity Effect: 8  
Comment: 1000 ppm in diet  
Citation: Lee and Peters, 1976

RECORD #15:  
Species: Rats  
Sex: Female  
Effect: LOAEL  
Route: Food  
Dose: 25.500  
Duration Exposure: 80.0 weeks  
Duration Observation: 80.0 weeks  
Number Exposed: 24  
Number Responses: NR  
Type of Effect: FUND  
Site of Effect: CNS  
Severity Effect: 7  
Comment: 400 ppm in diet  
Citation: Lee and Peters, 1976
RECORD #16: Species: Rats  Dose: 20.400
Sex: Male  Duration Exposure: 80.0 weeks
Effect: AEL  Duration Observation: 80.0 weeks
Route: Food
Number Exposed: 24
Number Responses: NR
Type of Effect: FUND
Site of Effect: CNS
Severity Effect: 6
Comment: 400 ppm in diet
Citation: Lee and Peters, 1976; Lee et al., 1978

RECORD #17: Species: Rats  Dose: 5.300
Sex: Male  Duration Exposure: 80.0 weeks
Effect: LOAEL  Duration Observation: 80.0 weeks
Route: Food
Number Exposed: 24
Number Responses: NR
Type of Effect: WGTDC
Site of Effect: BODY
Severity Effect: 5
Comment: 100 ppm in diet
Citation: Lee and Peters, 1976; Lee et al., 1978

RECORD #18: Species: Rats  Dose: 65.800
Sex: Female  Duration Exposure: 36.0 weeks
Effect: FEL  Duration Observation: 36.0 weeks
Route: Food
Number Exposed: 24
Number Responses: NR
Type of Effect: FUNP
Site of Effect: PNS
Severity Effect: 8
Comment:
Citation: Lee and Peters, 1976
| Record #19: | Species: Rats | Dose: 15.000 | 
| Sex: NS | Duration Exposure: 2.0 Years | 
| Effect: FEEl | Duration Observation: 2.0 Years | 
| Route: Food | 
| Number Exposed: 24 | 
| Number Responses: NR | 
| Type of Effect: FUNP | 
| Site of Effect: CNS | 
| Severity Effect: 8 | 

Comment: Briefly reported; 300 ppm in diet

Citation: E.I. Du Pont de Nemours & Co., n.d.

| Record #20: | Species: Rats | Dose: 15.000 | 
| Sex: Both | Duration Exposure: 2.0 years | 
| Effect: LOAEL | Duration Observation: 2.0 years | 
| Route: Food | 
| Number Exposed: 64 | 
| Number Responses: NR | 
| Type of Effect: WGTDC | 
| Site of Effect: BODY | 
| Severity Effect: 5 | 

Comment: 300 ppm in diet; abstract

Citation: Maita et al., 1980

| Record #21: | Species: Rats | Dose: 1.150 | 
| Sex: Both | Duration Exposure: 2.0 years | 
| Effect: NOEL | Duration Observation: 2.0 years | 
| Route: Food | 
| Number Exposed: 64 | 
| Number Responses: NR | 
| Type of Effect: WGTDC | 
| Site of Effect: BODY | 
| Severity Effect: 5 | 

Comment: 30 ppm in diet; abstract

Citation: Maita et al., 1980
| RECORD #22 | Species: Dogs | Dose: 40.000 | Sex: Both | Duration Exposure: 6.0 weeks |
|           | Effect: FEL  |             | Route: Capsul | Duration Observation: 6.0 weeks |
|           | Number Exposed: NR | | Number Responses: NR | |
|           | Type of Effect: DEATH | | Site of Effect: BODY | |
|           | Severity Effect: 9 | | Comment: Abstract, beagles | |
|           | Citation: Saito et al., 1980 | | |

| RECORD #23 | Species: Dogs | Dose: 4.000 | Sex: Both | Duration Exposure: 2.0 years |
|           | Effect: LOAEL |             | Route: Capsul | Duration Observation: 2.0 years |
|           | Number Exposed: 8 | | Number Responses: NR | |
|           | Type of Effect: FUND | | Site of Effect: CNS | |
|           | Severity Effect: 7 | | Comment: Abstract, beagles | |
|           | Citation: Saito et al., 1980 | | |

| RECORD #24 | Species: Dogs | Dose: 0.400 | Sex: Both | Duration Exposure: 2.0 years |
|           | Effect: NOEL |             | Route: Capsul | Duration Observation: 2.0 years |
|           | Number Exposed: NR | | Number Responses: NR | |
|           | Type of Effect: FUND | | Site of Effect: CNS | |
|           | Severity Effect: 7 | | Comment: Abstract, beagles | |
|           | Citation: Saito et al., 1980 | | |
RECORD #25: Species: Rats  Dose: 240.000  
Sex: Male  Duration Exposure: 1.0 days  
Effect: AEL  Duration Observation: 1.0 days  
Route: Oral (NOS)  
Number Exposed: NR  
Number Responses: NR  
Type of Effect: BEHAV  
Site of Effect: CNS  
Severity Effect: 6  
Comment: Reduced "orientation of hypermotility"  
Citation: Thuranszky et al., 1982  

RECORD #26: Species: Rats  Dose: 60.000  
Sex: Male  Duration Exposure: 1.0 days  
Effect: LOAEL  Duration Observation: 1.0 days  
Route: Oral (NOS)  
Number Exposed: NR  
Number Responses: NR  
Type of Effect: ENZYM  
Site of Effect: CNS  
Severity Effect: 2  
Comment: Altered neurotransmitter levels in unspecified tissue  
Citation: Thuranszky et al., 1982  

RECORD #27: Species: Minks  Dose: 6.600  
Sex: Female  Duration Exposure: 28.0 days  
Effect: LOAEL  Duration Observation: 28.0 days  
Route: Food  
Number Exposed: 2  
Number Responses: NR  
Type of Effect: HEMAT  
Site of Effect: BLOOD  
Severity Effect: 2  
Comment: 45 ppm in diet; dosage in males was 8.6 mg/kg/day  
Citation: Hornshaw et al., 1987
<table>
<thead>
<tr>
<th>Record #28:</th>
<th>Species: Ferrets</th>
<th>Dose: 27.500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: Male</td>
<td>Duration Exposure: 11.0 days</td>
<td></td>
</tr>
<tr>
<td>Effect: FEL</td>
<td>Duration Observation: 11.0 days</td>
<td></td>
</tr>
<tr>
<td>Route: Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Exposed: 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Responses: NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of Effect: DEATH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of Effect: BODY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity Effect: 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comment: 312 ppm; females at this dietary level (44.8 mg/kg bw/day) also died</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citation: Hornshaw et al., 1987</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Record #29:</th>
<th>Species: Ferrets</th>
<th>Dose: 2.800</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: Male</td>
<td>Duration Exposure: 28.0 days</td>
<td></td>
</tr>
<tr>
<td>Effect: LOAEL</td>
<td>Duration Observation: 28.0 days</td>
<td></td>
</tr>
<tr>
<td>Route: Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Exposed: 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Responses: NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of Effect: WGTDC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of Effect: BODY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity Effect: 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comment: 20 ppm in diet; females at this dietary level (3.3 mg/kg bw/day) not affected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citation: Hornshaw et al., 1987</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Record #30:</th>
<th>Species: Ferrets</th>
<th>Dose: 16.500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: Female</td>
<td>Duration Exposure: 28.0 days</td>
<td></td>
</tr>
<tr>
<td>Effect: LOAEL</td>
<td>Duration Observation: 28.0 days</td>
<td></td>
</tr>
<tr>
<td>Route: Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Exposed: 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Responses: NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of Effect: WGTDC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of Effect: BODY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity Effect: 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comment: 125 ppm in diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citation: Hornshaw et al., 1987</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECORD #31:</td>
<td>Species: Ferrets</td>
<td>Dose: 5.600</td>
</tr>
<tr>
<td>Sex: Male</td>
<td>Duration Exposure: 28.0 days</td>
<td></td>
</tr>
<tr>
<td>Effect: LOAEL</td>
<td>Duration Observation: 28.0 days</td>
<td></td>
</tr>
<tr>
<td>Route: Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Exposed: 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Responses: NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of Effect: HEMAT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of Effect: BLOOD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity Effect: 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comment: 50 ppm in diet; effect also observed in females (8.6 mg/kg bw/day)

Citation: Hornshaw et al., 1987

| RECORD #32: | Species: Ferrets | Dose: 1.100 |
| Sex: Male | Duration Exposure: 28.0 days |
| Effect: NOEL | Duration Observation: 28.0 days |
| Route: Food |
| Number Exposed: 5 |
| Number Responses: NR |
| Type of Effect: HEMAT |
| Site of Effect: BLOOD |
| Severity Effect: 2 |

Comment: 8 ppm in diet; no effects in females (1.6 mg/kg bw/day)

Citation: Hornshaw et al., 1987

| RECORD #33: | Species: Hamsters | Dose: 500.000 |
| Sex: Female | Duration Exposure: 1.0 days |
| Effect: FEL | Duration Observation: 1.0 days |
| Route: Gavage |
| Number Exposed: 4 |
| Number Responses: NR |
| Type of Effect: DEATH |
| Site of Effect: BODY |
| Severity Effect: 9 |

Comment: Given in carboxymethylcellulose (CMC)

Citation: Robens, 1969

0133d -120- 08/23/89
<table>
<thead>
<tr>
<th>RECORD #34:</th>
<th>Species: Hamsters</th>
<th>Dose: 250.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex:</td>
<td>Female</td>
<td>Duration Exposure: 1.0 days</td>
</tr>
<tr>
<td>Effect:</td>
<td>FEL</td>
<td>Duration Observation: 1.0 days</td>
</tr>
<tr>
<td>Route:</td>
<td>Gavage</td>
<td></td>
</tr>
<tr>
<td>Number Exposed:</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Number Responses:</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Type of Effect:</td>
<td>TERAD</td>
<td></td>
</tr>
<tr>
<td>Site of Effect:</td>
<td>FETUS</td>
<td></td>
</tr>
<tr>
<td>Severity Effect:</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Comment:</td>
<td>Given in CMC; statistical analysis not performed</td>
<td></td>
</tr>
<tr>
<td>Citation:</td>
<td>Robens, 1969</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RECORD #35:</th>
<th>Species: Hamsters</th>
<th>Dose: 125.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex:</td>
<td>Female</td>
<td>Duration Exposure: 1.0 days</td>
</tr>
<tr>
<td>Effect:</td>
<td>NOAEL</td>
<td>Duration Observation: 1.0 days</td>
</tr>
<tr>
<td>Route:</td>
<td>Gavage</td>
<td></td>
</tr>
<tr>
<td>Number Exposed:</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Number Responses:</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Type of Effect:</td>
<td>TERAD</td>
<td></td>
</tr>
<tr>
<td>Site of Effect:</td>
<td>FETUS</td>
<td></td>
</tr>
<tr>
<td>Severity Effect:</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Comment:</td>
<td>Given in CMC; statistical analysis not performed</td>
<td></td>
</tr>
<tr>
<td>Citation:</td>
<td>Robens, 1969</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RECORD #36:</th>
<th>Species: Mice</th>
<th>Dose: 250.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex:</td>
<td>Female</td>
<td>Duration Exposure: 2.0 days</td>
</tr>
<tr>
<td>Effect:</td>
<td>NOAEL</td>
<td>Duration Observation: 2.0 days</td>
</tr>
<tr>
<td>Route:</td>
<td>Oral (NOS)</td>
<td></td>
</tr>
<tr>
<td>Number Exposed:</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Number Responses:</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Type of Effect:</td>
<td>TERAD</td>
<td></td>
</tr>
<tr>
<td>Site of Effect:</td>
<td>FETUS</td>
<td></td>
</tr>
<tr>
<td>Severity Effect:</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Comment:</td>
<td>Abstract; NMRI mice more sensitive than SW mice. Teratogenicity was observed at higher unspecified doses; no maternal toxicity</td>
<td></td>
</tr>
<tr>
<td>Citation:</td>
<td>Roll, 1971</td>
<td></td>
</tr>
</tbody>
</table>
RECORD #37:  
Species: Mice  
Sex: Female  
Effect: FEL  
Route: Oral (NOS)  
Dose: 10.000  
Duration Exposure: 11.0 days  
Duration Observation: 11.0 days  
Number Exposed: NR  
Number Responses: NR  
Type of Effect: TERAD  
Site of Effect: FETUS  
Severity Effect: 8  
Comment: Abstract; NMRI mice  
Citation: Matthiaschek, 1973

RECORD #38:  
Species: Rats  
Sex: Female  
Effect: LOAEL  
Route: Gavage  
Dose: 40.000  
Duration Exposure: 10.0 days  
Duration Observation: 10.0 days  
Number Exposed: 10  
Number Responses: NR  
Type of Effect: TERAS  
Site of Effect: FETUS  
Severity Effect: 8  
Comment: Maternal food intake and bw gain reduced; study does not identify NOAEL  
Citation: Short et al., 1976

RECORD #39:  
Species: Mice  
Sex: Female  
Effect: LOAEL  
Route: Gavage  
Dose: 300.000  
Duration Exposure: 9.0 days  
Duration Observation: 9.0 days  
Number Exposed: 18  
Number Responses: NR  
Type of Effect: TERAS  
Site of Effect: FETUS  
Severity Effect: 7  
Comment: Slight evidence of fetotoxicity; statistical analysis not performed; 4/18 dams died; SW mice  
Citation: Short et al., 1976
RECORD #40: Species: Mice  Dose: 100.000
Sex: Female  Duration Exposure: 9.0 days
Effect: NOAEL  Duration Observation: 9.0 days
Route: Gavage

Number Exposed: 18
Number Responses: NR
Type of Effect: TERAS
Site of Effect: FETUS
Severity Effect: 7

Comment: SW mice; no evidence of maternal or fetal toxicity
Citation: Short et al., 1976

RECORD #41: Species: Rats  Dose: 132.000
Sex: Male  Duration Exposure: 13.0 weeks
Effect: FEL  Duration Observation: 13.0 weeks
Route: Food

Number Exposed: 20
Number Responses: NR
Type of Effect: REPRO
Site of Effect: NS
Severity Effect: 8

Comment: 2500 ppm in diet; males failed to inseminate control females; <50% of males with impaired breeding performance had testicular lesions
Citation: Short et al., 1976

RECORD #42: Species: Rats  Dose: 58.000
Sex: Male  Duration Exposure: 13.0 weeks
Effect: NOAEL  Duration Observation: 13.0 weeks
Route: Food

Number Exposed: 20
Number Responses: NR
Type of Effect: REPRO
Site of Effect: NS
Severity Effect: 8

Comment: 1000 ppm in diet
Citation: Short et al., 1976
<table>
<thead>
<tr>
<th>Record #</th>
<th>Species</th>
<th>Dose</th>
<th>Sex</th>
<th>Duration Exposure</th>
<th>Effect</th>
<th>Duration Observation</th>
<th>Route</th>
<th>Number Exposed</th>
<th>Number Responses</th>
<th>Type of Effect</th>
<th>Site of Effect</th>
<th>Severity Effect</th>
<th>Comment</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>Rats</td>
<td>30.000</td>
<td>Female</td>
<td>14.0 days</td>
<td>LOAEL</td>
<td>14.0 days</td>
<td>Food</td>
<td>20</td>
<td>NR</td>
<td>TERAS</td>
<td>FETUS</td>
<td>7</td>
<td>400 ppm in diet; lowest dosage tested</td>
<td>Short et al., 1976</td>
</tr>
<tr>
<td>44</td>
<td>Rats</td>
<td>95.200</td>
<td>Female</td>
<td>27.0 days</td>
<td>LOAEL</td>
<td>27.0 days</td>
<td>Food</td>
<td>10</td>
<td>NR</td>
<td>SURVI</td>
<td>OTHER</td>
<td>9</td>
<td>Reduced viability and growth of offspring; 1000 ppm in diet</td>
<td>Short et al., 1976</td>
</tr>
<tr>
<td>45</td>
<td>Rats</td>
<td>43.400</td>
<td>Female</td>
<td>27.0 days</td>
<td>NOAEL</td>
<td>27.0 days</td>
<td>Food</td>
<td>10</td>
<td>NR</td>
<td>SURVI</td>
<td>OTHER</td>
<td>9</td>
<td>No effect on survival of offspring</td>
<td>Short et al., 1976</td>
</tr>
<tr>
<td>RECORD #46:</td>
<td>Species: Minks</td>
<td>Dose: 5.700</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>----------------</td>
<td>------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex: Female</td>
<td>Duration Exposure: 20.0 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect: AEL</td>
<td>Duration Observation: 20.0 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Route: Food</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Exposed: 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Responses: NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of Effect: SURVI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of Effect: OTHER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity Effect: 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comment: Decreased average birth weight, possibly decreased kit survival; 40 ppm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citation: Hornshaw et al., 1987</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RECORD #47:</th>
<th>Species: Minks</th>
<th>Dose: 1.500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: Female</td>
<td>Duration Exposure: 20.0 weeks</td>
<td></td>
</tr>
<tr>
<td>Effect: LOAEL</td>
<td>Duration Observation: 20.0 weeks</td>
<td></td>
</tr>
<tr>
<td>Route: Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Exposed: 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Responses: NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of Effect: SURVI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of Effect: OTHER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity Effect: 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comment: Probably decreased kit survival; 10 ppm in diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citation: Hornshaw et al., 1987</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RECORD #48:</th>
<th>Species: Minks</th>
<th>Dose: 0.400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: Female</td>
<td>Duration Exposure: 20.0 weeks</td>
<td></td>
</tr>
<tr>
<td>Effect: NOAEL</td>
<td>Duration Observation: 20.0 weeks</td>
<td></td>
</tr>
<tr>
<td>Route: Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Exposed: 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Responses: NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of Effect: SURVI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of Effect: OTHER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity Effect: 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comment: No effect on reproduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citation: Hornshaw et al., 1987</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RECORD #49: Species: Ferrets  Dose: 7.000
Sex: Female  Duration Exposure: 24.0 weeks
Effect: FEL  Duration Observation: 24.0 weeks
Route: Food

Number Exposed: 12
Number Responses: NR
Type of Effect: REPRO
Site of Effect: OTHER
Severity Effect: 8

Comment: Reproduction precluded at 64 ppm in diet

Citation: Hornshaw et al., 1987

---------------------------------------------------------------

RECORD #50: Species: Ferrets  Dose: 2.100
Sex: Female  Duration Exposure: 24.0 weeks
Effect: LD50  Duration Observation: 24.0 weeks
Route: Food

Number Exposed: 12
Number Responses: NR
Type of Effect: REPRO
Site of Effect: OTHER
Severity Effect: 8

Comment: 16 ppm: reduced number of offspring/litter, litter weight
and offspring body weight at 3 weeks postpartum; survival of
offspring reduced

Citation: Hornshaw et al., 1987

---------------------------------------------------------------

RECORD #51: Species: Ferrets  Dose: 0.610
Sex: Female  Duration Exposure: 24.0 weeks
Effect: NOAEL  Duration Observation: 24.0 weeks
Route: Food

Number Exposed: 12
Number Responses: NR
Type of Effect: REPRO
Site of Effect: OTHER
Severity Effect: 8

Comment: No effects on reproduction

Citation: Hornshaw et al., 1987

---------------------------------------------------------------

NR = Not reported