Thiram, tetramethylthiuram disulfide, is extensively used as an agricultural fungicide for both foliage application and seed treatment. It is also used as a nut, fruit and mushroom disinfectant as well as a repellent for rodents and certain large animals that cause damage to field crops (1,2). The fungicide is an ingredient of certain medicated soaps, and suntan and antiseptic sprays. In addition, it is used as a rubber accelerator in tire industry and an antioxidant in plastic industry. It may also be used in the blending of lubricating oils. This chemical can be found in the environment as a degradation product of the two widely used fungicides, ferbam and ziram (3).

Thiram is a white crystalline solid compound, insoluble in water but soluble in many organic solvents such as chloroform. It is stable under normal storage conditions; however, there can be a loss of its activity on prolonged exposure to air, heat and moisture. It is decomposed by acids. Thiram can enter the body through inhalation of dust, spray or mist. Other routes include ingestion, and skin and eye contact. Workers from rubber and lubricating oil industries are at a greater risk of exposure. The exposure level of thiram in the air at workplace should not exceed 5 mg/cubic meter during any 8-hour workshift for 40-hour work week. No-adverse effect level of thiram in water has been reported to be 0.035 mg/l. According to a published report, the highest no-effect level for the rat is 48 ppm in the diet fed to the animals during a three-generation study (4). On the other hand, a recent study has shown that the no-effect level for the rat is 38 ppm (5). Residue tolerances for thiram when used as fungicide have been set at levels up to 7 mg/kg for variety of fruits and vegetables. The WHO recommended acceptable daily intake (ADI) is 5 μg/kg of body weight (6).

TOXICITY

Excessive exposure to thiram may produce irritation of mucous membranes, conjunctivitis, rhinitis, sneezing and coughing in the exposed subject. Skin irritation with erythema and urticaria may also occur. Allergic contact dermatitis has been reported in workers who had worn rubber gloves containing thiram. A similar type of contact dermatitis has been seen in rabbits following intracutaneous administration of 0.1 ml of 0.5% thiram (7). On the other hand, a single application of thiram to the skin of rats and rabbits in the form of an oily solution in doses of 1000-2000 mg/kg and 500-1000 mg/kg, respectively, did not produce either skin irritation or general toxicity. Similarly, repeated application of the compound to the skin of rabbits in a dose of 50 mg/kg did not produce any skin manifestations (8).

The acute oral toxicity (LD50) of thiram for mammals ranges from 230 to 2800 mg/kg (Table 1). Animals killed by single oral doses of thiram showed hyperemia, focal ulceration of the gastro-intestinal tract, focal necrosis of liver and renal tubules and patchy demyelination in the cerebellum and medulla (9). Symptoms of acute thiram poisoning in humans include nausea, vomiting, diarrhea, headache, lethargy, dizziness, ataxia, confusion, drowsiness, flaccid paralysis and death. If death does not occur, recovery tends to be complete within 1 or 2 weeks.

Chronic exposure of rats to 100, 300 and 500 ppm dietary thiram resulted in reduced growth rate, nervous dysfunctions, thyroid hyperplasia, calcification of brain and increased mortality rate (11). Another chronic toxicity study in rats showed that 300 ppm thiram in the diet caused rise in white blood cells, and SGPT and SGOT indicating liver damage (12). In this study, the author also observed fall in gamma globulin level in the serum of thiram-exposed rats. Other studies have shown growth reduction as the dietary level exceeds 100 ppm (13). In a study conducted by Russian workers, chronic oral administration of thiram retarded the growth of rats, decreased blood hemoglobin levels, inhibited blood catalase and peroxidase, and caused destructive-dystrophic changes in the spleen, liver, and other organs (14).

Production of abnormal eggs in large hen population has been attributed to feeding of maize treated with thiram (10). Chicks

<table>
<thead>
<tr>
<th>Species</th>
<th>Oral Toxicity (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>420-640, LD50</td>
</tr>
<tr>
<td>Mouse</td>
<td>2650-2500, LD50</td>
</tr>
<tr>
<td>Rabbit</td>
<td>350, LD50</td>
</tr>
<tr>
<td>Hamsters</td>
<td>250, toxic dose</td>
</tr>
<tr>
<td>Cat</td>
<td>230, lethal dose</td>
</tr>
<tr>
<td>Sheep</td>
<td>225, lethal dose</td>
</tr>
<tr>
<td>Pigs</td>
<td>1000, lethal dose</td>
</tr>
<tr>
<td>Mallard ducks</td>
<td>3980, LD50</td>
</tr>
<tr>
<td>Pheasants</td>
<td>485-932, LD50</td>
</tr>
</tbody>
</table>
fed 40 ppm of dietary thiram caused leg weakness while goslings lost weight and showed leg deformities at a level of 150 ppm. Lower egg production, weight loss of the ovary and oviduct and decrease in serum calcium level have been reported in bobwhite quail following long-term exposure ppm. Lower egg production, weight loss of the ovary and oviduct and decrease in serum calcium level have been reported to cause abortions in pregnant animals. Prolonged occupational exposure to thiram has been found to increase the incidence of hypertension, myocardiodystrophy, diseases of the hepatobiliary system, thyroid diseases, and gastrointestinal diseases (16).

Other effects of prolonged occupational exposure to thiram include lachrymation, photophobia, conjunctivitis, reduced vision acuity and corneal sensitivity, and increased pressure in the retinal artery (17).

Thiram has been found to be teratogenic in hamster (18) and mice (8). It causes mutagenic effects in mice characterized by chromosomal aberrations in bone marrow cells (19).

**METABOLISM**

Published reports suggest that the metabolism of thiram probably plays an important role in its toxicity. For example, Nitsche et al (20) reported that the fungicides ferbam, ziram and thiram are not stable under certain environmental conditions and can be degraded to toxic products such as carbon disulfide, hydrogen sulfide and dimethylamine. These researchers were able to determine dimethylamine, a possible carcinogen, as a degradation product of thiram under in vitro acidic conditions. On the other hand, carbon disulfide, another metabolite of thiram, was detected by Merlvede and Peters (21) in the expired air following oral administration of thiram to man. A recent report by Dalvi and Deoras (22) suggests an involvement of liver microsomal enzymes in the formation of carbon disulfide which was detected in the expired air of rats administered thiram intraperitoneally. Similarly, Hodgson et al (23) administered ferbam, a fungicide that degrades to thiram, orally to rats and found carbon disulfide as a metabolite in the expired air while other metabolites dimethylamine and dimethyldithiocarbamate were identified in the urine.

It has been reported that tetraalkyl-thiuram disulfides such as disulfiram react with thiol compounds (eg reduced glutathione) present in reticulocytes and perhaps other cells to yield dialkyldithiocarbamates as metabolites (24,25) which subsequently are biotransformed to carbon disulfide by liver enzymes (26,27). An identical liver metabolism of thiram to dimethyldithiocarbamate and carbon disulfide has been postulated (22).

Disulfiram, an ethyl analogue of thiram which is several times less toxic than thiram, has been shown to cause liver damage probably through its metabolism to carbon disulfide, a highly liver toxic compound (26,28). There is an evidence to suggest that thiram is also toxic to liver as manifested by inhibition of hepatic microsomal enzymes and elevation of the activity of some serum enzymes usually used as markers of liver damage (22, 29-31).

**MECHANISM OF ACTION/INTERACTIONS**

Several mechanisms for the toxic effects of thiram can be proposed. They are mostly related to its metabolism and inhibition of certain enzymes produced by thiram or its metabolites. Carbon disulfide, a metabolite of thiram, is a well known neurotoxicant and some of the central nervous system toxicity of thiram may be attributed to this metabolite. Similarly, this metabolite may account for part of the hepatotoxic effects seen in thiram intoxication. Another metabolite of thiram, dimethyldithiocarbamate, can be responsible for cholinesterase inhibition and consequently for neurological disorders caused by thiram (32, 33). Chelation of certain important elements by dimethyldithiocarbamate, which are essential as cofactors for many enzymes, may also result in decreased enzymes activity in the nervous system leading to neurotoxic effects.

Disulfiram (ANTABUSE) has been reported to be a potent inhibitor of dopamine β-hydroxylase (34). Since disulfiram and thiram are structural analogues and produce similar toxic effects, inhibition of dopamine β-hydroxylase by thiram leading to central nervous system manifestations is possible. Certain key sulfhydryl enzymes such as hexokinase and amino acid oxidases are also inhibited by disulfiram and thiram, thus providing another biochemical basis for their toxicity (9).

The basis for disulfiram as an alcohol aversion drug is that it inhibits aldehyde dehydrogenase and produces discomfort in alcoholic patients taking the drug and alcohol together. This is thought to be due to accumulation of acetaldehyde. Intolerance to alcohol has been observed in workers exposed to thiram, manifested by flushing of face, palpitation, rapid pulse, dizziness and hypotension (35). These toxic effects can also be attributed to the inhibition of aldehyde dehydrogenase by thiram and subsequent accumulation of acetaldehyde. Another interaction of thiram involves its chemical reaction with nitrite at acid pH in stomachs of guinea pigs in vivo which gives rise to N-nitrosodimethylamine, a potent carcinogen (11).

**REFERENCES**


