THIRAM

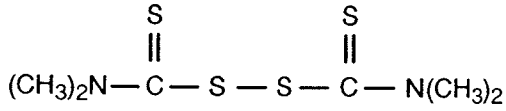
This substance was considered by a previous Working Group, in 1976 (IARC, 1976a). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Serv. Reg. No.: 137-26-8
Replaced CAS Reg. Nos: 12680-07-8; 12680-62-5; 39456-80-9; 66173-72-6; 93196-73-7
Chem. Abstr. Name: Tetramethylthioperoxydicarbonic diamide
IUPAC Systematic Name: Tetramethylthiuram disulphide
Synonyms: Bis(dimethylthiocarbamoyl)disulfide; bis(dimethylthiocarbamyl)disulfide; tetramethylthioperoxydicarbonic diamide; tetramethylthiuram bisulfide; *N,N,N',N'*-tetramethylthiuram disulfide; thiuram disulfide, tetramethyl-; thiuram TMTD; thiuramyl; TMT; TMTD; TMTDS



$C_6H_{12}N_2S_4$ Mol. wt: 240.4

1.1.2 *Chemical and physical properties*

(*a*) *Description*: White or yellow monoclinic crystals (Weast, 1989)
(*b*) *Boiling-point*: 129°C at 20 mm Hg [2.7 kPa] (Weast, 1989)
(*c*) *Melting-point*: 155.6°C (Weast, 1989)
(*d*) *Spectroscopy data*: Infrared (prism [10588]; grating [21299]), nuclear magnetic resonance (proton [6403]), ultraviolet and mass spectral data have been reported (Benson & Damico, 1968; Brinkhoff & Grotens, 1971; Gore *et al.*, 1971; US Environmental Protection Agency, 1975; Sadtler Research Laboratories, 1980).
(*e*) *Solubility*: Insoluble in water; soluble in chloroform (230 g/l), ethanol and diethyl ether (< 2%), acetone (80 g/l), benzene (2.5%); slightly soluble in carbon disulfide (Meister, 1990; Budavari, 1989; Royal Society of Chemistry, 1989)
(*f*) *Vapour pressure*: Negligible at room temperature (Royal Society of Chemistry, 1989)
(*g*) *Stability*: Decomposes in acidic media (Royal Society of Chemistry, 1989); some deterioration on prolonged exposure to heat, air or moisture (Worthing & Walker, 1987)

(*h*) *Conversion factor for airborne concentrations*[1]: $mg/m^3 = 9.83 \times ppm$

1.1.3 *Trade names, technical products and impurities*

Some common trade names are: Aapirol; Aatiram; Accel TMT; Accelerant T; Accelerator Thiuram; Accelerator T; Aceto TETD; Aules; Apirol; Arasan; Atiram; Basultra; Betoxin; Delsan; Ekagom TB; Falitiram; Ferna-Col; Fernasan; Fernide; Formalsol; Hermal; Hermat TMT; Heryl; Hexathir; Kregasan; Mercuram; Methyl Thiram; Methyl Tuads; Metiurac; Nobecutan; Nocceler TT; Normersan; Panoram 75; Pol-Thiuram; Polyram ultra; Pomarsol; Pomasol; Puralin; Radothiram; Radotiram; Rezifilm; Rhenogran TMTD; Rhodiauram; Robac TMT; Royal TMTD; Sadoplon; Sadoplon 75; Soxinol TT; Spotrete; SQ 1489; Tersan; Tetrasipton; Thillate; Thiosan; Thioscabin; Thiotox; Thirasan; Thiride; Thiulin; Thiurad; Thiuram; Thylate; Tigam; Tiradin; Tiuramyl; Trametan; Tridipam; Tripomol; Tuads; TUEX; Tulisan; Tutan; Tyradin; VUAgT-I-4; Vucafor; Vulcacit thiuram; Vulkacit Th; Zaprawa Nasienna T; Zupa S 80

In the USA, thiram is formulated as dusts, wettable powder and flowable suspensions. The usual carriers are marl, talc (see IARC, 1987a), clays, petroleum oils, graphite, vermiculite, mineral oil (see IARC, 1987b), charcoal and water (US Environmental Protection Agency, 1984). Formulated thiram products registered in European countries include dustable powders, dry seed treatments, flowable concentrates for seed treatment, liquids, liquid seed treatments, pastes, powders, suspension concentrates, water-dispersible granules, wettable powders and slurries for seed treatment (Royal Society of Chemistry, 1986).

Thiram can be combined in formulations with most fungicides and insecticides. In the USA, such products include thiram with phenylmercury-dimethyldithiocarbamate, malachite green, thiophanate, zineb (see IARC, 1976b, 1987c), molybdenum, vinclozolin and carboxin (Anon., 1989; Meister, 1990). Formulated thiram products registered in European countries include in addition, combinations with trichloronat, ziram (see monograph, p. 423), cycloheximide, benomyl, permethrin, fonofos, carbendazim, rotenone, thiophanate methyl, bendiocarb, thiabendazole, lindane (see IARC, 1987d), 4-indol-3-yl butyric acid, methyl 2-(1-naphthyl)acetate, 2-(1-naphthyl)acetamide and dicloran (Royal Society of Chemistry, 1986; Worthing & Walker, 1987).

In the USSR, technical-grade thiram contains 95-98% thiram. Thiram is formulated as a dust and as an aqueous suspension (Izmerov, 1982).

1.1.4 *Analysis*

Selected methods for the analysis of thiram in various matrices are given in Table 1.

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[1]Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming standard temperature (25°C) and pressure (760 mm Hg [101.3 kPa])

Table 1. Methods for the analysis of thiram

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Air	Collect on filter; extract with acetonitrile	HPLC/UV	0.005 mg per sample	Eller (1984)
	Collect on filter; extract with chloroform; measure absorbance at 440 nm	Spectrophotometric	0.5 mg/m^3	Taylor (1977)
Fruits and vegetables	Extract with chloroform; treat with copper iodide; measure absorbance at 440 nm	Spectrophotometric	Not reported	Williams (1984a)
Specified crop samples and water	Extract with chloroform; evaporate, dissolve in methanol; add to a mixture of methanolic 0.2% haematoxylin, aqueous 0.4% chloramine-T and phosphate buffer solution at pH 7.0; heat; dilute with water; read absorbance at 555 nm	Spectrophotometric	Not reported	Sastry *et al.* (1988)
Formulations (technical, dusts, dispersible powders)	Decompose by boiling with acetic acid and zinc acetate; pass through cadmium sulfate scrubber into absorption system containing methanol/potassium hydroxide; titrate with aqueous iodine	Colorimetric	Not reported	Williams (1984b)

[a]Abbreviation: HPLC/UV, high-performance liquid chromatography/ultraviolet detection

1.2 Production and use

1.2.1 *Production*

Thiram was first produced commercially in the USA in 1925 (US Tariff Commission, 1926). It is produced by passing chlorine gas through a solution of sodium dimethyldithiocarbamate (Wenyon, 1972), by the oxidation of sodium dimethyldithiocarbamate with hydrogen peroxide (see IARC, 1985, 1987e) or iodine (Spencer, 1973), from iron oxide (see IARC, 1987f), hydrogen peroxide, sodium hydroxide, dimethylamine and carbon disulfide (Japanese Ministry of Agriculture and Forestry, 1975) or by continuous mixing of cyanochloride and aqueous solution of sodium dimethyldithiocarbamate at pH 7.9 (Izmerov, 1982).

US production was 2000 tonnes in 1960 (US Tariff Commission, 1961) and 7900 tonnes in 1973 (US International Trade Commission, 1975a). In 1974, four US companies reported total production of 5800 tonnes (US International Trade Commission, 1975b). In 1981, an estimated 1360 tonnes of thiram were produced in the USA (Vlier, 1982). Thiram is produced currently in Belgium, the Netherlands, Spain and the USA (Meister, 1990). One company in India produced 300 tonnes of thiram for pesticide use in 1989 (Indian Ministry of Petroleum and Chemicals, 1990). In Japan, commercial production of thiram began in 1953; in 1970, four companies reported production of 140 tonnes and in 1974, 240 tonnes (Japanese Ministry of Agriculture and Forestry, 1975).

1.2.2 *Use*

The major use of thiram is in rubber processing as an accelerator and vulcanizing agent (see IARC, 1982). It is also used as a seed treatment to protect against fungal diseases and by

foliar application for control of diseases on fruit and vegetable crops and on lawns and turf (Izmerov, 1982; Vlier, 1982). In the USA, it was estimated that the following amounts of thiram (active ingredient) were used in 1981 for seed treatment: small grains (wheat, oats, barley and rye), 220 tonnes; soya beans, 60 tonnes; maize, 23 tonnes; cotton, 23 tonnes; sweet maize, 7 tonnes; beans, 5 tonnes; sorghum, 5 tonnes; and peanuts, 2 tonnes. About 55 tonnes were estimated to have been used for foliar treatment of apples, 170 tonnes for treatment of golf courses and 55 tonnes for treatment of sod (Vlier, 1982). Thiram has also been used for mould control in textiles and polyurethane (US Environmental Protection Agency, 1984), for slime control in the manufacture of paper and as a bacteriostat in soap (IARC, 1976).

1.3 Occurrence

Thiram can be found in the environment as a degradation product of ferbam (Lowen, 1961) and ziram (see monograph, p. 423).

The dermal and respiratory exposure of personnel operating commercial seed treating equipment was examined in eight industrial plants in the USA, where a liquid formulation of thiram and carboxin was applied to small grain cereals. It was estimated that there was no dermal exposure *via* the chest or arms, but hands were exposed to levels ranging from not detectable (< 0.5 mg/h) at four plants to a maximum of 3.7 mg/h at the remaining plants. One case of respiratory exposure at 0.75 mg/h was reported (Grey *et al.*, 1983).

Thiram has been found as a dust in the work room air of formulating plants in Italy. Levels of thiram in the air were 0.06 mg/m^3 in the packing room and 0.04 mg/m^3 in the mixing room (Maini & Boni, 1986).

1.4 Regulations and guidelines

The FAO/WHO Joint Meeting on Pesticide Residues evaluated thiram at its meetings in 1965, 1967, 1970, 1974, 1977, 1980, 1983, 1984, 1985, 1987, 1988 and 1989 (FAO/WHO, 1965, 1968, 1971, 1975, 1978, 1981, 1984, 1985, 1986, 1988a,b, 1989). A temporary acceptable daily intake for man of 0.005 mg/kg bw was valid until 1985, when it was withdrawn (FAO/WHO, 1986).

In the USSR, the maximum allowable concentration in drinking-water is 1 mg/ml. Thiram is permitted for use only for seed disinfection (Izmerov, 1982).

National and regional pesticide residue limits for thiram in foods are presented in Table 2.

Occupational exposure limits for thiram in air are given in Table 3. The limit in the USA is proposed to be revised to 1 mg/m^3 (American Conference of Governmental Industrial Hygienists, 1989; US Occupational Safety and Health Administration, 1989).

2. Studies of Cancer in Humans

In a group of 223 workers (42 men and 181 women) in the USSR, mostly aged between 20-50 years, who had been engaged in the manufacture of thiram for more than three years, one case of a malignant lesion of the thyroid was reported among 105 workers examined (Cherpak *et al.*, 1971; Kaskevich & Bezugly, 1973).

Table 2. National and regional pesticide residue limits for thiram in foods[a]

Country or region	Residue limit (mg/kg)	Commodities
Argentina	5[b]	Grapes
	3[b]	Broccoli, Brussels' sprouts, cabbage, cauliflower, celery, Damson plums, eggplants, escarole, lettuce, peaches, peppers, spinach, sweet maize, tomatoes
	2[b]	Apples, pears
	1.0[b]	Cherries, cucumbers, marrows, melons, plums, watermelons
	0.5[b]	Beans (with pods), chick peas, lentils, onions, peas, sugar beets (root), table beets (root)
	0.1[b]	Carrots, potatoes, sweet potatoes, turnips
Australia	7	Fruits, vegetables
Austria	25[b,c]	Hops
	2[c]	Fruit, vegetables
	0.05[b,c]	Other
Belgium	2[c]	Fruit, other vegetables
	0.5[c]	Bulb vegetables, grains
	0.2[c]	Potatoes
	0 (0.02)[c,d]	Other foodstuffs of vegetable origin
Brazil	7	Peas, string beans
	1.0	Bananas (peeled)
	0.5	Garlic, onions, tobacco
Canada	7	Apples, celery, peaches, strawberries, tomatoes
	1.0	Bananas (edible pulp)
	Negligible	Barley, maize, flax, oats, plums, safflower (oil), wheat
Chile	5[b,c]	Grapes
	3[b,c]	Apples, peaches, pears, tomatoes
	1.0[b,c]	Cherries, lettuce, plums
	0.5[b,c]	Carrots
	0.2[b,c]	Wheat
	0.1[b,c]	Potatoes
European Community	3.8[e]	Lettuce, strawberries
	3.0[e]	Other products
Finland	1.0[b]	Other (except cereal grains)
	0.5[b]	Carrots
	0.1[b]	Bananas, potatoes

Table 2 (contd)

Country or region	Residue limit (mg/kg)	Commodities
Germany	25[b]	Hops
	2[b]	Fruit, oilseed, raw coffee, spices, tea, tea-like products, vegetables (except cucumbers and tomatoes)
	1.0[b]	Cucumbers, tomatoes
	0.2[b]	Other vegetable foodstuffs
Greece	3.4	Grapes, strawberries
	3.0	Other fruit and vegetables
Ireland	4	Grapes, strawberries
	3	Other food products
Israel	5[b,c]	Celery, currants (black, red), grapes
	3[b,c]	Apples, peaches, pears, strawberries, tomatoes
	1.0[b,c]	Bananas (whole), cherries, plums
	0.5[b,c]	Endive, lettuce, melons
	0.2[b,c]	Beans (in pods), carrots, cucumber
	0.1[b,c]	Wheat, banana pulp, potatoes
Italy	3.8	Grapes, strawberries
	3.0	Other fruits, vegetables
	2.0	Potatoes, tobacco
Japan	1.0	Apples
	0.5	Peaches, pears, persimmons
Kenya	7	Apples, celery, peaches, strawberries, tomatoes
	1.0	Bananas (edible pulp)
	0.5	Onions (dry bulb)
Mexico	7	Apples, celery, peaches, strawberries, tomatoes
	0.5	Onions
Netherlands	4[c]	Lettuce
	3[c]	Berries, small fruit
	2[c]	Other fruit, other vegetables
	1.0[c]	Cucumber, melon
	0.5[c]	Bulb vegetables, cereals
	0.2[c]	Potatoes, pulses
	0 (0.2)[f]	Other
New Zealand	7[c]	Fruit, vegetables
Singapore	3	Fruit, grain, vegetables
South Africa	3[b]	Apples, apricots, peaches, pears, plums
Spain	4[g]	Grapes, hops, strawberries
	3[g]	Other fruits and vegetables (except potatoes)
	0.2[g]	Potatoes and other plant products

Table 2 (contd)

Country or region	Residue limit (mg/kg)	Commodities
Sweden	1.0[h]	Fruit and vegetables
	0.5[h]	Carrots
	0.1[h,i]	Potatoes
Switzerland	50[b,c]	Tobacco
	2[b,c]	Fruit, lettuce, vegetables (except potatoes)
	0.5[b,c]	Bananas (pulp)
	0.1[b,c]	Cereals
	0.05[b,c]	Potatoes
USA	7[j]	Apples, bananas (not more than 1 ppm in pulp after peel is removed), celery, peaches, strawberries, tomatoes
	0.5[j]	Onions (dry bulb)
USSR	Not permitted	
Yugoslavia	2[c]	Fruit, tobacco, vegetables
	0.05[c]	Other food commodities

[a]From Health and Welfare Canada (1990)
[b]Calculated as carbon disulfide
[c]As dithiocarbamates
[d]The figure in parentheses is the lower limit for determining residues in the corresponding product according to the standard method of analysis.
[e]These values should be reviewed (Commission of the European Communities, 1990)
[f]Residues shall be absent; the value in parentheses is the highest concentration at which this requirement is still deemed to have been met.
[g]Sum of dithiocarbamates expressed as carbon disulfide
[h]Sum of dimethyl-, ethylenebis-, and propylenebis-dithiocarbamates expressed as carbon disulfide
[i]At the limit of detection
[j]From US Environmental Protection Agency (1989)

Table 3. Occupational exposure limits for thiram[a]

Country	Year	Concentration (mg/m^3)	Interpretation[b]
Austria	1987	5	TWA
Belgium	1987	5	TWA
Denmark	1987	2	TWA
Finland	1987	5, skin notation	TWA
		10, skin notatin	STEL
Germany	1989	5[c]	TWA
Indonesia	1987	5	TWA
Italy	1987	5	TWA
Mexico	1987	5	TWA
Netherlands	1987	5	TWA
Poland	1987	0.5	TWA

Table 3 (contd)

Country	Year	Concentration (mg/m^3)	Interpretation[b]
Romania	1987	2	TWA
		5	MAC
Switzerland	1987	5	TWA
United Kingdom	1987	5	TWA
		10	STEL (10 min)
USSR	1982	0.5	MAC
Venezuela	1987	5	TWA
		10	Ceiling
Yugoslavia	1987	5	TWA

[a]From Izmerov (1982); Cook (1987); Deutsche Forschungsgemeinschaft (1989)
[b]TWA, time-weighted average; STEL, short-term exposure limit; MAC, maximum allowable concentration
[c]Calculated as total dust

3. Studies of Cancer in Experimental Animals

Several studies on the carcinogenicity of thiram were summarized in a previous monograph (IARC, 1976), but, because of deficiencies in various aspects of study design, performance and/or reporting, the present Working Group did not consider them further. The studies in question are those of the US National Technical Information Service (1968), Innes *et al.* (1969) and Chernov *et al.* (1972).

3.1 Oral administration

Rat: Groups of 50 male and 50 female SPF Fischer 344 rats, eight weeks old, were fed thiram (purity, 99.8%) at 0, 0.05 or 0.1% (the maximum tolerated dose was estimated to be > 0.06%) in the diet for 104 weeks and basal diet for an additional eight weeks, at which time all survivors were killed. There was no significant difference in survival between treated and control animals. The incidences of leukaemia were decreased: males—10/50 control, 4/49 low-dose and 2/50 high-dose ($p < 0.05$); females—14/49 control, 6/50 low-dose ($p < 0.05$) and 2/50 high-dose ($p < 0.01$). The incidence of pituitary chromophobe adenomas in females was significantly lower in both treated groups: control, 22/49; low-dose, 11/50 ($p < 0.05$) and high-dose, 10/50 ($p < 0.01$); and that of C-cell adenomas of the thyroid was significantly lower ($p < 0.01$) in high-dose females (0/50 *versus* 7/49 controls). There was no statistically significant difference in the incidence of tumours at other sites (Takahashi *et al.*, 1983; Hasegawa *et al.*, 1988).

Groups of 24 male and 24 female Fischer 344 rats, 7-8 weeks old, were fed 0 or 500 mg/kg (750 mg/kg for the first three weeks) of diet thiram [purity unspecified] for 104 weeks. The experiment was terminated at week 130. Average time to death was 122-127 weeks in the treated animals and 107-122 weeks in the controls. There was a significant decrease in the incidence of monocytic leukaemia in treated rats (treated females, 1/24;

control females, 11/24 [$p < 0.001$]; treated males, 4/24; control males, 12/24 [$p < 0.02$]). The concentration used was considered by the author to be a maximum tolerated dose, since, in a prelimary experiment, 1000 mg/kg of diet were not acceptable to the animals and 750 mg/kg of diet were poorly consumed in this experiment (Lijinsky, 1984). [The Working Group noted the small number of animals used.]

3.2 Combination with nitrite

Rat: Groups of 24 male and 24 female Fischer 344 rats, 7-8 weeks of age, were fed 0 or 500 mg/kg (750 mg/kg for the first three weeks) of diet thiram alone or in combination with 2000 mg/kg of diet sodium nitrite for 104 weeks in order to assess the possibility of formation of carcinogenic *N*-nitroso compounds (*N*-nitrosodimethylamine) *in vivo*. Of the rats receiving the combined treatment, 18/24 males and 15/24 females developed tumours of the nasal cavity (adenocarcinoma, adenoma, olfactory carcinoma, squamous-cell carcinoma). No nasal cavity tumour was found in untreated rats or in rats receiving thiram or sodium nitrite alone. Five male and five female rats receiving combined treatment developed squamous-cell papillomas of the forestomach; 2/24 males and 1/24 females receiving sodium nitrite alone, but none of the untreated or thiram-treated rats, developed forestomach papillomas (Lijinsky, 1984). [The Working Group noted that this study was not directly relevant to an evaluation of the carcinogenicity of thiram.]

4. Other Relevant Data

The toxicology of dithiocarbamates has been reviewed (WHO, 1988).

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

Administration of thiram with nitrite to guinea-pigs by gavage resulted in the formation of *N*-nitrosodimethylamine (Sen *et al.*, 1974). Similarly, thiram reacted with nitrite *in vitro* at acid pH to form *N*-nitrosodimethylamine (Elespuru & Lijinsky, 1973; Sen *et al.*, 1974).

In rats administered thiram intraperitoneally, carbon disulfide was found in expired air in a dose-dependent fashion (Dalvi & Deoras, 1986).

4.2 Toxic effects

4.2.1 *Humans*

In a group of 223 workers (42 men and 181 women) in the USSR, mostly aged between 20 and 50 years, engaged in the manufacture of thiram generally for more than three years, various clinical and pathological manifestations, including ocular irritation, coughing, thoracic pain, tachycardia, epistaxis, dermal lesions, myocardiodystrophia, clinical and subclinical liver dysfunction and asthaenia, were reported, often in excess of those seen in a

group of 193 persons not in contact with thiram. Thyroid gland disorders were more common in the exposed group (7.6% *versus* 1.04%); one case of a malignant lesion of the thyroid and seven of enlarged thyroid gland were reported among 105 workers examined (Cherpak *et al.*, 1971; Kaskevich & Bezugly, 1973).

Contact dermatitis has been reported after exposure to thiram (Penneys *et al.*, 1976; Rudzki & Napiórkowska, 1980; Kruis-de Vries *et al.*, 1987).

4.2.2 *Experimental systems*

Oral LD_{50} values for thiram in mice of 1500-2000 mg/kg bw (Kirchheim, 1951), 2300 mg/kg bw (Matthiaschk, 1973) and 3300-4500 mg/kg bw (Lee *et al.*, 1978), in rats of 865 mg/kg bw (Lehman, 1951), 375-1000 mg/kg bw (Ben-Dyke *et al.*, 1970) and 1400-5400 mg/kg bw (Lee *et al.*, 1978) and in rabbits of 210 mg/kg bw (Worthing & Walker, 1987) have been reported. The dermal LD_{50} in rats is more than 2000 mg/kg bw (Ben-Dyke *et al.*, 1970).

Intraperitoneal administration of 120 mg/kg bw thiram to rats caused an increase in plasma transaminase activity 24 h after treatment, which was associated with a reduction in hepatic microsomal benzphetamine *N*-demethylase and cytochrome P450 activities (Dalvi *et al.*, 1984). Different results were reported in another study, which showed impairment of microsomal aniline hydroxylase and carboxylesterase activities 24 h after oral administration of thiram (1 g/kg) to rats, whereas cytochrome P450 and ethylmorphine *N*-demethylase activities were unchanged (Zemaitis & Greene, 1979). Epoxide hydrolase activity was enhanced in rat liver after exposure to thiram (1 mmol/kg bw [240 mg/kg bw]) by gavage; glutathione *S*-transferase activity was slightly enhanced by doses of up to 4 mmol/kg [960 mg/kg bw] (Schreiner & Freundt, 1985).

Like most dithiocarbamates, thiram induced the accumulation of acetaldehyde in the blood of rats administered ethanol (see WHO, 1988).

Chronic feeding of rats with thiram (about 60 mg/kg bw per day) caused neurotoxicity, with onset of ataxia in some animals, 5-19 months from the beginning of exposure. Morphological examination showed chromatolysis of motor neurones. Some behavioural changes, not related to morphological changes, were also observed (Lee & Peters, 1976).

Thiram was given in the diet at 1000 mg/kg for six weeks, two weeks after a single intraperitoneal dose of *N*-nitrosodiethylamine (200 mg/kg bw) to male Fischer rats that were also subjected to a two-thirds hepatectomy three weeks after the start of the study. A marginal increase in the number and area of glutathione *S*-transferase-positive liver foci was seen at eight weeks compared to rats treated with the nitrosamine and partial hepatectomy alone (Ito *et al.*, 1988).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Pregnant NMRI mice given daily oral doses of thiram at 10-30 mg/animal on days 5-15 or 6-17 of gestation had increased resorptions during the intermediate and late stages of organogenesis. Fetal malformations were characterized by cleft palate, micrognathia, wavy ribs and distorted bones (Roll, 1971; Matthiaschk, 1973).

Daily administration of 132 mg/kg bw thiram in the feed for 13 weeks decreased fertility in male Charles River CD rats; daily administration of 96 mg/kg bw to female rats for 14 days prolonged the dioestrous phase of the oestrus cycle. These effects were accompanied by loss of body weight. Daily administration of 136-200 mg/kg bw thiram to rats by gavage during the organogenetic period (gestation days 6-15) increased the mortality rate of conceptuses; the weight of surviving embryos was decreased at doses as low as 40 mg/kg bw per day. In Swiss-Webster mice, no significant developmental effect was observed with doses of up to 300 mg/kg bw per day given by gavage on days 6-14 of gestation. A number of female rats died during the experiment. Administration to dams of 0.1% in feed during pre- and postnatal periods reduced the growth and survival of pups (Short *et al.*, 1976).

In Syrian hamsters, administration of thiram at doses of 250 mg/kg bw and higher on day 7 or 8 of gestation resulted in an increased rate of resorptions, decreased fetal weight and an increased number of terata (Robens, 1969).

Administration of 250 ppm [mg/kg] and above of thiram in the diet to laying hens for one week decreased the weight of ovaries (Serio *et al.*, 1984). As reported in an abstract, administration of 8.8 mg/kg bw per day to quail reduced egg laying by 50% (Wedig *et al.*, 1968). The ED_{50} value for embryolethality was 1.9 μg/egg when thiram was injected into the air chamber of hens' eggs prior to incubation (Gebhardt & van Logten, 1968). Injection of 20 μg/egg and above on day 3 of incubation increased early embryonic death and caused malformations (small eye cup, lid and corneal defects and open coelom) in chick embryos (Korhonen *et al.*, 1982).

4.4 Genetic and related effects (see also Table 4 and Appendices 1 and 2)

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems*

Thiram induced point mutation in bacteria, but data on the induction of DNA damage were conflicting. In *Aspergillus nidulans*, thiram induced gene mutation and aneuploidy; both mutation and chromosomal aberrations were induced in plants. Recessive lethal mutation was induced in *Drosophila melanogaster*, but the response was not dose-related.

Testing for mutation at the *hprt* locus of Chinese hamster V79 cells gave a negative result in one study and a positive result in another, in which a six-fold higher concentration was used and survival was less than 3%. In other studies with cultured mammalian cells, a negative response was obtained in an assay for sister chromatid exchange and there was a weak response in a test for chromosomal aberration. In single studies with human lymphocytes, thiram induced unscheduled DNA synthesis and sister chromatid exchange, but only in the presence of an exogenous metabolic activation system.

Thiram induced micronucleus formation in mouse bone marrow, chromosomal aberrations in mouse spermatocytes and morphologically abnormal sperm in mice *in vivo*. A negative response was obtained in one of three studies of micronucleus formation. [This difference may be attributable to the use of Chinese hamsters rather than mice.]

Table 4. Genetic and related effects of thiram

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, Prophage induction	–	–	10.0000	Zdzienicka *et al.* (1981)
SAD, *Salmonella typhimurium*, repair (TA1538 *vs* TA1978)	+	–	50.0000	Zdzienicka *et al.* (1981)
BSD, *Bacillus subtilis rec* strain, differential toxicity	(+)	0	2.0000	Shirasu *et al.* (1976)
BSD, *Bacillus subtilis rec* strain, differential toxicity	–	–	800.0000	Ueno & Ishizaki (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	5.0000	Byeon *et al.* (1976)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	2.5000	Hedenstedt *et al.* (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	25.0000	Zdzienicka *et al.* (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	50.0000	Zdzienicka *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	–	25.0000	Moriya *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	25.0000	Rannug & Rannug (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	20.0000	Crebelli *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	(+)	(+)	25.0000	Byeon *et al.* (1976)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	0	2.5000	Hedenstedt *et al.* (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	0	25.0000	Zdzienicka *et al.* (1979)
SA5, *Salmonella typhimurium* TA1535, reverse, mutation	+	0	50.0000	Zdzienicka *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	(+)	–	2500.0000	Moriya *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	+	0	5.0000	Hedenstedt *et al.* (1979)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	25.0000	Byeon *et al.* (1976)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	+	0	5.0000	Hedenstedt *et al.* (1979)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	+	25.0000	Zdzienicka *et al.* (1979)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	(+)	50.0000	Zdzienicka *et al.* (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	25.0000	Byeon *et al.* (1976)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	0	2.5000	Hedenstedt *et al.* (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	+	25.0000	Zdzienicka *et al.* (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	50.0000	Zdzienicka *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)

Table 4 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	+	20.0000	Crebelli *et al.* (1985)
EC2, *Escherichia coli* WP2 *hcr*, reverse mutation	-	-	2500.0000	Moriya *et al.* (1983)
ANF, *Aspergillus nidulans*, forward mutation	+	-	0.5000	Zdzienicka *et al.* (1981)
ANN, *Aspergillus nidulans*, chromosomal nondisjunction (aneuploidy)	+	0	20.0000	Upshall & Johnson (1981)
PLM, *Triticum* (spring wheat), chlorophyll mutations	+	0	0.0000	Mamalyga *et al.* (1974)
HSC, *Hordeum vulgare*, chromosomal aberrations	+	0	250.0000	George *et al.* (1970)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	+	0	1000.0000	Donner *et al.* (1983)
G9H, Gene mutation, Chinese hamster lung V79 cells *in vitro, hprt* locus	-	-	1.6000	Donner *et al.* (1983)
G9H, Gene mutation, Chinese hamster lung V79 cells *in vitro, hprt* locus	+	0	5.0000	Paschin & Bakhitova (1985)
SIC, Sister chromatid exchange, Chinese hamster CHO cells *in vitro*	-	-	2.4000	Donner *et al.* (1983)
CIC, Chromosomal aberrations, Chinese hamster CHL cells *in vitro*	(+)	-	0.4000	Ishidate (1988)
UHL, Unscheduled DNA synthesis, human lymphocytes *in vitro*	-	+	5.0000	Perocco *et al.* (1989)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	-	+	15.0000	Perocco *et al.* (1989)
MVM, Micronucleus test, BALB/c mouse *in vivo*	+	0	500.0000 × 2 i.p.	Dulout *et al.* (1982)
MVM, Micronucleus test, (CBA×C57Bl/6J)F_1 mouse *in vivo*	+	0	100.0000 × 1 i.p.	Paschin & Bakhitova (1985)
MVC, Micronucleus test, Chinese hamsters *in vivo*	-	0	0.5000 × 1 i.p.	Donner *et al.* (1983)
CGC, Chromosomal aberrations, primary spermatocytes, Swiss mouse	+	0	80.0000 × 3 p.o.	Prasad *et al.* (1987)
SPM, Sperm morphology, (CFW×C57Bl)F_1 mouse	+	0	50.0000 × 1 i.p.	Zdzienicka *et al.* (1981)
SPM, Sperm morphology, (CFW×C57Bl)F_1 mouse	+	0	50.0000 × 1 i.p.	Zdzienicka *et al.* (1982)
SPM, Sperm morphology, (CFW×C57Bl)F_1 mouse	+	0	30.0000 × 5 i.p.	Zdzienicka *et al.* (1982)
SPM, Sperm morphology, Swiss mouse	+	0	80.0000 × 3 p.o.	Prasad *et al.* (1987)

[a] +, positive; (+), weakly positive; -, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)
[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw

5. Summary of Data Reported and Evaluation

5.1 Exposure data

The major use of thiram is as an accelerator and vulcanization agent in the rubber industry. It is also used as a fungicide on seeds and as a foliar fungicide on turf, fruit and vegetables. It has been in commercial use since 1925.

Thiram has been formulated for use as dusts, wettable powders and flowable suspensions and also in combination with other pesticides.

Exposure may occur during its production, its use in the rubber industry and its application as a fungicide, and, at much lower levels, from consumption of foods containing residues. Thiram is also an environmental degradation product of the two fungicides, ferbam and ziram.

5.2 Carcinogenicity in humans

No adequate data were available to the Working Group.

5.3 Carcinogenicity in experimental animals

Thiram was tested adequately for carcinogenicity by oral administration in one study in rats. No increase in incidence was seen for tumours at any site.

When thiram was administered orally to rats in combination with nitrite, a high incidence of tumours of the nasal cavity was observed in males and females.

5.4 Other relevant data

Thyroid abnormalities were observed in a group of subjects exposed occupationally to thiram.

Thiram marginally increased the frequency of enzyme-positive foci in rat liver. It decreased fertility in rats and caused embryolethality and embryotoxicity in rats and hamsters and malformations in mice and hamsters.

No data were available on the genetic and related effects of thiram in humans.

Thiram induced various kinds of chromosomal damage and altered sperm morphology in rodents *in vivo*. It induced unscheduled DNA synthesis and sister chromatid exchange in cultured human cells. It was genotoxic to insects, plants, fungi and bacteria.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of thiram.

There is *inadequate evidence* in experimental animals for the carcinogenicity of thiram.

Overall evaluation

Thiram *is not classifiable as to its carcinogenicity to humans (Group 3).*

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[1]For definition of the italicized terms, see Preamble, pp. 26-28.

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