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of Soviet Literature
on Toxicity and Hazards
of Chemicals

# Thiram

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# Thiram

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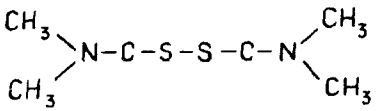
## THIRAM

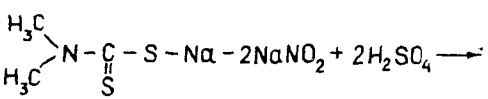
Thiram (bis-(dimethylthiocarbamyl)-disulfide; Tetramethyl-thiuram disulfide) is a crystalline substance, white or creme-coloured, with an unpleasant odour.
Molecula formula: $[(CH_3)_2 NCS]_2 S_2$
Structural formula:

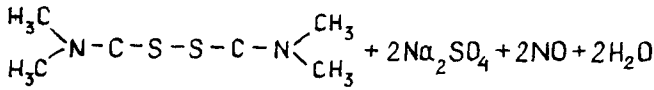


Molecular weight: 240.44
Synonyms: Aapicol, aathiram, aroson, Quinigex, pomersan, pomasol, tersan, thiuram, tulisan, tugan, tuads, tetrathion A, thiradin, fernason [1, 4].
Melting point: 140-145°C [2] 55-156°C [4]
Density: 1.29-1.33 g/cm$^3$ [2,5]
Thiram is a flammable substance and its air-dust mixtures are dangerously explosive. The lower limit of explosiveness is 20.2 g/m$^3$. The self-inflammation temperature of weighted dust is 580°C [2].
Thiram is well soluble in chloroform and acetone, poorly soluble in alcohol and ether; insoluble in water [4]. Solubility in rubber: 0.125% [5].
The tetramethylthiuram disulfide content (TMTD) is not less 95-98%. The content of iron and its compounds is under 0.008% [2].

## PRODUCTION

Thiram is manufactured by continuous mixing of cyanochloride and aqueous solution of sodium dimethyldithiocarbamate at pH 7.9. To manufacture the base product with 90% of output the dithiocarbamate are oxidized with a mixture of nitrogen oxides (oxide and dioxide). A method of thiram manufacture by electrolytic oxidation of sodium dimethyldithiocarbamate in alkaline solution according to the scheme has been developed:





In the Soviet Union thiram is manufactured as dust, containing 50 per cent of TMTD and 50 per cent of the filler [1], as well as in the form of an aqueous suspension (0.5-5%).[7].

## USE

Thiram is widely used in the rubber and cable-manufacturing industries as an ultra-accelerator and vulcanizing agent [5]. In agriculture it is used for dry and semidry disinfection of seeds of cereals (wheat, rye, barley, oat), grain-leguminous crops (corn, millet, buckwheat, pea, soybean), root and tuber crops and vegetables (sugar and fodder beet, carrot, cabbage, cucumbers, onion, gourd family) as well as cereal grasses, alfalfa, lupine, etc. The seeds are treated with thiram 2-3 months before sowing directly on farms as well as on calibrating plants and ginneries using standard treatment machinery and special stationary systems [4.6].

In potato tuber dusting with powerlike thiram the consumption is 6 kg/ton, suspension consumption is 30 l/ton (or 1.0 – 1.5 kg of thiram per 1 ton of tubers) [7].

The rate of 80 per cent thiram consumption for seed treatment is 1.5 –2.0 kg/t for winter wheat, 3–4 kg/t for pea, 2.5–2.0 kg/t for clover, 6–8 kg/t for sugar beet, 4–3 kg/t for flax, 10 kg/t for lintered cotton and within 30 kg/t for delintered cotton. For vegetable crops the rate of seed treatment is 3–8 kg/t, for drug and flower plants it is 2–3 kg/t. Thiram is most frequently used in combination with insecticides (fenthiuram and fenthiuram-molibdenum preparations and fungicide additives [4]. For seed treatment thiram is also used in combination with copper trichlorophenolate and the -isomer of hexachlorocyclohexane and heptachlor [6].

## CONCENTRATIONS

Thiram was detected in apples: 0.045–5.140 mg/kg in intact fruits, 0.048–0.142 mg/kg after peeling. After a month of apple storage in the refrigerator at –5 – –10°C thiram level reduced by 16-17% (reaching 0.024 – 1.84 mg/kg) [8]. With regard to rubber materials, the rate of thiram and other dithiocarbamates (total) passage into distilled water, unboiled and boiled milk is 0.45 – 1.93 mg/l, 0.74 – 1.14 mg/l and 1.03 – 3.70 mg/l respectively [9].

The level of thiram and other dithiocarbamates detected in water and model media, simulating food products, after contacts with rubber goods was 0.2 –0.8 mg/l, and in some cases – 2.0 mg/l. Dithiocarbamates were determined by Clark's group method in terms of carbon bisulfide [10].

In extracts from stomach pumps about 10 mg/l of thiram were detected [11]. Thiram was determined by a specific method based on thin sorbent layer chromatography and total dithiocarbamate migration using the colorimetric technique [9].

## ENVIRONMENTAL FATE TESTS

Thiram is stable in storage. It is resistant to acids and oxidizers, as well as to other environmental factors (UV-irradiation, aeration). The half-life period in water and in neutral medium is 46.7 days and 9.4 hours in acid medium (pH 3.5). Some 5.2% of original thiram persist in neutral water medium still on the 200th day.

Thiram is resistant to high temperatures. Some 40% of the compound persist after boiling in water (pH 5) for 30 min in a vessel with a reflux condenser. In alkaline medium (pH 7), 60 – 30% of thiram persist after 2–4 hour boiling. Following the vegetating crops treatment thiram persists on plants within 7–10 weeks [4].

During thiram hydrolysis in plants and in water ethylene thiourea, tetramethyl thiourea, dimethylamine salt of dimethyl dithiocarbamic acid, carbon disulfide and elementary sulphur are formed [6].

The rate of thiram disintegration varies with different crops and parts within one crop [12]. Thus, the half-life on leaves and apples is 19.6 and 12.5 days respectively [4].

Almost 70% of thiram are transformed into zinc dimethyldithiocarbamate, Zimate [10].

## BIOCONCENTRATION, MAMMALIAN METABOLITES AND CLEARANCE TIME

It was shown in the experiments on white male rats using single thiram intragastrical administration of $LD_{50}$ and in a chronic 10-month experiment with thiram used in 1/10 and 1/800 $LD_{50}$ doses that the period of thiram semiwithdrawal from blood was 5.6 days, from the liver – 5.5 days [13].

After two hours of intragastrical administration thiram is detected in blood and in all organs and tissues. The maximum accumulation of the compound in blood and tissues is observed on the 4th day. The highest thiram levels were found in the adrenal glands (346.3 $\pm$ 28.3 mcg/g), whereas the levels were lower in the thymus gland (179 $\pm$ 45.5 mcg/g), spleen (73.8 + 14.4 mcg/g), blood (48.2 + 1.2 mcg/g), lungs (30.0 mcg/g) and urine (16.3 mcg/ml). In muscles and brain tissues the level of thiram accumulation is the lowest. TMTD residues are found in the rats' parenchimatous organs after three weeks of its single administration into stomach. During long (8 months) thiram intake by rats in doses of 4, 2, 1 and 0.5 mg/kg it was found almost in all organs and tissues, the levels being the highest in adrenal glands, thyroid gland, lungs and feces. The lowest thiram level was in the muscles [6]. No linear relationship

between thiram concentration in tissues and the intragastrical dose of the compound revealed [14].

Thiram is discharged from the organism with urine and feces. After two days of thiram intragastrical administration in $LD_{50}$ doses amine salt of dimethyl dithiocarbamic acid (DDCA) was found in animal blood, liver and spleen and in the lungs carbon bisulfide and amine salt of DDCA were detected. On the sixth day of thiram administration tetramethyl thiourea was found in the liver [6].

The level of the expired carbon bisulfide depends on the thiram dose administered. Carbon bisulfide is discharged within four days reaching its maximum on the second day [15].

In the organisms of the warm-blooded animals, thiram is reduced by glutathione to dithiocarbamate, while the latter is oxidized to tetramethylthiuram disulfide or transformed into a corresponding metallic complex [6].

## MAMMALIAN TOXICITY ARRAY

At gastrointestinal administration the toxicity of thiram is low. Thus, $LD_{50}$ for rabbits is 210 mg/kg [4], $LD_{50}$ for white rats (mg/kg) according to various authors, is: 740 [1]; 400 [4, 12]; 534 [17]; 940 [18]. For white mice $LD_{50}$ of thiram (mg/kg) administered similarly is: 2950 [1]; 1150 [16]; 1250 [20].

The absolute thiram lethal dose for 15–20 g white male mice at intragastrical administration is 4000 mg/kg, the minimum lethal dose is 125 mg/kg [19]. The lethal thiram dose for man, when delivered into the stomach, is nearly 50 mg/kg [4].

The acute peroral poisoning of animals with thiram is characterized by slow development of the clinical picture: the second day is marked by rumpled fur, hurried breathings, then ataxia, tremor, dyspnea, abdominal distention and less of weight. Death is preceeded by convulsions. The rats die on the 3 – 6th day. Single intragastrical thiram administration in a dose of 400 mg/kg caused a decrease in eosinophils by 63% in the blood of rats.

The thiram dose of 500–100 mg/kg caused a decrease in eosinophils in the blood of cats by 87% [1].

Acute poisoning of cats with thiram (in doses of 35-140 mg/kg) was characterized by disordered respiration rhythm, rate and amplitude, as well as bradycardia [6].

After 3 hours of maximum tolerance thiram dose administration the experimental animals (rats, rabbits, cats) revealed an increased activity of the alkaline phosphatase in leukocytes [21]. After a single intragastrical thiram administration to rats and cats in doses of 400 and 600 mg/kg, 500 and 1000 mg/kg respectively an increase in transaminase activity was observed [22].

Thiram in doses of 300 and 400 mg/kg caused a slight increase in transaminase activity (by 22 and 34% respectively) at single intragastrical administration to white rats weighting 150–200 g, while in doses of 100 and 200 mg/kg it did not affect the activity of the above enzyme [23].

Single thiram administration to 170–250 g male and female rats doses of

370 mg/kg (1/2 $LD_{50}$) did not change the activity of asparate aminotransferase and cholinesterase, the level of total protein in blood serum. There was only a tendency toward an increase in -globulin protein fraction in blood. Weltman's reaction did not change essentially, the thymol test was negative. Thiram inhibits the detoxicating liver function when used in high doses: the rats had an essentially longer sleep after hexenal load [24]. One hour after acute poisoning with thiram (in a dose of 1/5 of $LD_{50}$) male and female rats showed an increase in SH-group number by 25/30% in blood, kidneys and spleen [25], as well as a decrease in total glycogen and polysaccharide in the liver [26].

After 18 hours of single thiram intragastrical administration to rats in maximum tolerance doses the processes of oxidative phosphorylation were disturbed. There was an increase in activity of cytochrome-C-oxidase, pyruvate dehydrogenase and a-ketoglutarate oxidase [27], while catalase activity did not change [28]. Maximum decrease in cytochrome-C-oxidase activity in acute experiments on male and female rats was recorded in the liver (94%) and brain (by 83%), while it was lower in the heart, kidneys and spleen [28].

At single thiram intragastrical administration in dose of 400 mg/kg to male and female rats caused a decrease in thyroid gland function (in terms of $J^{131}$ absorption) with simultaneous activation of the adrenal cortex [29].

After 6 hours of intragastrical administration, thiram used in a 1/3 of $LD_{50}$ caused a decrease in the chyme, in lipase, protease and amylase activity by 71, 46 and 52 per cent respectively [18].

The pathomorphological studies have shown that acute thiram poisoning is associated with disturbances in hemodynamics of the brain, parenchymatous organs and gastrointestinal tract. Apart from that, it is marked by pronounced dystrophic changes in the liver, kidneys, heart and zone fasciculata of the adrenal gland cortical substance, focal necrosis of the stomach mucous membrane. In 3–4 weeks after single delivery of toxic thiram doses (50–200 mg/kg) into the organism no morphological changes are found [6].

A single inhalation of thiram dust in concentrations of 300–900 $mg/m^3$ caused an irritation of mucous membranes of the upper respiratory tracts and eyes in cats part of the animals died. The dissection revealed plethora of the internal organs and punctate hemorrhages in the lungs [1]. Twenty four hours after single inhalation effect of thiram dust in concentrations of 816 and 317 $mg/m^3$ the cats showed an abruptly increased transaminase activity in blood serum [22].

Single inhalation treatment of white rats with thiram in concentrations of 130–200 $mg/m^3$ within one hour resulted in disorders of higher nervous activity in animals and a decrease in the rate of extensor chronaxie [20].

The threshold of acute thiram effect on rats is 75 mg/kg at intragastrical administration, 112 $mg/m^3$ at inhalation [30].

The toxicity and trends of thiram effect do not change depending on the administration mode [30].

Thiram resorption through the skin is poorly pronounced. Single application of thiram to rabbit skin in a dose of 1000–2000 mg/kg does not produce any toxic or irritative effect. Daily thiram application to the skin in a dose of 50 mg/kg resulted in abrupt hyperemia, skin ulceration, loss of weight

in rabbits on the eighth day. Part of the animals died on the 21st – 23rd day of the experiment [4].

TMTD is characterized by a pronounced cumulative effect. The cumulation coefficient at intragastrical administration in doses of 1/10 and 1/20 $LD_{50}$ was 2.1 and 1.85 mg/kg respectively [12].

Chronic intoxication developed in animals (rats and rabbits) at inhalation thiram effect in concentrations of 150 and 50 mg/m$^3$ one hour daily within four months, as well as in rabbits at daily intragastrical thiram administration in a dose of 20 mg/kg within 3.5 months [19, 20].

Prolong (during 18 months) daily thiram delivery into gastrointestinal tract in doses of 4, 2, 1 and 0.5 mg/kg did not affect the life expectancy of rats, but the animals revealed a number of changed functional indices, including the pathomorphological changes in the stomach, liver, adrenal glands, spleen and lungs [6]. Thiram doses of 1.0 and 0.1 mg/kg at prolong daily intake by rats resulted in changes of the SH-group level in the blood serum [33].

According to some authors the daily intragastrical uptake of 1 mg/kg of thiram by white rats during six month has been considered reliable on the evidence of the majority of tests [31, 32].

With regard to the indicators of the general toxic effect the values 0.5 mg/kg and 0.1 mg/kg are considered as a threashold of chronic thiram effect at intragastrical administration to rats [13, 31, 32].

0.05 mg/kg value proved to be an inactive thiram dose according to the changes of SH-group level in blood serum of white rats at chronic 6-month treatment [35]. The same value is estimated as inactive for rats on the basis of other indices [31].

0.04 mg/kg value was received as an inactive dose in a chronic 6-month experiment on rats with intragastrical thiram administration [32].

Thiram has a polytropic mode of action. At chronic intoxication, the animals revealed significant changes in peripheric blood (changed levels of hemoglobin, erythrocytes, leukocytes and eosinophils), the liver, nervous system [19, 20, 31], adrenal glands [31].

Chronic thiram intoxication was associated with a decrease in a protein level in parenchimatous organs, particularly in kidneys and cardiac muscle. Pathomorphological changes have been registered in the stomach, pancreas, liver, adrenal glands, spleen and lungs [6].

Industrial thiram, at multiple intragastrical administration to dogs in doses of 10–20 mg/kg, lowers bile secretion and the level of bile acids in bile are renewed [34].

Long (4–6 months) thiram administration in relatively small quantities (1/20 and 1/50 $LD_{50}$) inhibits the exocrine pancreas activity. Thiram affects directly the acinar cells of the gland and causes changes in the mechanism of its humoral regulation [18].

After long (2–4 months) thiram intragastrical administration in doses of 1/20 $LD_{50}$, significant shifts in erythrograms and an increase in the activity of alkaline leukocyte phosphatase were recorded in rats, rabbits and cats.

The 4-month intragastrical thiram administration to male rats in a dose of 1/50 $LD_{50}$ (14.8 mg/kg) resulted in decreased activity of endogenous tissue

respiration of the liver by 63%, of the brain by 47%, a decrease in the activity of liver cytochrome oxidase by 63%, succindehydrase by 48%, and a decline in the total activity of the cytochrome system by 45%. A drop in the activity of liver and brain glycolysis was observed. Accumulation of pyruvic and lactic acids in blood was recorded [35].

Thiram administered daily to male and female Wistar rats in a dose of 1/30 $LD_{50}$ for 15-80 days caused an increase in ceruloplasmin activity and copper level in the brain and liver [36], as well as a decrease in pyridoxine and nicotinic acid utilization and development of hypovitaminosis symptoms [37].

In workers, using and applying thiram, high concentrations of the product (50–200 $mg/m^3$) resulted in the development of chronic conjunctivitis, subatrophic changes in mucous membranes of the eyes and respiratory tracts, caused an increase in liver dimensions and asthenia of toxic etiology [38].

The examination of large groups of workers within the 20 to 50 age bracket, handling thiram at seed treatment stations, seed-testing laboratories, and plants manufacturing 80% thiram dust, after a year or more of work showed por alcohol endurance, hyperemia of the face and upper part of the body, tachycardia, fever sensation, sweating, headache, nausea, sometimes vomiting [39, 40, 41, 42]. In most cases, thiram concentrations in the zone of the workers' respiration were within 0.17–3.3 $mg/m^3$ reaching 16.9 $mg/m^3$ only in the finished products store. After over three years of work the workers handling thiram revealed changes in the cardiovascular system of myocardial dystrophy type, changes in the hepatobiliary system, gastro-intestinal pathology, changes in the thyroid gland (hyperplasia, diffusive enlargement, etc.). In people handling thiram for over five years, hematological shifts were recorded (hypochronic anemia, a tendency toward leukopenia, changes in monocytogram). Vegetovascular dystonia and astheno-vegetative syndrome are registered usually in one third of the examined workers [39, 41, 42]. Two stages are distinguished in the development of chronic thiram intoxication: 1 – the stage of initial manifestations and 2 – the stage of pronounced intoxication manifestations [43].

The preclinical forms of liver lesions in workers in the age of 18-40, engaged in thiram production for 1-10 years, were detected by determining serous cholinesterase, alkaline phosphatase, ceruloplasmin, urokinase, histidase and urobilin [44], a shift in protein blood composition (a decrease in the albumin level and an increase in the globulin number due to alpha-1-globulin and gamma-globulins, a decrease in the albumin-globulin coefficient) [45], as well as disorders of intrahepatic blood-content [46].

In low concentrations (0.17–0.20 $mg/m^3$), thiram combined with seed dust, noise and vibration has the same unfavourable effect on the workers as thiram in concentrations exceeding the MPC of the working zone [47].

Thiram in concentrations 1.5–5 times higher than the MAC, in combination with other chemical substances, caused a significant drop in arterial pressure in the operators of rubber accelarator industry, with the lowest levels registered in women [48].

When TMTD was found on the clothes and exposed parts of face and hand skin of the workers (medium TMTD concentration in the wash off was 0.3 $mg/cm^2$) no skin irritation was detected [49].

## SPECIAL TOXICITY STUDIES

**Carcinogenicity.** The blastomogenic thiram activity was studied on C57 Bl strain mice and not thoroughbred white mice. Thiram was administered to the animals intragastrically once a week (six times) as suspension in a starch paste in a dose of 300 mg/kg. In 2–6 weeks after the end of administration the mice revealed atypical large cells with hyper or hypochromic nuclei in the lungs. After 3 months 4% of animals had adenomas with tubular structure, and by 6 months the adenomas had a papillary structure. RNA level in bronchial epithelium and atypical cells was increasing. At long (9 months) thiram administration with food in a dose of 2 mg/kg there were no mature tumours in black mice of C57Bl strain but pretumour changes were detected in the lungs [2].

**Mutagenicity.** The antimitotic thiram effect in doses from 1000 to 0.001 mg/kg was shown in experiments on the cultures of human embryonal fibroblasts, transferred cells of human amnion and the Detroit strains of cells. The cytotoxic effect was distinctly revealed after 48 – 96 hours. The cells were damaged in the interface or preprophase and telophase [50].

In experiments on white not thoroughbred male mice the intragastrical (with milk) or intraperitoneal (with isotonic NaCl solution) thiram administration in doses of 100 and 1000 mg/kg resulted in an increase in chromosome aberration level in bone marrow. Chromosome disorders were of chromatid rupture type. The highest number of cells with aberrations after intraperitoneal thiram administration in a dose of 100 mg/kg the number of aberrant metaphases was 2.5 times higher than after a similar thiram dose administered into the stomach [51].

Dose dependence of thiram mutagenous effect is observed. At thiram administration to mice in doses of 20, 100 and 1000 mg/kg the number of cells with chromosome disorders after 24 hours was 1.14%, 3.9% and 7.83% respectively [12].

Intragastrical administration of thiram with water in concentrations of 20 and 0.8 mg/l within six months did not cause any cytogenetic effect in white male rats [52].

**Neurotoxicity/behaviour.** The white rats, subjected to inhalation effects of thiram dust in a concentration of 350–400 mg/m$^3$ two hours daily within 15 days, were marked by significant functional changes in the nervous system (longer chronaxie, changes in rheobase) [19]. Thiram dust in a concentration of 100 mg/m$^3$ at single inhalation effect did not cause any symptoms of intoxication in cats but reduced the conditioned reflexes according to the narcotic phase type with power relations retained. At thiram inhalation in a concentration of 500 mg/m$^3$ the cats lost the reflexes to buzzer and light. In 20–25 days after the onset of the thiram inhalation effect with a concentration of 12 mg/m$^3$ the cats revealed phase changes of the conditioned reflex activity: the periods of pronounced disturbances gave way to normalization periods. There was a parallelism in changes of the higher nervous activity and the eosin reaction [53].

**Potentiation.** Thiram and narcotic effects were marked by synergism con-

ditioned by blocking of the tissue respiration enzymes [27].

Thiram mixed with copper trichlorophenolate at 2:1 ratio at 4 month inhalation effect four hours daily caused more distinct changes in the thyroid glands of rats and rabbits than individual mixture components. Low concentrations of the mixture (1.17 mg/m$^3$) caused hyperfunction and higher concentrations (5.4–11.3–31.9 mg/m$^3$) –hypofunction of the thyroid gland in animals [54].

In experiments on white male rats and white mice it was shown that in high doses (300 mg/kg) thiram slows down corazole detoxication and amplifies its toxicity, while in low doses (1/50 $LD_{50}$) the effect is attenuated or not revealed whatsoever. Thiram prolongs the duration of hexanol sleep [55].

At simultaneous thiram delivery to rat organisms with water and air in the acute experiment with doses of 1/2 $Lim_{ac}$ (37 mg/kg + 48 mg/m$^3$) and 6-month chronic experiment in doses at MAC levels for each of the two media (0.8 mg/l + 0.90 mg/m$^3$) the toxic effect was summed up. It was found by means of the dispersion analysis that the summarized thiram effect was predominantly affected by the inhalation factor [30].

**Reproduction.** The 4.5 month chronic experiment on male rats with inhalation thiram effects in concentrations of 3.8 ± 0.028 and 0.45 ± 0.058 mg/m$^3$ revealed changes in estrous cycle duration and some of its phases (prolongation of the diestrus phase). An increase in relative weight of ovaries and histological changes in them were recorded (revival of follicle formation, ovogenesis inhibition growth of folicular atresia). The experiments on infantile female mice showed that thiram inhibited the activity of hypophysis gonadotropic function [56, 57].

In inhalation treatment of white not thoroughbred female rats with thiram in a concentration of 1 mg/m$^3$ within four months the estrous cycle was disturbed basically due to the longer interestrus period. Female gonads are characterized by activation of follicular atresia.

Similar experiments on male rats showed a decrease in spermatogeny index, cell degeneration of spermatogenic epithelium, appearance of giant multinucleate cells [58].

Intragastrical thiram administration to male rats in concentrations of 20 and 0.8 mg/l (1.0 and 0.04 mg/kg respectively) with water within six months did not reveal any gonadotropic effect [52].

The threshold thiram dose in terms of gonadotoxic and embryotoxic effects on the warm-blooded animals (reduced fecundity, disturbed postnatal development) was 0.1 mg/kg [10].

The analysis of embryonic material collected from rats subjected to thiram dust effects in concentrations of 3.8 and 0.45 mg/m$^3$ within 4.5 months showed an increase in total embryonic mortality, decrease in fetal weight and fetal number per one female [59].

It should be pointed out that although the chronic and acute intoxication with thiram results in genital function disturbances it is observed at thiram administration to animals in doses 30 and 300 mg/kg at single administration or 0.5 – 1.0 – 5.0 – 25.0 mg/kg during 6 months to cause distinct structural and functional changes in the maternal organism. Hence, the changes in the genital

function are of a general toxic type rather than specific [60].

In the analysis of the physical condition of 267 newborns of mothers engaged in technical rubber production (TRP) subject to the effects of different chemical agents (thiram, captax, altax) it was estimated that the total number of newborn girls was significantly higher than the number of newborn boys. The ratio was 121:100 [62].

**Sensitization.** Sensitization was not detected in a group of guinea pigs after 6-fold intragastrical thiram administration at 2-day interval in a dose of 0.75 mg.

At subcutaneous administration in a similar dose thiram causes an anaphylactic reaction in guinea pigs after intravenous administration of the resolving thiram dose of 6.75 mg (in 2.5 ml of saline). The reaction was associated with generation of humoral antihaptene antibodies contributing to its realization. Thiram administered to the organism through the respiratory tracts (intratracheal administration) in a dose of 0.75 mg in 0.5 ml of saline may cause sensitization that may manifest itself as an asthmatic syndroms [62].

The sensitizing properties of thiram were proved in experiments on male and female albino-rabbits at 4-fold (every other day) intracutaneous administration of 0.5% suspension or 15-fold daily skin application of 2% suspension of the substance. The allergic skin lesion was most strongly pronounced in animal sensitization with thiram and Freund's adjuvant. The humoral antihaptene antibodies contribute to dermatitis development [63].

Male and female guinea pigs were sensitized by single subcutaneous thiram administration in doses of 30 – 0.75 – 0.0075 – 0.000075 mg ( in 0.3 ml of saline).

The allergic reactions were most pronounced in animals sensitized by single doses of 0.75 mg of the allergen, less pronounced at a dose of 0.0075 mg. Antitissue autoantibodies were not found in guinea pigs sensitized with thiram in a dose of 0.000075 mg. An increase in the sensitizing thiram doses up to the toxic ones 30 mg inhibits the allergic reaction caused by this substance [64]. A case of systemic allergosis manifested in bronchial asthma and urticaria, resulting from contacts with thiram, was described in a worker, 56 years of age [65].

## SAMPLING/PREPARATION/ANALYSIS

Thiram is determined by a group colorimetric technique or by chromatography is a thin sorbent layer.

The colorimetric technique is based on the interaction reaction between thiram, hydroquinone and copper acetate with copper dialkyl dithiocarbamate formation of yellow-brown colour. The determination sensitivity is 0.01 mg/ 6 ml [2, 66].

The other colorimetric technique is based on the ability of dithiocarbamic acid to decompose under the effect of mineral acids with discharge of carbon disulfide that is transferred into intensively coloured copper diethyl dithiocarbamate; colour intensity of the latter is used to judge about dithiocarba-

mate level in the test solution [15].

Thiram is determined also by chromatography in a thin sorbent layer. The method is based on the substance extraction from the test solution by an organic solvent with subsequent chromatography in a thin silica gel layer [67].

## TREATMENT OF POISONING

For people subjected to thiram effects it is recommended to include ascorbic acid or galascorbin and practise parenteral administration of vitamin $B_6$, cocarboxylase, oral administration of glutamic acid. In leukopenia cases it is recommended to use pentoxyl, hemostimulin to stimulate erythrocyte hemopoiesis, folic acid, iron compound. Symptomatic therapy is used on indications, i. e. antispastic, sedative and bile-expelling agents, oxygen therapy. The above treatment complex proved to be effective in practice [39].

In cases of thiram poisoning it is recommended to use copper compounds for therapeutic purposes, apart from vitamin $B_6$ and zinc salts [36].

Estimation of thiram and amino salt of dimethyl dithiocarbamic acid in blood and urine is recommended in cases of suspected poisoning as a diagnostic test.

## RECOMMENDATIONS/LEGAL MECHANISMS

Equipment tightness in all stages of the technological process of thiram dust production, moistening of thiram powder prior to loading it into the equipment are recommended [41]. Measures of personal safety are to be strictly taken at thiram handling [4].

Annual preventive medical check-ups of workers dealing with thiram are carried out by a group of doctors consisting of a therapeutist, neurologist, gynecologits, otolaryngologist and, on indications, an endocrinologist [41].

In the Soviet Union the following standards of thiram concentration in different zones are established:

MAC of thiram is 0.5 $mg/m^3$ in the air of the work zone (aerosol, danger class 2).

The MAC in the atmospheric air of human settlements is 0.01 $mg/m^3$ (maximum single intake) and 0.006 $mg/m^3$ (average daily intake).

The MAC in the water reservoirs used as a source of drinking water as well as for various economic and recreational purposes – is 1 mg/l (the limit sanitary-toxicological value).

No thiram is allowed in water reservoirs where fish is caught. No residual quantities in food products are permissible.

Thiram is allowed to be used only for seed disinfection. The treatment of vegetating food crops (tobacco, etc.) is forbidden [4].

For dithiocarbamates (thiuram, cymate) the total permissible migration level from rubbers is 0.05 mg/l [10].

## REFERENCES


1. Agayeva T. N. On TMTD toxicology. In: Pesticide hygiene and toxicology and the clinical picture of poisonings, Kiev, Zdorovye Publ., 1966, Issue 4, p. 163-166.

2. Thiram-D, GOST 740-76, USSR State Committee on Standards, M., Standard Publishers, 1976.

3. Chemist's manual. L.-M., Khimiya Publ., 1971, v. 2, p.p. 536-537.

4. Pesticide reference book (application hygiene and toxicology). Edit. by acad. L. I. Medved, Kiev, Urozhai Publ., 1974, p.p. 222-227.

5. Blokh G. A. Thiram sulfides. In: Organic rubber accelerators, L.-M., Khimiya Publ., 1972, Second printing, p.p. 35, 336-337.

6. Antonovich E. A., Vekshtein M. Sh. TMTD toxicology and the aspect of its application hygiene in agriculture. In: Pesticide application hygiene, toxicology and the clinical picture of poisonings. Kiev, VNIIGINTOX, 1970, Issue 8, p.p. 221-240.

7. Shevel N. E. TMTD suspension efficiency against potato scab. In: Chemistry in agriculture, R. E., 1968, No. 4, p.p. 29.

8. Residual pesticide level in food products. Edit. by prof. L. I. Shtenberg, N., Meditsina Publ., 1973, p.p. 164.

9. Razarinova N. F., Grushovskaya N. Yu., Shurupova E. A. On migration of rubber accelerators (dithiocarbamic acid derivatives) and the products of their transformation from rubbers into model media and milk. In: Voprosy pitaniya, 1974, No. 4, p.p. 64-68.

10. Stankevich V. V., Shurupova E. A., Pinchuk L. W. On the criteria of the hygienic estimation of rubbers containing tetramethyl thiram disulfide and intended for contact with food products. In: Gigiena i sanitariya, 1976, N 1, p.p. 22-24.

11. Taradai E. P., Shumskaya N. I., Provorov V. N. Sanitary-hygienic evaluation of medical rubbers. In: Gigiena i sanitariya, 1972, No. 4, p.p. 99-100.

12. Antonovich K. A. et al. Comparative toxicological evaluation of dithiocarbamates. In: Gigiena i sanitariya, 1972, No. 9, p.p. 25-30.

13. Antonovich E. A. On the distribution, accumulation, metabolism and discharge of dithiocarbamates from the organism. In: Pesticide application hygiene, toxicology and the clinical picture of poisoning, M., Meditsina Publ., 1973, Issue 10, p.p. 97-105.

14. Elisenko M. A. Basic regularities of pesticide accumulation and distribution in the organisms of warm-blooded animals. In: Pesticide application hygiene, toxicology and the clinical picture of poisonings, Kiev, VNIIIGINTOX, 1970, Issue 8, p.p. 54-57.

15. Svetly S. S. Comparative data on carbon bisulfide content in the air expired by laboratory animals at inhaling TMTD and fenthiuram. In: Pesticide application hygiene, toxicology and the clinical picture of poisonings, Kiev, VNIIGINTOX, 1969, Issue 7, p.p. 299-303.

16. Vorobyeva R. S. On the possible dependence between the chemical structure and biological action of the derivatives of 2-mercapto-benzothiazol and dithiocarbamic acid. In: Toxicology of new chemical substances introdu-

ced into the rubber and fire-manufaturing industries, M., Meditsina Publ., 1968, p.p. 203-216.

17. Svetly S. S. On the comparative toxicity of fenthiuram and its components. – Gigiena i toksikologiya, Proceedings of a city conf. of young scientists-hygienists of Kiev, Kiev, Zdorovye Publ., 1967, p.p. 161-164.

18. Zakirov U. B., Kadyrov U. Z. Mertursunova S., Gulyamov T. The effect of tetramethyl thiuram disulfide on the external secretary function of the pancreas. In: Farmakologiya i toksikologiya, 1976, No. 1, p.p. 58-59.

19. Vorobyeva R. S., Mezentseva N. V. Experimental study of comparative toxicity of new rubber accelerators. In: Gigiena truda i profzabolevaniya, 1962, No. 7, p.p. 28-33.

20. Vorobyeva R. S., Kasparov A. A. Thiurams, tetramethyl thiuram disulfide. In: Toxicology of new chemical substances introduced into rubber and tyre industries. M., Meditsina Publ., 1968, p.p. 93-101.

21. Karpenko V. N., Voskoboinik O. D. On some qualitative changes in the formed blood elements at intoxication with carbamic pesticides. In: "Gigiena truda", Kiev, Zdorovye Publ., 1973, Issue 9, p.p. 146-150.

22. Ageyeva T. M. Changes in some biochemical indices of peripheric blood at exposure to TMTD. In: Ucheniye zapiski, Baku, 1972, v. XXXVI, p.p. 6-7.

23. Anina I. A. The effect of some carbamates on blood serum transaminase activity. In: "Toxicology and pharmacology of pesticides and other chemical compounds, Kiev, Zdorovye Publ., 1967, p.p. 11-14.

24. Tsapko V. G. The state of some liver functions in acute poisoning of experimental animals with cuprocin, sevin, eptam and TMTD. In "The Pesticides Application Hygiene toxicology and the clinical picture of poisonings, Kiev, VNIIGINTOKS, 1970, Issue 8, p.p. 234-239.

25. Korablev M. V., Kurbat N. M. The effect of dithiocarbamic acid derivatives on the level of sulfohydrilic groups in rat organs and tissues. In: Zdravo okhraneniye Belorussii, 1965, No. 3, XI, p.p. 34-35.

26. Voitenko G. A., Anina I. A. et al. The effect of pesticides, the derivatives of carbamic, thio- and dithiocarbamic acids on the oxidative processes. In: Pesticide application hygiene, toxicology and the clinical picture of poisonings Kiev, VNIIGINTOKS, 1969, iss. 7, pp. 275-279.

27. Korablev M. V., Simorot R. P. On the effect of dithiocarbamic acid derivatives on the enzymatic activity of cytochromoxidase, succindehydrogenase and catalse. In: Pharmacology and toxicology, 1965, No. 2, p.p. 234-237.

28. Dyadicheva T. V. On the effect of sevin, jalan and TMTD on some endocrine organs. – "Pesticide application hygiene, toxicology and the clinical picture of poisoning", Kiev, VNIIGINTOKS, 1969, Issue 7, p.p. 304-309.

29. Knyazeva L. M., Bateyev V. I. The effect of tetramethyl thiuram disulfide (TMTD) on the morphology and some histochemical indices of rat liver. In: Transact. of young medical scientists of Uzbekistan, Tashkent, 1972, v. 2 p.p. 139-141.

30. Zhilenko V. N., Sanotsky I. V., Shumskaya N. I. On tetramethy thiuram disulfide toxicology. – Thes. of reports at the XIV scientific session on chemistry and technology of organic compounds of sulphur and sulphurous

oils, Riga, Zinatne Publ., 1976, p. 89.

31. Vaisman Ya. I., Zaitseva N. V., Mikhailov A. V. Hygienic ratting of rubber production waste water in reservoirs. In: Gigiena i sanitariya, 1973, No. 2, p.p. 17-21.

32. Zhilenko V. N. On the toxicological characteristic of total and mutagenous TMTD effect at its delivery into animal organism with water. In: Gigiena i sanitariya, 1975, No. 12, p.p. 94-95.

33. Mikhailov A. V. Biological action of rubber accelerators at chronic experimental intoxication. In: Collection of articles "Voprosy san. okhrany vodoyemov i san. tekhniki", Perm. Polytechnical Institute, Perm, 1973, No. 141, p.p. 117-119.

34. Burov Yu. A. The effect of tetramethyl thiuram disulfide (thiuram) and diphenyl guanidine (DPG) on the bile secretory function of the liver. Farmakologiya i toksikologiya, M., 1964, No. 5, p.p. 714-716.

35. Broklina-Kaminskaya, T. L. The effect of long action of pesticides, the derivatives of carbamic, thio- and dithiocarbamic acids on the oxidative processes in animal organisms. In: "Gigiena truda", Issue 1 (5), Kiev, Zdorovye Publ., 1969, p.p. 91-94.

36. Fridman S. M. The state of copper metabolism at experimental poisoning with tetramethyl thiuram disulfide. "Voprosy biokhimii i immunologii cheloveka i zhivotnykh. Ufa, 1974, p.p. 23-28.

37. Abramova T. I., Fridman S. M. On the development of pathogenetic methods of diagnosis of industrial intoxications with tetramethyl thiuram disulfide. In: Gigiena truda i profzabolevaniya, 1973, No. 3, p.p. 45-48.

38. Kasparov A. A. Labour hygiene aspects in production and application of rubber accelerators (thiuram, Captax). In: Gigiena truda i profzabolevaniya, 1957, No. 1, p.p. 24-31.

39. Bezugly V. P., Kaskevich L. M., Sivitskaya I. N. Clinical characteristic of pathological states caused by TMTD and their treatment. In: Gigiena truda, Kiev, Zdorovye Publ., 1974, issue 10, p.p. 170-173.

40. Cherpak V. V., Bezugly V. P., Kaskevich L. M. Sanitary-hygienic characteristic of labour conditions and health status of workers handling tetramethylthiuram disulfide (TMTD). In: Vrachebnoye delo, 1971, No. 10, p.p. 136-139.

41. Bezugly V. P., Kazakevich R. L., Kazakevich L. M. et al. Some indices of the health status of workers engaged in tetramethylthiuram disulfide production. In: Gigiena truda, Kiev, Zdorovye Publ., 1975, issue 2, pp. 172-174.

42. Kaskevich L. M., Bezugly V. P., Sivitskaya I. N. et al. Some clinical features of tetramethylthiuram disulfide (TMTD) effect on human organism. In: Gigiena truda i prof. zabol. Transact. of Irkutsk medic. Instit., 1972, Issue 110, p.p. 115-116.

43. Kaskevich L. M., Bezugly V. P. The clinical picture of chronic intoxications caused by TMTD. In: Vrachebnoye delo, 1973, No. 6, p.p. 128-130.

44. Gerusova G. P., Meyerson E. A., Makarova N. V. The state of liver function in operators of rubber accelerator industry. – In: Voprosy gigieny truda, Volgograd, 1977, v. XXVII, Issue 5, p.p. 17-18.

45. Makarova N. V. Changes in blood serum protein fractions in the wor-