# IRPTC

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of Soviet Literature
on Toxicity and Hazards
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# Captan

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# Captan

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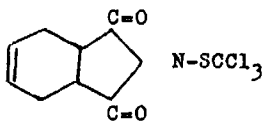
## CAPTAN

Captan (N-trichloromethylmercapto-1,2,3,6-tetrahydrophthalimide) is a white crystalline substance, devoid of almost any odour. It belongs to the group of organochloric pesticides.

Molecular formula: $C_9H_8O_2NCl_3S$, molecular weight: 300.59 (2).

Structural formula:

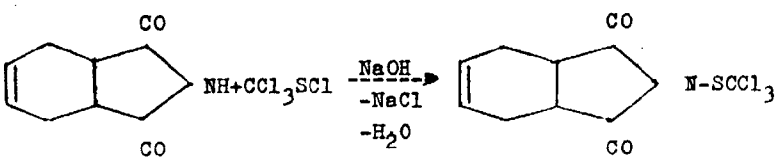



Synonyms: zacaptan, vancide-89, SR-406, memecur, orthocide-staub, orthocide 83, phthocide 50, flint 406, fungicide 406.

Melting point: 172°C. It is practically insoluble in water (1, 2, 3).

## PRODUCTION PROCESS (ES)

Captan is manufactured by the reaction of tetrahydrophthalimide with perchloromethylmercaptan in an aqueous-alkali medium with intensely stirring at low temperature (to preclude hydrolysis of captan and perchloromethylmercaptan).



The yield of captan is up to 90 per cent, provided the process conditions are strictly observed (1).

Technical captan is a yellow or grey substance with a specific odour, containing 96 per cent of pure captan and also water, NaCl, and unreacted tetrahydrophthalimide. In the Soviet Union captan is manufactured in the form of 50 per cent wettable powder (3).

## USE

Captan is used as a fungicide against many fungous agricultural diseases. The protective effect of the preparation lasts for 7-10 days, and the plants should therefore undergo repeated treatment from 2 to 5 times depending on the type of culture. The concentration of the aqueous suspension (0.15-0.5 per cent) depends on the frequency of treatment and the length of intervals between treatments. The consumption rates are as follows (kg/hectare): 7.5-10 for spraying apple and pear trees during the vegetation period, from 5 to 7.5 for apricots, peach, sour and sweet cherries, plums and vine grapes, from 3 to 3.5 for raspberries, gooseberries and currants, from 3 to 4 for tomatoes, potatoes, and melons, and to 2.5 for strawberries, before flowering and after harvesting (3).

## CONCENTRATIONS

Captan does not accumulate in tissues of poultry or pigs fed on fodder containing residual quantity of captan.

The amount of captan contained in vegetable foods depends on the concentration of captan suspensions used for spraying.

After treating cherries with a 0.24 per cent captan suspension, its amount following two weeks was 4 mg/kg; with the suspension concentration of 0.12 per cent, the residual amount found was 1 mg/kg (3).

In 20 days after treatment with a 0.5 per cent suspension of captan, apples contain 2.0-0.5 mg/kg of the preparation.

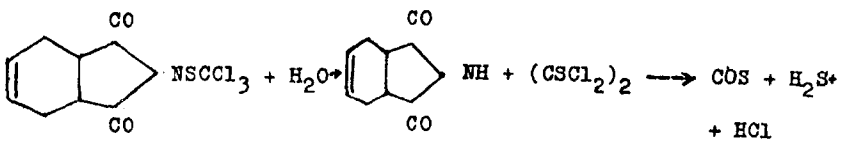
Grapes treated with a 0.1-1.0 per cent suspension of the preparation contained 0.46-3.29 mg/kg in 30 days and only 0.12 mg/kg in 60 days. The grape juice obtained from grapes which had been treated with captan 45 days before, contained 0.28-0.33 mg/kg of the preparation. Vine produced from this juice did not contain captan in 25 days after pressing.

Quantities of 0.1-0.7 mg of captan was found in grapes in 12,24 and 68 days after spraying (6).

## ENVIRONMENTAL FATE TEST

The microorganisms of soil quickly destroy captan to the corresponding imides which are then converted into acids. The molecule is then fully destroyed. The process is completed in a few months (7).

Captan relatively easily reacts with water:




The reaction is sufficiently fast in an alkaline medium and the group $SCCl_2$ is practically fully destroyed in this reaction.

The main products of captan decomposition on plants are phthalimide and tetrahydrophthalimide (7).

## BIOCONCENTRATION / CLEARANCE TIME / MAMMALIAN METABOLITES

Captan accumulation in albino rats (males and females) was studied. The preparation was administered intragastrically in a dose of 26 mg/kg for three months (or the preparation was given at three-day intervals). Another group of animals

was given the preparation in doses of 10 and 5 mg/kg for a month. The Oslenson method was used to determine captan in the organs of the animals in 10, 20, 30, 60 and 90 days.

When captan was given every day in a dose of 26 mg/kg, its greatest amounts were contained in the gonads. The amounts of captan in the other organs decreased in the following series: lungs, kidneys, brain and liver.

In the rats who were given captan in a dose of 10 mg/kg, the preparation concentration decreased in the organs in the following series: brain, lungs, gonads, kidneys, and liver. When captan was given in a dose of 5 mg/kg, its highest amount was found in the brain. Next followed the kidneys, lungs, gonads and the liver.

The study of captan distribution in separate organs showed that its greatest amount is contained in the gonads ($176\pm10.2$ mcg/g); next followed the brain ($88.6\pm8.7$ mcg/g), the lungs ($108.5\pm5.6$ mcg/g) the kidneys ($94.6\pm6.4$ mcg/g) and the liver ($31.6\pm2.5$ mcg/g).

With the intermittent administration of captan (once in three days) in a dose of 26 mg/kg, the internal organs were arranged in the following order by the decreasing contents of captan: gonads, brain, kidneys, lungs and liver. Rats, who had been given captan in a dose of 10 mg/kg, contained its highest amounts in the gonads; next followed the brain, the kidneys, the lungs and the liver.

When captan was given in a dose of 5 mg/kg, the gonads and the brain contained equal amounts of the preparation (9).

Thus, the preparation is mainly accumulated in the brain and the gonads. It was established that if captan is given at intervals (intermittent administration), its excretion from the body is slowed down and its concentration in the internal organs is increased.

During the entire period of observation (in the experiment with daily administration of 26 mg/kg of captan), the preparation was accumulated in the quantity of 175.0-10.2 mcg/g, while with intermittent administration, 310.0±12.6 mcg/g of captan were accumulated (8,9).

Accumulation of captan after a single intragastric administration of 500 mg/kg to albino rats was studied. Captan was determined in the blood, urine, liver, heart, lungs, brain, spleen, ovaries and testes. Measurements were taken at intervals ranging from 30 minutes to 100 days after the administration.

In 60 minutes after administration captan was found in the blood. In 70 minutes following the administration, its quantity was 0.02 mg/g. The captan content of blood varies in the course of 11 hours, but remains at a high level. The concentration begins decreasing in 14 hours after the administration and attains its minimum by the end of the second day.

The blood carries captan into the brain and especially to the gonads (in 90 minutes), while the liver, kidneys and the lungs are free from the preparation during this time.

In the course of the next 40 days, the captan content in the blood increases again and is maintained at a high level which indicates the formation of stable compounds of captan in biosubstrates from which they are slowly eliminated.

It has been established that considerable amounts of captan are accumulated in the kidneys (0.075 mg/g), in the brain (0.05 mg/g), the gonads (0.045 mg/g), the liver (0.044 mg/g) and smaller amounts are accumulated in the lungs (0.025 mg/g). Captan is mainly accumulated in the liver, the kidneys and the gonads and it explains their dysfunction. It has been revealed that a persistent dysfunction of the mentioned organs is mainly due to the slow elimination of captan from the body (10).

$LD_{50}$ of captan given intragastrically was (according to different authors) 138-1312 mg/kg for albino mice, 2000-7000 mg/kg for albino rats, 740-1670 mg/kg for rabbits and 908-925 mg/kg for guinea pigs (4, 11, 12, 13).

If the animals were kept on low-protein diet, the toxicity of captan increased ($LD_{50}$ for rats lowered to 480 mg/kg) (3). The sensitivity to captan varies in different species. The highest sensitivity is in albino mice. Albino rats were comparatively resistant (12, 13).

The clinical picture of acute intoxication caused by captan is characterized by prevalence of the symptoms of excitation of the nervous system followed by inhibition in 2-3 hours after the administration. The animals perish mainly in the first days of the intoxication (10, 12).

The section of the dead animals showed gastric flatulence and hemorrhage into the internal organs (12).

According to the classification of pesticides by their toxicity, (skin uptake), captan belongs to the 3rd class of danger (weak skin-resorptive toxicity, $LD_{50} > 1000$ mg/kg, the skin-oral coefficient $> 3$) (14).

The cumulative properties of captan were studied by administrating the preparation to albino rats, albino mice and guinea pigs intragastrically ).

Albino rats were given captan intragastrically every day (for 60 days) in the doses of 530, 265, 132 and 53 mg/kg. Doses of 530 and 265 mg/kg killed some animals, decreased body weight of others, changed the morphological composition of peripheral blood, and disordered the function of the liver, spermatozoa, and the estral cycle.

A dose of 132 mg/kg produced less marked changes in the morphology of the blood, liver function or the estral cycle.

A dose of 53 mg/kg did not develop signs of intoxication in rats (13, 15).

The intragastric administration to albino rats of captan in a dose of 1/30 and 1/50 $LD_{50}$ (85 and 53 mg/kg) for 28 days changed the activity of cholinesterase (true and false) and of transaminase (glutamine-asparagine and glutamine-alanine) (16).

The cumulation effect for albino rats calculated by the Kagan and Stankevich method was 7.1 which indicates a weak cumulative action of captan (11, 13, 15).

Albino mice were given captan into the stomach for 60 days in doses of 27.0, 13.8, 6.9 and 2.5 mg/kg. The doses of 27 and 13.8 mg/kg killed some animals; others lost weight, the morphological composition of their peropheral blood changed along with the disorders in spermatozoa and the estral cycle. The doses of 6.9 and 2.5 mg/kg did not develop intoxication in mice (13, 15).

The cumulation effect for albino mice, as calculated by the Kagan method, was 4.8, which indicates moderate cumulative properties of captan (13, 15).

Guinea pigs were given captan into the stomach for two months, the doses being 100 and 50 mg/kg. The dose of 100 mg/kg killed some animals. The doses of 100 and 50 mg/kg given to guinea pigs disordered liver function. Captan was proved to have no cumulative effect in this experiment (12, 17).

Toxicity of captan in a chronic experiment was studied by giving 57, 20, 11.5 and 6.1 mg/kg doses of the preparation to rats during a year. The doses of 57 and 20 mg/kg caused disorders in the morphological composition of the peripheral blood, in the hepatic function, and the working capacity of the animals. The animals who had been given 11.5 mg/kg of the preparation had insignificant affections of the glycogenforming function of the liver. A dose of 6 mg/kg captan did not cause any signs of intoxication (13, 18).

In a chronic experiment on guinea pigs and rabbits, captan was gives intragastrically in doses of 20, 10, 5 and 2.5 mg/kg for 5 and 6 months respectively. The doses of 20 and 10 mg/kg disordered the enzyme-forming and the excretory function of the liver in the animals. The doses of 5 and 2.5 mg/kg did not produce any intoxication in the animals (17).

The experiment on rats consisted in continuous (daily) and intermittent (once in three days) administration of 78 mg/kg of captan into the stomach for two months. Daily administrations decreased the erythrocyte and leucocytes counts, decreased prothrombin and cholesterol of blood, increased the transaminase level, and affected the spermatozoid function and the estral cycle. The intermittent action of captan caused erythrocytosis and leucocytosis in the rats, increased the prothrombin level and the cholesterol of blood, caused marked changes in the spermatozoid function and the estral cycle. It was revealed that the dysfunctions of the organs under the intermittant administration was stronger pronounced, compared to the daily doses, due to the decreased elimination of the preparation from the body (19).

The response of rats to various conditions of captan administration was studied by giving the preparation intragastrically in doses of 26, 15 and 5 mg/kg for three months. Daily doses of 26 and 15 mg/kg affected the morphological composition of peripheral blood, the liver function and the function of the spermatozoa. Doses of 5 mg/kg did not produce any signs of intoxication. Intermittent action of captan produced more marked changes in the function of the organs. The changes were observed with the doses of 26, 15 and 5 mg/kg (20).

## SPECIAL TOXICITY STUDIES

Mutagenicity. The mutagenic effect of captan was studied on albino mice and rats. Intragastric doses of 20, 10 and 5

mg/kg given for 6 months, increased the frequency of the dominant lethal mutations in the sex cells of experimental animals. Cytogenetic analysis of the mice, given 1/120 $LD_{50}$ of captan intraperitoneally for 35 days, revealed increased frequency of chromosome aberrations in the bone marrow cells (21, 22).

The effect of captan on the sex ratio in the progeny ($F_1$) of males was studied on albino mice, albino rats and rabbits.

Intragastric administration of captan to male rats in doses of 20, 10 and 5 mg/kg for six months caused disorders in the sex ratio in the progeny $F_1$ (prevalence of females). The progeny of the experimental animals revealed delayed sex maturation and decreased gain in body weight (21).

Females also predominated in the progeny ($F_1$) of male rabbits who had been given 50, 30, 15, 10 and 5 mg/kg of captan for a month. A similar effect was produced by the doses of 10, 5 and 2, and 1 mg/kg given intragastrically for 4 months.

The intragastric administration of captan to male albino rats in doses of 0.05, 0.01 and 0.006 mg/kg for 4 months, produced less marked changes in the sex ratio compared with rabbits (23).

Reproduction. The effect of captan on the gonads was studied in experiments on albino rats (males and females) with doses of 20, 10, 5 and 2.5 mg/kg, and on albino mice (also males and females) with doses of 4, 2.6 and 1 mg/kg.

Female rats who had been given 20, 10 and 5 mg/kg of captan, had their, estral cycle changed and embryogenesis affected. The study of the growth of progeny ($F_1$) of female rats has shown that the sex ratio in the progeny was affected (prevalence of females), the mortality rate among the progeny increased (mostly males), the gain in weight was slow, the sex maturation was delayed, and the estral cycle affected (13, 18, 24).

Captan given to male rats in doses of 20 and 10 mg/kg affected the spermatozoid function and their fertilizing power (15, 18).

Female mice who had been given captan in doses of 4, 2.6 and 1 mg/kg, had their estral cycle and embryogenesis affected. Doses of 4 and 2.6 mg/kg of captan affected the spermatozoid function in male mice (13, 18).

The studies have shown the selective affection of the gonadal function by captan.

The disordered gonadal function involved histochemical changes in the system hypothalamus-hypophysis-adrenal cortex.

It has been shown that changes in the sex ratio of the progeny develops against the background of the inhibited gonadotropic activity of the hypophysis (25).

Sensitization. The sensitizing action of captan was studied on albino rats guinea pigs, and rabbits. It has been found that the preparation produces a weak allergic reaction in the animals when give subcutaneously in a dose of 1 mg/kg and with the external application of the preparation.

Teratogenicity. The embryotropic action of captan was studied by intragastric administration of 10, 5 and 2 mg/kg doses of captan to albino rats during the entire pregnancy, from the first day to 10th and from the 10th to the 18th day. The embryogenesis was proved to be affected by these doses of captan during the entire period of pregnancy, both in the first and the second halves. A higher sensitivity of embryos to captan in the second half of pregnancy was shown. No abnormalities in the development of the embryo was detected. Selectivity of the embryotropic action of captan was shown (27).

## PRIMARY IRRITATION

The local action of captan was studied by applying its paste for ten days and by a single application to the skin of

rabbits. Powder was given in a single dose into the conjunctival sac of the rabbit eye in the quantity of 5, 10, 20 and 50 mg. The preparation was proved to have a marked local irritating action (3, 11).

## SAMPLING / PREPARATION / ANALYSIS

A method is recommended for determining captan in the air by the reaction of formation of polymethine dye - dianalide of glutaconic aldehyde. The sensitivity of the determination is 2.5 g in 2 ml of the initial solution. Maleic anhydride and tetrahydrophthalic acid imide do not interfere with the determination (28, 29).

The procedure is as follows. An amount of 0.5 or 0.1 N solution of sodium hydroxide is added to the standard solutions containing from 2.5 to 60 g of captan in 2 ml of pyridine and the solutions are heated on a boiling bath for 4 minutes.

Air is sampled into a funnel with a porous glass plate or on an ashless filter. Captan is then washed off with 5 ml of pyridine and an aliquot of the solution is used for the determination (28).

A qualitative method (thin-layer chromatography) is recommended for the analysis of captan in foodstuffs.

Thin-layer chromatography is used for the quantitative determination of captan (for isolation of captan) with subsequent elution and determination by reaction with resorcinol.

For qualitative analysis of various objects, captan is separated by a single-step benzen extraction. Benzen is removed by distilation. The dry residue is dissolved. The obtained solution is used for the determination. The extract does not require purification for the qualitative assessment.

When berries and leaves are analysed (50 g of berries and 20 g of leaves) captan is extracted by benzen. The extract

is evaporated and microsublimation is carried out. The sublimed preparation is washed off with sulphuric ether. The obtained solution is used for qualitative and quantitative analyses. When captan presence on leaves is analysed, purification on a column packed with alumina is required.

Captan is extracted from apples by the same procedure as for leaves and berries. Intact fruits should be used. An aliquot corresponding to 20 g should be used for the analysis. For the qualitative analysis, the extract is purified by microsublimation in vacuum; for the qualitative analysis, the product is given an additional shaking with a mixture of activated carbon, Zeolite-545, and sodium sulphate.

Microsublimation in vacuum should be used for qualitative analysis of captan in river and artesian water.

Captan is extracted by benzen for the qualitative analysis of captan in soil by using a soxhlet extractor.

In the qualitative analysis, the detected minimum of captan on a chromatogram was 0.5 mcg in vine and grape juice, and 5 mcg in apples, soil and water.

If captan is present together with phthalan, they should be first separated on the thin-layer chromatogram (30).

## TREATMENT OF POISONING

Ingested captan should first be removed by lavage of the stomach using a 2 per cent solution of sodium bicarbonate and ample water (through a sound). Activated carbon and saline purgative should then be given to the victim.

Symptomatic treatment should be given to the poisoned.

Fat should be ruled out from the diet of the patient during the first days after poisoning since fats promote absorption of captan from the intestine.

Workers exposed to captan should thoroughly protect the respiratory organs, the skin and the eyes from contact with captan by using individual protection means (3, 11).

To preclude accumulation of captan in dangerous concentration in foods and fodder, the terms for the last treatment before harvesting should be established. In the USSR, these terms are 30 days for fruits and 20 days for other cultures (3, 5, 15, 32).

The maximum allowable concentration of captain in water intended for domestic and recreational purposes should be 2 mg/litre (the organoleptic criterion of harmfulness).

The maximum allowable residual quantity of captan in foods (kernel fruits, seeds, grapes, vegetables) should be 0.35 mg/kg.

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