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Parathion

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Parathion

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PARATHION

Parathion was manufactured in the USSR under the name "thiophos".

Molecular formula: $C_{10}H_{14}O_5NSP$

Structural formula: $(C_2H_5O)_2\overset{\overset{S}{\|}}{P}O\langle\bigcirc\rangle NO_2$

Molecular mass: 291.26

Definition: organophosphorus pesticide.

Synonyms: O,O-diethyl-O-(4-nitrophenyl)-thiophosphate, Thiophos, NIIUF-100, E-605, alkron, aphamite, vapophos, genithion, kylphos, corothion, lethalaire, niran, paradust, paraphos, sulphos, folidol, fosferon, ekatox, etilon (1).

Parathion was manufactured in the USSR as concentrates of emulsions containing surface-active substances in addition to parathion, and as dusts containing parathion and an inaftive vehicle. Trialkylthiophosphates may be present as impurities (2)

Parathion is no longer manufactured in the USSR because of its high toxicity.

PRODUCTION

The main method of production of thiophosphates, including parathion, is the reaction

$$(RO)_2\overset{\overset{S}{\|}}{P}Cl + HOAr \longrightarrow (RO)_2\overset{\overset{S}{\|}}{P}OAr$$

where R = C_2H_5 and Ar = C_6H_5.

In this reaction, organic and inorganic bases are used as hydrogen chloride acceptors. Of organic bases, tertiary amines (e.g., triethyl amine or pyridine) can be used to the best advantage. The yield is high if the reaction proceeds in the presence of caustic alkalis or carbonates of alkali metals. (2) Technical-grade parathion is obtained by interacting diethylchlorothiophosphate with sodium paranitrophenylate in an aqueous solution. Diethylchlorothiophosphate is prepared by interaction of an alcohol solution of an alkali with phosphorusethiotrichloride. (3)

USE

Parathion is a contact insecticide and acaricide. It is used to control spider mites, plant lauses, and mealworms on various crops (citruses, grapevines, mulberry plants, etc.). The application rate of a 30% parathion emulsion is 0.3 kg/ha for field and truck garden crops and 0.75 kg/ha for orchard crops. (3)

PATHWAYS INTO THE ENVIRONMENT

Parathion enters the environment mainly as a result of spraying and dusting of farm crops. Spraying and dusting result in a parathion hydroaerosol and dust being detected, respectively, in the air. Parathion is found in treated crops, soils, and water. Parathion may also enter the air from soils and plants following their treatment as well as through evaporation. The evaporation index of parathion from soil surface is 3, which means that 3.5 to 6.5 kg of parathion will evaporate from 1 hectare of soil per year (6). Parathion is capable of migrating in the soil. The migration index is 2, which corresponds to 20 cm per year. (6)

CONCENTRATION

In soil, parathion is detectable in residual amounts over a period of 16 years. (7) Its stability in the soil depends on the form in which it is supplied. The half-life of emulsions is 12.4 months and that of granular parathion is 25.5 months.

In the water of water bodies, parathion levels varied from 0.001 to 0.007 mg/litre during the treatment period (8).

Parathion and other pesticides were detected in 4.9% of 8368 samples of food commodities of plant origin examined. Parathion was detected in 19 of 1334 such samples. (9)

ENVIRONMENTAL FATE TESTS

Parathion persists longer in the environment than other derivatives of thiophosphoric acid. The decomposition of parathion is accelerated by microorganisms contained in water and soil. (13)

In a dry atmosphere, parathion is resistant to light; in the presence of moisture, it is readily hydrolyzed to non-toxic components. (6)

The times taken to hydrolyze parathion by 50% in water at various pH values are as follows:

pH	1	2	3	4	5	6	7	8	9
50% hydrolysis in hours	34	27	21	17.5	19.5	13.0	7.8	4.1	2.7

Upon hydrolysis, paranitrophenol and a number of phosphorus-containing acids are formed (diethylphosphoric, diethylthiophosphoric, and monoethylthiophosphoric acids and inorganic acids such as H_3PSO_3 and H_3PO_4). O,O,O-triethylthiophosphate and O,O,S-triethylthiophosphate have also been detected. On cotton leaves, an isomerization product, O,O-diethyl-S-4-nitro-

phenylthiophosphate, is formed. In aqueous solutions, under the effect of snow, parathion is degraded more rapidly. Its aqueous solutions are more stable in the dark. In a model ecosystem, parathion was degraded by 20% over 40 days. In soil, parathion is degraded at a relatively fast rate: its half-life is 2 months at most, and it is completely degraded within a single growing season. Parathion does not cumulate in the soil when treatment is repeated several years in succession.

Parathion may undergo isomerization to S-ethyl and S-(4-nitrophenyl) derivatives; also, thionic sulfur may undergo oxidation to a highly toxic P-O analogue (13).

BIOCONCENTRATION/CLEARANCE TIME/MAMMALIAN METABOLITES

When administered into the stomach of laboratory animals, parathion rapidly (in less than 30 minutes) reaches all organs. Radioactive phosphorus (P^{32}) incorporated into parathion, is found in the liver, kidneys, adrenal glands, ovaries, and medulla oblongate of rats, guinea pigs, and rabbits; the level of P^{32} decreased appreciably by day 4, and only traces were present on day 10. Parathion enters all organs also when it is applied to the skin, but in this case it accumulates more slowly. Considerable amounts of P^{32} are found in the gallbladder and thyroid. (14)

Phosphorus from labelled parathion was found in the blood as soon as within the first few minutes after intragastric administration; its quantity in the blood was, however, small, indicating that parathion is continuously eliminated. Analysis of the urine shows that the urinary level of P^{32} is high; the label was found in the greatest quantity 3 hours postadministration to decline rapidly thereafter. The bulk of P^{32} was contained in the aqueous fraction, which confirms that parathion is rapidly hydrolyzed in the body. (14)

The oral LD_{50} (with intragastric administration) were 3-30 mg/kg for white rats, 9-25 mg/kg for white mice, 15-25 mg/kg for guinea pigs, 50 mg/kg for rabbits, and 8 - 9 mg/kg for cats. The intraperitoneal LD_{50} were 5-6 mg/kg for mice and 4 mg/kg for rats. The intravenous LD_{50} for rabbits and dogs was 10 mg/kg. The LD_{50} with application to skin were 6-10 mg/kg for rats and 50-100 mg/kg (technical-grade parathion) or 870 mg/kg (chemically pure parathion) for rabbits. Female rats were more sensitive than male rats: the oral LD_{50} were 3-6 and 15-30 mg/kg, respectively. (15, 16)

Inhalation for 2 hours of an emulsion containing 33.3% of parathion in a concentration of 12 mg/m^3 was lethal to all rats. Inhalation of parathion on a single occasion in a concentration of 14 mg/m^3 killed some guinea pigs, while the concentration of 50 mg/m^3 was lethal to all guinea pigs. Deaths among rabbits occurred with inhalation of parathion in a concentration of 50 mg/m^3.

Among rats inhaling parathion dust on a single occasion, deaths occurred with parathion concentrations of 15-20 mg/m^3. The threshold concentration of parathion with single administration (as assessed from changes in conditioned reflexes) was 10 mg/m^3.

No changes (including those in cholinesterase activity) occurred in animals with daily inhalation of parathion vapors containing parathion in a concentration of 0.12 mg/m^3.

In humans, parathion concentrations of 0.1 to 0.8 mg/m^3 in the air of the working environment, were found to reduce cholinesterase activity in the blood, while those of 6-13 mg/m^3 were reported to cause acute poisoning.

Repeated administration of parathion into the stomach in a daily dose of 0.2 mg/kg killed all cats after 50-80 days; the dose of 1 mg/kg killed cats after 45-46 days. Intragastric

administration of parathion at 0.5 mg/kg daily for 20 days caused no deaths among rats, whereas the daily dose of 3 mg/kg was lethal to all rats within 5 days. When parathion was added to the diet, no changes occurred in dogs with a parathion concentration of 0.02 ppm (ineffective concentration); with concentrations of 2-5 ppm cholinesterase activity in the blood plasma and erythrocytes was reduced. With a parathion concentrations of 50 ppm in the diet, some of the test rats died; with concentrations of 75-100 ppm, all rats died within a few weeks, and with a concentration of 100 ppm severe intoxication and death of all rats occurred within the first week.

Paratnion is absorbed through the skin, airways, and gastrointestinal tract. It inhibits cholinesterase activity in the brain and other tissues. It is excreted in the urine mainly as its breakdown products. In experiments where 20 to 80 mg of parathion was applied to the skin of monkeys, p-nitrophenol was detected in the urine at 24 hours postapplication and continued to be excreted for 18- to 30 days thereafter.

When P^{32}-labelled parathion was applied to the skin of rabbits, considerable amounts of the label were found in the gallbladder, thyroid, liver, and kidneys. In the blood, the label was detected as soon as a few minutes after application. Parathion undergoes very rapid degradation in the body. A few minutes postadministration, only 30 to 40% of parathion remained unchanged in the body. It is entirely degraded after 60 minutes.

In parathion-poisoned animals, a state of depression develops first, succeeded by one of motor excitation; the breathing becomes more frequent and increasingly irregular; hypersalivation and lacrimation, vomiting, fibrillar twitching of various muscle groups, dyscoordination of movements, ataxia, tremor, clonic and tonic convulsions, and involuntary urination and defecation all occur. During intervals between

seizures, the animals are in a state of strong depression and fail to respond to external stimuli. The inhibition of respiration progresses and death occurs as the result of respiratory paralysis.

On postmortem examination, vessels of visceral organs are congested and the lungs and brain are often edematous. Histological examination reveals tissues overfilled with blood, pulmonary edema, bronchospasm, hemorrhages around vessels and bronchi, and emphysematous areas with torn interalveolar septa. In the myocardium and liver, dilatation of vessels, hemorrhages, and dystrophic changes in the form of cloudy swelling and vacuolar degeneration with occasional intralobular small focal necrotic areas are noted. In the kidneys, hyperemic glomeruli and convoluted tubules, hyaline casts, and cloudy swelling of the epithelium of convoluted tubules are observed; some animals have inflammatory changes in the form of acute extracapillary glomerulonephritis. The spleen contains small necrotic areas.

In humans, parathion poisoning develops as follows. During or shortly after occupational exposure to parathion, headache, dizziness, acute abdominal pain, nausea, vomiting, and profuse salivation develop to which profuse perspiration, anxiety, deterioration of vision, dimness of vision, general weakness, twitching of the tongue and eyelids, and difficulties in speaking (sometimes repetition of the last syllable of a word or of the last word of a phrase) are added shortly afterwards. Body temperature remains unchanged or falls. Bradycardia occurs. Blood pressure may be elevated at first, but if poisoning is severe, it tends to decrease to a very low level as toxic symptoms develop. Bronchospasm and pulmonary edema are possible. There develops cardiovascular insufficiency. Fibrillations involve muscles throughout the body. Convulsions appear,

and Cheyne-Stokes respiration is often noted during intervals between convulsions. There occur mental disturbances such as depression, confusion, and disorientation. Subsequently the patient loses consciousness; reflexes are then completely absent and there is paralysis of the obturator muscles of the rectum and urinary bladder. Respiratory embarassment progressively increases. Breathing is sometimes noisy because of the presence of abundant secretions in the airways. Death usually ensues after several hours as the result of respiratory arrest.

Pronounced clinical signs and symptoms of poisoning generally appear after cholinesterase activity in the blood has decreased by 50-70%. Some symptoms may, however, be present when cholinesterase activity has decreased only slightly. (15, 16, 17)

On postmortem examination of those who died as a result of parathion poisoning, pulmonary edema is present, the stomach and intestine are unchanged, the heart and liver are usually of normal size, vessels are congested, the spleen is slightly enlarged, the kidneys are overfilled with blood, the meninges are plethoric, and punctuate hemorrhages are present in the white and gray brain substance. In nervous tissue, perivascular spaces are considerably dilated, particularly in the subcortical region. Pyramidal cells are strongly changed; nerve cell processes have a broken appearance. (18)

SPECIAL TOXICITY STUDIES

Mutagenicity. No mutagenic effects of parathion were noted in experiments with microorganisms. Such effects were, however, observed in plants. (19)

Neurotoxicity/Behaviour. Cholinolytics, such as atropine, Dropacin, and Pentaphen, were found to reduce parathion toxicity to a considerable extent. (20) Effective agents for the

treatment of parathion poisoning are cholinesterase reactivators (diproxime, Toxogonine, Diethyxime). (21, 22)

Reproduction. Parathion was reported to affect the reproductive performance and fetal development in birds and laboratory animals. (23)

Sensibilization. Allergic dermatitides and eczemas were noted in those exposed to parathion. (24)

Embryotropic action. Parathion was found to have embryotoxic effects. (17) Developmental anomalies of the central nervous system, atrophy of extremities, and malformation of wings were noted in studying the effect of parathion on embryogenesis in quails. Embryotoxic effects were also observed in rats. Subcutaneous hematomas in fetuses, reduced weight of fetuses and of the placenta, increased malformation rates, stillbirths, high postnatal mortality, reduced weight gain, and destructive changes in spermatogenic cells, were all observed. (23)

Primary irritation. No irritant action is shown by parathion, which enhances the risk of its being absorbed through the skin because the poison on the skin may pass unnoticed.(15)

EFFECTS ON ORGANISMS IN THE ENVIRONMENT

Organophosphorus compounds are less toxic for fish than organochlorine compounds. The concentration of parathion which was lethal to 50% of crucian carps was 1.5 mg/litre; the concentration of 0.2 mg/litre was lethal to 33% and that of 0.4 mg/litre, to 67% of perches (25).

The effects of parathion on various animals were studied using a 30% parathion preparation applied at a rate of 400 g/ha, that is, the concentration and application rate previously employed in spraying crops were used. Young rabbits exposed to parathion gained in weight more slowly than did control animals; the litter size was smaller and the offspring of para-

thion-exposed rabbits died more frequently. In pheasants, egg laying occurred 15 to 25 days later than normal, the egg-laying period was longer, and fewer eggs were laid. (26)

SAMPLING/PREPARATION/ANALYSIS

To determine perathion in the air, gas chromatography is used (10). Parathion is absorbed from the air into dimethyl-formamide, extracted by benzene, and determined on a chromatograph with detector from electron capture.

From products of plant origin, parathion is extracted with sulfuric ether; p-nitrophenol is then separated by washing the extract with a caustic alkali solution, and this is followed by alkaline hydrolysis and colorimetric determination of p-nitrophenylate. (11)

Parathion in cabbage and cucumbers is determined using thin-layer chromatography. Extraction is carried out with organic solvents (acetone, diethyl ether, chloroform) and chromatography is performed in a thin layer of aluminium. The mobile solvent is a mixture of hexane and acetone. Parathion is detected after irrigation of the plate with a caustic soda solution. (12)

TREATMENT OF POISONING

If parathion has entered the body by mouth, a gargle and an adsorbent are given. If it is present on the skin, this should be treated with aqua ammonia or chloramine B and then washed with soap and water. If parathion has got into the eyes, these should be washed with water or a 1% sodium hydrocarbonate. Concurrently with those measures, an antidote therapy should be instituted using cholinolytics (e.g., large doses of atropine sulfate) and cholinesterase reactivators (e.g., dipiroxime). At the initial stage of poisoning (when nausea, vomiting, bronchospasm, and excitation occur), 2-3 ml of a 0.1% atropine sulfate solution and 1 ml of a 15% dipiroxime solution are injected

intramuscularly. When muscular fibrillations and convulsions have developed, 4-6 ml of a 0.1% atropine solution and 1 ml of a 15% dipiroxime solution are injected intramuscularly, followed by intramuscular injections every 8-10 minutes of 2-3 ml of a 0.1% atropine sulfate solution. Dipiroxime injections (1 ml per injection) are repeated every 2-3 hours until blood cholinesterase activity has restored, but no more than 1 g of the drug should be administered within the first 24 hours. Further administration of dipiroxime in the absence of parathion in the blood is ineffective as well as undesirable because of possible side-effects. Consomitantly with dipiroxime, 3 ml of a 40% isonitrosamine solution is injected intramuscularly to abolish the effect of parathion on the central nervous system; if necessary, a repeat injection is done after 30-40 minutes. (20) If a state of coma and paralysis has developed, still larger doses of atropine sulfate should be given. If treatment is instituted at the stage of convulsions, 20-25 mg of atropine sulfate is administered within the first hour and up to 50 mg daily for 2-3 days subsequently, during the period of maintenance atropinization. During the coma and paralysis stage, 30 to 50 mg of atropine sulfate is sometimes given within the first hour. Atropinization is continued until respiration becomes normal, bronchorrhea ceases, and tachycardia appears. Apart from dipiroxime, other cholinesterase reactivators are used, such as Ephoxime (Tocosgonine), Diethyxime, and isonitrosine. Ephoxime is injected intramuscularly in a dose of 1 ml of a 15% solution. Diethyxime is also injected intramuscularly, in a dose of 5 ml of a 10% solution (a single dose is 7-10 mg/kg). Injections are repeated every 2-3 hours during the first 24 hours.

Other cholinolytics have been recommended in addition to atropine sulfate, such as Amizyl (2-3 ml of 0.1% solution

intravenously), Tropacin (1 ml of 1% solution), Aprophen (2 ml of 1% solution), Pentaphen (1 ml of 1% solution), and Cyclodol (Artane) (1 ml of 1% solution). Injections are repeated if required. Some of the above drugs are more effective in relieving symptoms of excitation of the central and peripheral N-cholinergic systems. A combination of atropine sulfate and intravenous magnesium sulfate or ganglioplegics (Benzohexonium, Pachycarpine) may be used.

To eliminate the poison from the body, forced diuresis using osmotic diuretics (hypertonic solutions of glucose or mannitol) or Euphylline is carried out. Alkalization of the plasma is indicated in cases of parathion poisoning.

Resuscitation measures are indicated in cases of asphyxia and comatose state. In such cases, intubation or tracheotomy with long-term suction and artificial respiration are necessary.

To control or prevent pneumonia, antibiotics are given.

In cases of chronic parathion intoxication involving an asthenic-vegetative syndrome, physical methods of treatment (hydro- and electrotherapy), vitamin therapy, intravenous infusions of glucose, sedatives (bromides, etc.), and general supporting treatment are employed. The management of a diencephalic syndrome should include the use, not only of sedatives, but also of neuroplegics and ganglioplegics as well as tranquilizers.

Should an asthmatic state develop, desensitizing agents are used, including hormones (ACTH, cortisone), cholinolytics (atropine sulfate, etc.), spasmolytics (theophylline), and antihistaminics.

If acute poisoning with parathion has occurred only once and has been relatively mild, the working capacity is usually retained. The same is true of mild chronic intoxications

(moderate asthenization with signs of vegetovascular dystonia). In such cases, the affected person must not be allowed to work with pesticides until complete recovery has ensued.

When diencephalic disturbances have developed, further contact with parathion is contraindicated. When an asthmatic state has set in, the affected person should be transferred to another job not associated with exposure to pesticides and in an environment containing as little dust as possible. (21, 22)

REMOVAL

For decontamination, alkali solutions are used, such as a mixture of synthetic surface-active agents and organic solvents and alkaline additives (1 litre per 10 litres of water). Three to 5% solutions of caustic alkalis, or soda ash, or chlorinated lime slurry may be used (1 kg per 4 litres of water), followed by washing with large quantities of water (27).

PREVENTION

In the USSR, the manufacture of parathion (Thiophos) has been discontinued and its use in agriculture is now prohibited in view of its high toxicity.

The main prophylactic measures are as follows. Adolescents (up to the age of 18 years), pregnant and lactating women, men over 55 years of age, and women over 50 years of age are not allowed to work with parathion. All those handling parathion must be given instructions on safety precautions and undergo medical examinations prior to and in the course of (once a year at least), work with parathion. Cholinesterase activity in the blood should be determined before and during parathion work. Those found to have this activity reduced by 25% or more should be transferred to another job not involving organophosphorus pesticides, until the enzyme activity has returned

to normal. Work with parathion should also be discontinued at the appearance of first signs of malaise. The duration of parathion work must not exceed 4 hours daily. The workers must be provided with means of individual protection, such as respirators, goggles, coveralls impregnated with water releppent, aprons of rubberized fabric, and rubber boots and gloves. Spraying and dusting operations should be carried out during morning and evening hours only, and under the guidance of experts and under general supervision of a medical worker. The overalls contaminated with parathion must be shaken, soaked in a soap and soda solution for 6-8 hours, washed in a hot soap and soda solution 2 or 3 times, and then rinsed thoroughly. The containers must be decontaminated with a 5% solution of caustic soda or soda ash. For this purpose, the containers are first filled with this solution which is left in them for 6-12 hours, after which they are repeatedly washed with water. (28)

In the USSR, the MAC of parathion in the air of workplaces is 0.05 mg/m^3 (in this hygienic standard it is specified that parathion is dangerous when applied to the skin). The MAC in water bodies used for economic, drinking, or recreational purposes is 0.003 mg/litre.

The presence of residual parathion in foods is not allowed in the USSR. (29)

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