POISONING BY ORGANIC PHOSPHORUS INSECTICIDES*

BY

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The need to increase food production in all parts of the world has led to the use of many potentially dangerous substances for the control of weeds and insect pests. The value of D.D.T. in the control of mosquitoes, flies, and certain insects is undisputed, and many other chlorinated hydrocarbons have found a special use in pest control. Some of these substances are extremely toxic to man. Control of weeds with sprays containing dinitro-*ortho*-cresol (D.N.O.C.) has increased the yield in cereal crops, but in Great Britain alone seven agricultural workers have died from D.N.O.C. poisoning in the past five years. The average period during which D.N.O.C. is used is only six weeks in each year.

The organic compounds of phosphorus have been most recently introduced into the group of potent agricultural chemicals. These are effective insecticides but extremely dangerous to man unless they are handled with extraordinary care. There has been a tendency to release agricultural chemicals for use by workers of varying experience before the toxic properties have been adequately studied. We know little enough about the acute toxicity of some of these substances, and almost nothing about the long-term effects of repeated small doses.

Substances Now Used

During the 1939-45 war organic compounds of phosphorus possessing a nicotine-like action were described by Schrader, in Germany, and recommended for use as insecticides. It was recognized, also, that these substances might prove effective agents in chemical warfare. At the end of the war the formulae and methods of synthesis of these substances were made available simultaneously to scientists in Great Britain and the United States of America, and in both countries many of them have been developed and tested for use in the control of insect pests. Hexaethyl-tetraphosphate (H.E.T.P.), tetraethyl-pyrophosphate (T.E.P.P.), and diethyl-*para*-nitrophenyl-thiophosphate ("parathion") are now used in many countries throughout the world. They are effective in the control of a wide variety of pests such as aphides and red spider, and are of particular value against insects which may be resistant to D.D.T. and the older insecticides (Porter, 1948). More recently octa-methyl-pyrophosphoramide (O.M.P.A.) has been studied, but its use is not recommended on crops which will be used for food.

These substances are alkylpolyphosphates and potent cholinesterase inhibitors resembling in their effects upon man di-isopropyl fluorophosphate (D.F.P.). O.M.P.A. does not inhibit cholinesterase *in vitro* but becomes converted *in vivo*, probably by the liver, to an active anticholinesterase substance (DuBois *et al.*, 1950). H.E.T.P. owes its action as an insecticide to the presence in the manufactured product of T.E.P.P. These substances are heavy syrupy liquids which hydrolyse readily in the presence

of moisture or alkali and lose their toxicity. Pure parathion is a clear, colourless, and odourless oily liquid, but the commercial product contains amine impurities which give it a brownish coloration and a distinctive unpleasant odour. Parathion is only slightly soluble in water and hydrolyses slowly. At 25° C. and pH 7 only 50% hydrolysis occurs in 120 days (Grob, 1950). Moreover, it is more soluble in lipoids than in aqueous media. These properties enhance greatly its efficiency as an insecticide, and also its action as a poison to man and domestic animals. In a single dose both T.E.P.P. and nicotine are more toxic than parathion, but experience and experiment have demonstrated that the effects of parathion are more insidious and more deadly, especially if exposure is repeated day after day.

Cases of Poisoning

H.E.T.P. and T.E.P.P. are mixed with a suitable wetting agent to prevent hydrolysis of the concentrated material, which is diluted with water immediately before use. Sixteen cases of poisoning with these substances have been recognized in the United States of America since 1947. Although moderately severe symptoms occurred in persons affected, there were no deaths. By contrast more than 100 cases of poisoning and at least six deaths have been reported among persons handling parathion in one spraying season. Towards the end of 1948 the use of parathion increased and in many cases replaced H.E.T.P. and T.E.P.P. because of its more prolonged insecticidal action.

In the United States of America concentrated parathion is adsorbed on to attapulgus or bentonite clay to form wettable powders containing 15 or 25% of the active ester. These may be blended with inert materials to form 1 to 2% dusts or diluted with water for use as aqueous sprays. Methods of applying dusts and sprays vary considerably and include dusting from aeroplanes, mechanical spraying from tractors, and hand-spraying. In greenhouses, aerosols or smoke canisters containing parathion are used. In Great Britain parathion is supplied to the user as a concentrated liquid for dilution and use as an aqueous spray. Until 1950 relatively small quantities of parathion had been applied and only four cases of poisoning have been recognized up to the time of writing.

Poisoning has occurred in agricultural workers such as field-workers, entomologists, dusting pilots, fruit pickers, and nurserymen, and in industrial workers, including chemists, formulators, packers, and men employed on maintenance in manufacturing plants.

A welder accidentally cut into a pipe containing parathion. Within ten minutes he experienced nausea, vomiting, vertigo, and headache. He recovered completely in twenty-four hours.

A pilot employed in dusting crops from aeroplanes had been up twice in one day and crashed into a row of trees on his third flight. The man who assisted in loading for the last flight said that the pilot had remarked about his eyesight diminishing, but passed it off as a minor matter. The investigation in this case revealed little, as both the aeroplane and the pilot were destroyed by fire (Abrams and Leonard, 1950).

A plant foreman and a fellow worker were splashed with parathion. The foreman made his assistant wash with soap and water and change his clothing at once, but neglected to do so himself. Eight hours later nausea, vomiting, abdominal cramps, diarrhoea, and constriction of the pupils developed. These symptoms persisted and he was admitted to hospital nine hours after the onset of his illness. At this time there was fibrillary twitching of voluntary muscles and signs of pulmonary oedema. Treatment with atropine produced a temporary improvement, but death occurred in coma twenty-one hours after exposure to parathion.

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Signs and Symptoms

The symptoms and signs of parathion poisoning are similar to those produced by D.F.P. and T.E.P.P. They are due to inhibition of both pseudo- and specific cholinesterase. It is possible that other factors, such as accessibility to the central nervous system, may operate in altering the clinical manifestations produced by different cholinesterase inhibitors. It has been suggested that an additional mechanism of toxic action is responsible for some of the symptoms of parathion poisoning which have not been observed with D.F.P. or T.E.P.P. *In vitro* the depression of cholinesterase activity by parathion is 1/30 of that caused by D.F.P. or neostigmine and 1/300 of that caused by T.E.P.P. All four substances affect plasma cholinesterase more than that of red blood cells, brain, and muscle. The rate of inhibition by parathion is slower, but this does not result in lessened toxicity. In experimental animals the toxicity of parathion equals that of D.F.P. and is one-tenth that of T.E.P.P. Both in animals and in man symptoms of poisoning with T.E.P.P. are more transient (Grob, 1950).

Inhibition of cholinesterase occurs as the result of the combination of the inhibitor with cholinesterase. In the case of D.F.P. irreversible combination occurs almost immediately and recovery depends upon regeneration of cholinesterase. This takes several weeks in the case of plasma cholinesterase and several months for red blood cell and tissue cholinesterase. Although no symptoms may be present until the cholinesterase activity of the effector organs is reduced to between 25 and 50% of normal, an individual is unduly susceptible to the effects of any cholinesterase inhibitor until normal cholinesterase activity of the enzyme is restored. The combination of cholinesterase with T.E.P.P. or parathion is reversible for several hours after combination occurs, but subsequently becomes irreversible (Grob, 1950). It is therefore important that atropine should be given promptly and in adequate doses.

Parathion is lipid-soluble and readily penetrates the skin. Absorption may also occur through the conjunctiva or by inhalation or ingestion. It causes no local symptoms or signs in the skin, so that absorption by this route may pass unrecognized until the characteristic symptoms begin. Grob, Garlick, and Harvey (1950) report the toxic effects of exposure to parathion in 32 men and 8 women. Death occurred in 6 men, severe symptoms in 2 men and 2 women, and mild to moderate symptoms in 24 men and 6 women. In most of these cases exposure occurred in mixing liquid parathion with attapulgius clay, but included among the fatal cases are field workers and others reported from several sources.

Length of Exposure to Parathion

The length of exposure to parathion before the occurrence of symptoms varied from several days to several weeks. In the fatal cases and in most of the others exposure averaging twelve days had occurred during the month preceding the onset of symptoms, but in five persons with symptoms of mild to moderate severity no exposure is known to have occurred prior to the day on which illness developed. Warning symptoms, including intermittent nausea, vomiting, giddiness, weakness, drowsiness, and fasciculation of the eyelids, were noticed by five persons before more serious manifestations of poisoning appeared. These symptoms were present at intervals for one week, but were ignored by the workers. The concentration of parathion in the working atmosphere at the time that this incident occurred is not known.

Half of the patients studied by Grob, Garlick, and Harvey (1950) began to have symptoms while still exposed to parathion. In other cases the illness began from one to eight hours after the last exposure. The first symptoms are usually anorexia and nausea characteristically increased by smoking or taking food and followed within half to two hours by vomiting, intense abdominal cramps, excessive sweating, and salivation. Giddiness, apprehension, and restlessness usually follow the onset of anorexia, but occasionally these may be the initial symptoms of intoxication.

Constriction of the pupils is found in all patients with moderately severe symptoms, but may be minimal or absent in mild cases. Where parathion has been conveyed direct to the eye pin-point constriction of the pupil occurs and may be unilateral. It is resistant to dilatation with atropine, and may take several weeks to return to normal size. Muscular twitchings beginning in the eyelids and tongue follow shortly after the occurrence of nausea and vomiting. In severely poisoned persons the twitching spreads to the muscles of the face and neck and involves the extraocular muscles, causing jerking movements of the eyes suggestive of nystagmus. Generalized muscular twitching and extreme weakness may develop in spite of adequate doses of atropine, and death can occur from this neuromuscular paralysis.

In addition, diarrhoea, tenesmus, involuntary defaecation and micturition, and signs of pulmonary oedema with broncho-constriction occur in acutely ill persons. A raised blood pressure, returning to normal as symptoms subside, is a constant finding in parathion poisoning. This is unusual, since most directly acting cholinergic drugs cause the blood pressure to fall (Grob, Garlick, and Harvey, 1950). Symptoms and signs of effects upon the central nervous system develop *pari passu* with the muscarine-like and nicotine-like effects. Giddiness and apprehension are accompanied or followed soon by intense headache, and in mild cases insomnia or unusual dreaming may be noticed. In more severe cases ataxia, tremor, drowsiness, diminished concentration, mental confusion, and sometimes disorientation and slurring of speech occur. Multiple repetition of the last syllable of a word is characteristic.

Coma develops gradually, and occurs from one to nine hours after the onset of symptoms. All the patients who died and two who recovered were deeply comatose, with absence of all peripheral reflexes. Coma lasted on an average for three hours. Generalized convulsions almost invariably occur in comatose patients. Three people who subsequently died regained consciousness for several hours following the administration of atropine. Examination of the fundus in one patient revealed two dioptres of papilloedema, and the cerebrospinal fluid was found to be under pressure but otherwise normal.

In fatal cases death has occurred from one to twenty-one hours after the last exposure to parathion, and, on an average, nine hours after the onset of symptoms. The immediate cause is not known, but may be due to the combined effects of neuromuscular paralysis and direct depression by parathion of respiratory and circulatory centres in the medulla.

Cholinesterase Activity

Except for a moderate leucocytosis of 12,000 to 20,000 white blood cells, there were no abnormal findings in ancillary investigations. The urine was normal. Cholinesterase activity of plasma and red blood cells was determined. In four persons severely poisoned, two of whom

died, plasma cholinesterase activity was less than 5% of normal, and that of the red blood cells 14% of normal. In six less severe cases the enzyme activity was reduced to 10% and 22% respectively. The rate of return to normal activity was determined in eighteen cases and found to be for plasma cholinesterase 27% for the first three days, 5% on the fourth day, and only 3% by the tenth day. The enzyme in the red blood cells returned at the rate of 10% for the first three days and subsequently at the rate of 1 to 2% daily. The rate of recovery of cholinesterase activity of both plasma and red blood cells seems to be independent of the degree of exposure or the initial depression. At necropsy, which was performed in five cases, capillary dilatation hyperaemia and oedema of the lungs is described in four cases, oedema of the brain in addition in two cases, and in one there was some pneumonitis present, which was not considered sufficient to cause death (Grob, Garlick, and Harvey, 1950).

Death has occurred after absorption of parathion through the skin and in other instances where the main portal of entry seems to have been the respiratory tract. It has not been possible to determine the exact dosage of parathion which has proved fatal in any single case, either on the day on which symptoms appeared or as a result of previous exposures. On the basis of animal experiments the acute lethal dose has been estimated at 12–20 mg. (1/5–1/3 gr.). Gilman (1950,—personal communication) considers that this calculated lethal dose is too high and suggests that the fatal dose is probably a fraction of a milligram per kilogram, a total dose of less than 10 mg. There is no indication at present that any permanent disability results from poisoning by parathion. Acute symptoms last from eighteen to thirty hours in severe cases, and from six to twenty-four hours in patients less severely affected. Mild anorexia, giddiness, and anxiety, with headache and insomnia, may persist for several days, and in a few cases for several weeks. Persons of all ages and of either sex appear to be equally susceptible to the effects of parathion (Grob, Garlick, and Harvey, 1950).

Too little is known about the possible effects of long-term exposure to small amounts of parathion. Provided that the recommendations on the interval between spraying and harvesting of edible crops are rigidly observed it is unlikely that residues on food sprayed with the stable compounds—parathion and O.M.P.A.—will be sufficient to cause symptoms in persons eating such foods. It is less certain that workers harvesting crops or loading and unloading market trucks are not at risk. Twenty-two men developed symptoms of parathion poisoning while picking pears in an orchard which had been sprayed ten days previously. In handling large quantities of materials even slightly contaminated with parathion the risks of absorption through the skin and respiratory tract should be considered and the safety of workers ensured by suitable protective clothing and alternation of work.

Treatment

Symptoms due to overstimulation of the autonomic nervous system and those due to the action of parathion on the central nervous system will respond to the administration of atropine in adequate doses: 1 to 2 mg. (1/60 to 1/30 gr.) should be given at the onset of symptoms and repeated at hourly intervals until the pupils are dilated or the symptoms and signs of pulmonary oedema and excessive salivation and sweating have subsided. Atropine does not protect against the effects at the neuromuscular junction, and artificial respiration may be necessary if neuromuscular paralysis develops. Facilities for prolonged artificial

respiration must be available for immediate use in all cases of parathion poisoning.

Where exposure has occurred from splashing of the skin, the clothing should be removed immediately and the patient bathed with soap and water. Since hydrolysis of parathion occurs more rapidly in the presence of alkali, the addition of a mild alkali to the water assists in removing it from the skin. It is important that the person who removes contaminated clothing should be protected against absorption of parathion through the skin by wearing natural rubber gloves. If parathion has been ingested, vomiting should be induced, and this is probably advisable in all cases, since it is likely to be swallowed with nasal mucus. Postural drainage may be necessary when fluid has accumulated in the lungs before atropine has become effective.

The onset of neuromuscular paralysis may occur suddenly and without warning. The patient must be under constant observation so that artificial respiration may be started immediately if this complication develops. It is suggested that equipment for carrying on artificial respiration should be placed at the patient's bedside as soon as he is admitted to hospital. Where muscular weakness results in difficulty in swallowing, tracheotomy should be performed without delay. Relapse has occurred following apparent recovery after the administration of atropine, so that the patient must be kept under observation for at least twenty-four hours after symptoms have subsided. Since susceptibility to small doses of any cholinesterase inhibitor persists until cholinesterase activity of plasma and tissues is restored to normal, persons who have been affected should not return to work with organic phosphates until cholinesterase activity has been shown to be normal. The treatment of poisoning by H.E.T.P. or T.E.P.P. is the same as that of parathion poisoning.

Experience in the United States of America in the 1949 spraying season has demonstrated that, unless all the recommendations made for the safe handling of organic phosphorus insecticides are carried out in detail, serious illness and even death will occur. The stability of parathion and its ready solubility in lipoids may account for the fact that most recorded cases have been observed from the use of either H.E.T.P. or T.E.P.P. Moreover, exposure to minute amounts of H.E.T.P. or T.E.P.P. in spray mist or drift causes immediate constriction of the pupils. The interference with vision is so great that a man is obliged to give up work at once and so avoids any further exposure (W. E. Ripper, 1950—personal communication).

Preventive Measures

Preventive measures both in the factory and in the field should be directed against the risks of absorption by any route. The skin must be protected by overalls which fasten tightly at the neck and at the wrists. Natural rubber gloves, apron, and boots are essential in handling concentrated materials, and sprayers should wear waterproof clothing, including a hat which protects the head and the back of the neck. Complete protection from inhalation can be achieved only by means of a full-face gas-mask with canister designed for protection against organic vapours, acid gases, and smokes (R. A. Fulton, 1950—personal communication).

Chemical cartridge respirators with a facepiece of the half-mask type may reduce the inhalation hazard considerably, but such respirators must be tested and approved for use. The cartridge must be changed at least twice daily, and the facepiece washed in warm water and soap after use. This type of respirator does not give adequate

protection for aeroplane pilots, greenhouse sprayers, or those handling concentrated parathion in enclosed spaces. Moreover, up to 16 mg. of parathion may filter through in an eight-hour period, and this together with absorption through the skin around the mask may constitute a fatal dose. Several accidents, some fatal, have occurred where faulty or untested respirators have been used.

Protective clothing, including socks and underclothing, must be laundered each day. Adequate facilities for washing must be available and persons exposed to parathion are advised to remove all working clothes and take a bath at the end of each day's work. If parathion is splashed on to clothing this must be changed completely, and all areas of the skin which have been in contact with the soiled clothing must be washed immediately. The hands and face should be washed thoroughly in hot water and soap before eating and smoking. Whereas these precautions may be enforced in factories it is almost impossible to ensure that they are carried out in the field.

Routine estimations of cholinesterase activity of plasma and red blood cells should be made at weekly intervals in all persons exposed to parathion, H.E.T.P. and T.E.P.P. Davies and Rutland (1950) have investigated the variation in cholinesterase activity of plasma and red blood cells in 200 healthy adults of both sexes. Normal activity may vary from the mean by as much as 40% (see Table). Moreover,

Plasma and Red Blood Cell Cholinesterase: Normal Limits of Variation in Healthy Adults (Mean = 100)

Group	Coefficient of Variation	Mean Normal Limits %
Plasma cholinesterase:		
Service	19.9	60.2-139.8
Males (G.P.)	19.1	61.8-138.2
Females (G.P.)	23.7	52.6-147.4
All Groups	21.2	57.6-142.4
R.B.C. cholinesterase:		
Service	11.8	77.2-122.8
Males (G.P.)	14.4	71.2-128.8
Females (G.P.)	12.1	75.8-124.2
All Groups	15.7	68.6-131.4

After Davies and Rutland (1950).

there is an individual variation of up to 26% for red blood cell cholinesterase and 37% for the plasma enzyme. There may also be a seasonal difference. It is therefore obvious that the significance of reduced cholinesterase activity in random samples of blood is difficult to assess. Every effort should be made to estimate cholinesterase activity in each individual before exposure to organic phosphorus insecticides occurs, and subsequently at weekly intervals. Clearly a more decisive and a more simple test of exposure to these substances is urgently required. Organic phosphorus insecticides should be used only by experienced operators who fully understand the hazards and who are adequately protected and constantly supervised in their work.

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FOOD-POISONING IN SHEFFIELD IN 1949

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During the long hot summer of 1949 seven small outbreaks of food-poisoning in Sheffield produced 36, 4, 20, 37, 9, 1, and 1 cases of illness respectively. Of these 108 cases only 13 were notified by general practitioners and three by hospitals. The remainder came to light through a few of the victims contacting the public health department direct and by the staff of the department making inquiries among other persons likely to be affected.

A food preparer with a septic hand was found to be associated with each of the four outbreaks described below, but the association was not necessarily the cause of the third and fourth outbreaks.

First Outbreak

At 10 p.m. on Wednesday, July 27, 1949, the superintendent of the Infectious Diseases Hospital informed the medical officer of health that he had admitted two patients who were very ill with food-poisoning. A visit was paid immediately to their home and the possible cause of the trouble was ascertained to be a chicken-and-rabbit preparation bought from a near-by shop the previous day.

The shop was visited the following morning and the source of the meat product was traced to a small local food factory which was very clean and well equipped. The chicken and rabbit had been prepared the previous Saturday by two men who boiled the carcasses in a large cauldron, removed the flesh from the bones by hand, and immediately reheated the flesh before packing it into moulds, adding melted gelatin, and then pressing. After cooling, the preparation was stored in a refrigerator until the Monday evening, when it was distributed to five shops where it was kept in refrigerators until sold on the Tuesday and Wednesday. The manufacturer estimated that between 500 and 700 persons would eat the meat.

Although food-poisoning is notifiable in accordance with the Food and Drugs Act, 1938, the great importance of immediate notification seemed not to be generally realized. Inquiry was therefore made at the shops, and lists of customers were obtained. When these were visited, a total of 36 persons who had been supplied from one or other of four of the five shops were found to have been affected. Of these, 35 had eaten the chicken and rabbit, and one had eaten black-pudding from the same food factory. Of other persons who had eaten the chicken and rabbit in company with those who were later affected, only three groups (comprising one, two, and three persons respectively) remained unaffected. Two dogs in different households fed on the leavings of the victims remained well.

Of those persons affected, 13 had consumed the meat on the day of purchase and 23 on the following day. One man was unaffected after eating the product on the