MODERN INSECTICIDES: THEIR TOXICITY AND CONTROL *

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Insecticides represent one sub-group of pesticides used to kill or repel insects, other pesticides being rodenticides, molluscicides, herbicides, and fumigants. These agents, some natural and many of them synthetic, generally belong to different chemical groups.

The insecticidal agents have been employed for the interior, and parts of the exterior, of dwellings and other buildings, and for the control of various insects and insect vectors of disease especially in tropical and subtropical areas. Many of these agents are toxic to man and other mammals, and their widespread use is an occupational hazard to sprayers. There is also the danger to the general population from food which may contain minute amounts of these substances. There is great hazard during their synthesis and manufacture—often far more acute than in their subsequent use, since the primary materials or processes may be more toxic than the end product.

The agents that have been used include arsenic, lead, phosphorus and thallium compounds; fluorides, cyanides, thiocyanates, nicotine, naphthalene, and numerous chlorine-containing compounds such as dicophane (DDT, chloropheno-

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thane), benzene hexachloride (BHC, lindane, gammexane), toxaphene, indane derivatives, e.g. chlordane and dieldrin; and the phosphate ester insecticides, e.g. parathion, malathion, and TEPP. A most valuable and detailed reference compendium on insecticides is available.[12]

The comparative toxicity of the insecticides for man may be arranged in the following scale. Approximate fatal doses estimated for adults are given in brackets, but it must be remembered that serious symptoms and death may occur with smaller amounts when the agents are in solution in organic solvents:

(*a*) *Extremely toxic*; fatal dose less than 1 mg. per kg. of body weight: organic phosphate esters, e.g. TEPP (10 - 20 mg.), nicotine (40 mg.), and cyanides (HCN 50 mg.).

(*b*) *Highly toxic*; fatal dose 1 - 50 mg. per kg. of body weight: Organic phosphate esters, e.g. parathion (100 mg.), arsenicals (above 120 mg. for arsenic trioxide), potassium cyanide (200 mg.), dinitroorthocresol (200 mg.) dinitrophenol (1 g.), sodium fluoride (1 g.), and naphthalene (3 g.).

(*c*) *Moderately toxic*; fatal dose 50 - 500 mg. per kg. of body weight: Pentachlorophenol (2 g.), toxaphene (2 - 7 g.), chlordane (more than 5 g.), gamma benzene hexachloride (may be 5 - 7 g., for technical product about 30 g.), and dicophane (DDT) (30 g.).

(*d*) *Slightly toxic*; fatal dose 0·5 - 5 g. per kg. of body weight: Phenothiazine (10 g.), rotenone (10 g.), derris powder (10 - 100 g.), and pyrethrum (15 — 100 g.).

CLINICAL CONSIDERATIONS AND CONTROL

Two classes of insecticides will be considered here: (A) Chlorinated hydrocarbons, and (B) organic phosphate esters.

The clinical signs of early poisoning by either the hydrocarbon or the organophosphorus compounds are not specific, and may be difficult to distinguish from an ordinary illness. The late signs of poisoning have certain characteristic features. Specific tests can establish the diagnosis of poisoning by the organophosphorus esters, e.g. depression of the blood cholinesterase, but in the chlorinated hydrocarbons it is in dicophane poisoning that a satisfactory test has been devised—the excretion of dichlorophenylacetic acid.

A. Chlorinated Hydrocarbons

1. *Dicophane* (*DDT, Chlorophenothane*)

This agent has been widely used as a slow-acting residual insecticide. Since certain insects, e.g. house flies and certain mosquitoes, have become resistant to this compound, other insecticides have been introduced.

Dicophane is poorly absorbed when applied to the body in solid form, but more readily when it is in solution. It is distributed in all tissues, but especially in fat, and is slowly and incompletely excreted in the urine as dichlorophenylacetic acid.

Wide individual variation in susceptibility to poisoning occurs in different animal species.

Acute poisoning in man. Dicophane is a 'cerebro-spinal poison', causing twitching of the eyelids, generalized coarse tremors and convulsive seizures, and death from respiratory failure, although heart failure due to ventricular fibrillation may also occur from sensitization of the mycoardium to hypothalamic sympathetic stimulation. In many cases the solvent has been the cause of toxic symptoms.

Treatment. The poison must be removed by gastric lavage if it has been swallowed, followed by the administration of a saline purgative and avoiding castor oil and oils or fats which promote absorption of the poison.

Phenobarbitone sodium is especially useful by subcutaneous injection, or orally, to control tremors and convulsions or other nervous symptoms, because of its selective depressant action on the motor cortex. If convulsions are severe pentobarbitone sodium is given intravenously.

Calcium gluconate injection (10 ml. of 10% solution) is given intravenously every 4–6 hours, as a nonspecific cell protectant.

Adrenaline injection must be avoided.

Control. During spraying operations with dicophane dermal exposure is much greater than respiratory exposure. A plastic cape, a hard hat with a plastic visor, and rubberized gauntlet gloves give a fully clothed man (with long-sleeved shirt and long trousers or overalls, and shoes) almost complete protection, and similar protection is afforded to other insecticides, e.g. dieldrin. For personnel working in the field, to whom the full covering with protective clothing may not be acceptable, consideration should be given to the use of a wide-brimmed, waterproof tropical helmet and plastic-netting veil with other appropriate clothing. Details are given by Wolfe *et al.*[16] The operator should stand as far as possible out of the spray drift. Hands and face should be washed before eating or smoking, and a daily bath with soap and water, and daily washing of contaminated clothing should also be strongly advised to workers. It is also important to keep the concentration of the suspension as dilute as possible.

Chronic poisoning. Repeated oral doses of dicophane were taken by volunteer men for periods up to 18 months; as much as 35 mg. daily, which is about 200 times the daily rate at which a man receives dicophane from his diet, did not produce any symptoms or signs of illness. This indicates a large safety factor with dicophane in the amounts occurring in the general diet.[13a]

2. *Gamma Benzene Hexachloride*

The gamma isomer stimulates the central nervous system.

Acute poisoning in man. Hyperirritability, muscular incoordination, clonic-tonic convulsions, and death may occur.

The delta isomer is a depressant of the central nervous system, while the alpha and beta forms produce some stimulation followed by depression. Technical benzene hexachloride is about equal to dicophane in acute toxicity to man, the gamma isomer being the most toxic fraction of the mixture; a dose of about 1 oz. of the mixture or ¼ oz. of the gamma form could be fatal to an adult.

Treatment. The measures used are the same as for dicophane poisoning. There is no specific antidote.

Control measures. See dicophane (DDT).

Chronic poisoning. The use of vaporizing and fumigating devices releasing this insecticide, for example as 'lindane', continuously day after day, has demonstrated that human beings can acquire sensitivity; angioneurotic oedema, urticaria, irritation of eyes and respiratory tract (tracheitis, asthma) have been produced, also more severe local effects, and possibly systemic effects such as polyneuritis and anaemia.[3]

3. *Toxaphene (Chlorinated Camphene)*

This potent insecticide belongs to the cyclodiene group, which also includes chlordane, dieldrin, aldrin, endrin, isodrin, heptachlor, all these being highly chlorinated cyclic hydrocarbons.

Toxaphene has a slow action, so that other agents must be used in contact sprays to ensure rapid knockdown of insects. It has been used as a substitute for dicophane.[2]

When in solution it is rapidly absorbed from the skin and other portals of entry into the body.

Acute poisoning in man. The symptoms are those of a convulsant drug affecting the brain and the spinal cord. Generalized epileptiform convulsions may occur as well as loss of consciousness and death in a few hours.

Treatment. The measures used are those described for dicophane poisoning.

Control measures. See dicophane (DDT).

4. *Chlordane*

This chlorinated hydrocarbon is a volatile liquid that has been widely used as a domestic and agricultural insecticide.[4,5] Commercial products contain a mixture of related compounds. In some fatal cases the effects have been complicated by the presence of other agents with pharmacological activity.

Chlordane is irritant to the skin (contact dermatitis) and mucous membranes. It is absorbed from the alimentary canal, respiratory tract and the skin. Preparations in the form of wettable powder have also proved toxic.

Acute poisoning in man. The symptoms are similar to those observed in poisoning by dicophane and other hydrocarbon insecticides, but are of longer duration. Irritability, salivation, laboured respiration, muscle tremors, convulsions and death may occur.

Nausea, vomiting, diarrhoea, and abdominal pain may follow the ingestion of toxic doses.

Blurred vision, cough, ataxia, confusion, delirium, and mania are further symptoms noted after inhalation and after absorption of poisonous amounts from the skin.

Symptoms may appear within 45 minutes after ingestion. Death may occur within 24 hours, frequently between 48 and 96 hours, from respiratory paralysis, but may be delayed for many days after a single oral dose. About 100 mg. per kg. of body weight of a technical mixture given orally has killed an adult.

Treatment. Poison should be removed from the skin with soap and water, or from the stomach by lavage, followed by a saline purgative, avoiding castor oil, fatty substances, and milk. A suitable barbiturate may be given, as in the treatment of dicophane poisoning.

Control measures. See dicophane (DDT).

Chronic poisoning. There may be disturbances of the central nervous system and particularly the optic nerve. Albuminuria may be produced.

5. *Dieldrin*

This agent has been used in insecticidal sprays in houses and in the field, e.g. in malaria campaigns. It is significantly more toxic than dicophane so that there is greater hazard to the operators of spray equipment. Absorption may occur from the dermal, oral, and respiratory routes. Dry dieldrin is absorbed from the skin about as easily as dieldrin in solution, in this respect differing considerably from dicophane.[15] Detailed studies of the exposure of spray-men and the hazards have been reported by Fletcher *et al.*[10,13b]

Acute poisoning in man. Giddiness and headache occur, and twitching of muscles, followed by epileptiform convulsive seizures one to several times a day or night, with loss of consciousness, lasting up to 2 hours. Mental disorder ranging from loss of memory, insomnia, and nightmares to mania have also occurred. In some cases the first convulsion occurred 15–20 days after the last exposure, perhaps due to deposition of the poison in the body and its release or activation later under conditions of stress. A recent report on poisoning was made by Patel and Rao.[14]

Treatment. Immediate washing of contaminated skin gives some protection, and other general measures are adopted. When a person has had dieldrin poisoning he should be taken off work with that insecticide, and should be examined medically for at least 2 years.

Control measures. Hands, face, and all exposed skin should be washed at frequent intervals, even though no contamination is visible, and the entire body washed with soap and water at the earliest practical moment after the day's work. Working clothes should be washed daily with soap and water. The spray-men should wear shoes and socks and a protective uniform which includes a veil of plastic netting, as described under dicophane.

B. Organic Phosphate Esters

These agents, for example parathion (thiophos) have a potent and prolonged anticholinesterase action; they are cholinergic. They are among the most toxic agents used for pest control, for instance by fruit growers and in agriculture.[1] They may be absorbed through the skin, respiratory tract, conjunctiva, and the alimentary canal. Absorption through the skin, and death, have resulted from splashes of the liquid on the skin not being removed immediately.

The symptoms are due to the inactivation of the enzyme cholinesterase, with resultant widespread effects: stimulation of the post-ganglionic parasympathetic activity, depolarization of skeletal muscle, and initial stimulation followed by depression of the central nervous system. Respiratory failure is due to broncho-constriction, neuromuscular block, and central action.

Acute poisoning in man. The principal early features may be grouped in 3 categories:

(*a*) Muscarinic symptoms: sweating, salivation, lacrimation, visual disturbances (including constricted pupils), gastro-intestinal hyperactivity, nausea, vomiting, abdominal pain.

(*b*) Nicotinic symptoms: muscle tremors in the eyelids, tongue, face and neck, followed by weakness and incoordination. The symptoms may not appear until the work is finished.

(*c*) Central nervous symptoms: early features are headache, giddiness, apprehension, and later (in severe poisoning) ataxia, confusion, speech difficulty, convulsions, severe respiratory and circulatory signs, and coma.

The acute effects last 6–30 hours, but headache, giddiness, and weakness may persist for 48–72 hours, occasionally for as long as 3 weeks after exposure. In some subjects the small pupils may not return to normal size for 3–6 weeks. The average interval between last exposure to parathion and death has been 10½ hours, and between the onset of symptoms and death 9 hours.

The diagnosis can be established by estimation of the blood cholinesterase. A convenient field kit has been devised for making the test.[9]

Treatment. The victim must be withdrawn from exposure to the insecticide. Nothing should be given by mouth to unconscious patients. Respiratory depressants should not be administered, for example morphine and barbiturates. A free airway must be maintained, and artificial respiration may be needed for many hours with administration of oxygen. Pulmonary secretions are removed by postural drainage or by suction with a catheter. Washing the skin thoroughly with soap and water, irrigation of the eyes, gastric lavage, and a saline purgative are other measures that may be indicated.

Antidotes must be given as soon as possible, e.g. (*a*) atropine sulphate, 2 mg. by intramuscular injection and repeated every 15–30 minutes, as necessary, is given to antagonize the poison, and (*b*) pyridine-2-aldoxime methiodide (2-PAM) 1–2g. (in 5% solution) is given by intravenous injection. Consciousness is restored, muscle fasciculations are stopped, and other symptoms are relieved. This drug is generally regarded as a specific anticholinesterase inhibitor, i.e. it reactivates the inhibited cholinesterase,[7,11] but this may not be the only action.[6]

Chronic poisoning. The inhibition of cholinesterase by the phosphate esters lasts 4–6 weeks, as determined by a decrease in the blood cholinesterase. Therefore, absorption of small amounts daily may eventually produce symptoms. The symptoms may then resemble those occurring in acute poisoning, but delayed weakness and paralysis of the extremities may occur (ankles and wrists) and loss of reflexes, and this may progress also to involve the respiratory muscles.

Control. Prophylactic measures must minimize absorption (*a*) from the skin—by clean protective clothing, bathing each day after work, and change to uncontaminated clothing; (*b*) from the respiratory tract—by adequate exhaust ventilation, or by wearing comfortable face-masks or respirators; (*c*) from the gastro-intestinal tract—by removal of protective clothing and thorough washing of the hands before eating, drinking, or smoking; and (*d*) by destruction or decontamination of containers and spilled material.

Strict supervision is necessary by foremen and supervisors.

Medical supervision should include routine medical examination at (weekly) intervals.

Periodic determination of the cholinesterase of the blood plasma and red blood corpuscles will help to prevent cumulative effects in those frequently exposed to these insecticides. Those with reduced cholinesterase activity should be removed from all exposure until this has returned to normal; this may take several months as the enzyme activity returns at the rate of about 1% a day.[8]

GENERAL CONTROL MEASURES TO PREVENT POISONING

1. *Education.* The dangers of poisoning by insecticides must be publicized through newspapers, magazines, films and over the radio.

Poisons should be stored in well-marked containers under lock and key. Empty containers should be burned to destroy residual poison.

2. *Stringent laws.* Proper precautionary labelling must be enforced with warnings on labels in non-fading ink (including skull and cross-bones) and information about the active ingredients, the solvent, and the antidote.

3. *Poison centres* should be established throughout the country, according to local needs and facilities in towns and cities.

4. *Cooperation of pharmacists and physicians.* At a local level they should assist in educating parents, with leaflets, pamphlets, and displays. Local doctors should be provided with information on the pharmacology of toxic agents in use and the methods used in the treatment of poisoning.

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