Toxicity of Insecticides to Humans

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Introduction

To date, entomologists have estimated the identification and description of some 625,000 to 1,500,000 species of insects (22). Out of this gargantuan group some 600 species are considered injurious to man, his crops and animals, with less than 100 species responsible for an annual economic loss in the United States of 4 billion dollars (7).

Today we are fortunate to have a wide variety of insecticides from which to choose when an attack upon insects is anticipated. Recently THE JOURNAL OF ECONOMIC ENTOMOLOGY published a list of common insecticide names that are to be used in the JOURNAL (8). The list is confined to organic compounds and does not mention the commonly used botanicals and inorganics. Nevertheless, 80 compounds are listed and testify to the impetus of present day insecticide development. I would estimate that approximately 35-40 insecticides of all types are commonly used in American agriculture and pest control, while the charmed circle of materials probably numbers near 25.

This paper will deal with the better known toxicological aspects of commonly used insecticides. No attempt is made to cover the entire field. Rather, specific groups of materials will be discussed.

Past, Present and Future Outlook

The original discovery of toxic compounds was one of chance performed long before the time of written history. Early man stumbled upon minerals and plants capable of inactivating his animals or harming himself and soon learned to utilize them for profit. For unknown centuries his target was not insects, but political foes, husbands, wives and others who might be profitably removed. Poisoning people became an accomplished profession in the classical period of Greek history and progressed through the ages as a commonplace practice until 1846, when Marsh announced a chemical test for arsenic. Several plant poisons were used over the ages but arsenic was called king of the poisons. Arsenic was effectively used by the notorious Italian Borgias. The Borgias are said to have prepared their poison, called "The Gift of the Borgia", by mixing arsenic with ptomains as follows: "A hog was killed with arsenic. Its abdomen was opened and sprinkled with more of the same drug. The animal was then allowed to putrefy. The liquor which trickled from the decaying carcass was collected and evaporated to a powder" (16). This made an extremely efficient poison.

In the late 1800's the arsenicals appeared as insecticides and were recognized as London Purple, Paris Green, lead and calcium arsenate, and other compounds of arsenic. Then, as now, the arsenicals are considered excellent stomach poisons. Concurrent to the development of the arsenicals was that of the plant poisons which have served as contact poisons.

Considerable change has been apparent since the development of our present organic insecticides. These materials generally act as both stomach and contact poisons and often are fumigants as well. New problems of acute and chronic toxicity have accompanied the organics but their benefits have more than offset the problems. Compounds developed during the last ten to fifteen years offer broad range insect control, or specificity, as dictated by the choice of the user.

Economic considerations coupled with the desires and needs of a consuming public will serve as guideposts to the development of new insecticides. Inasmuch as we have several excellent broad range insecticides available today, I should imagine that a good number of the future insecticides will be highly specific and incorporate great safety to the user. Certainly low mammalian toxicity aspects of any new insecticide will weigh heavily in its development.

Discussion

Excluding nicotine, most poisons derived from plants and used as insecticides are considered innocuous to warm blooded animals. Insecticides prepared from plants are nicotine, rotenone, pyrethrum, sabadilla and ryania.

Nicotine is a rapid, violent poison to warm blooded animals either through oral intake or skin absorption. When combined with sulfuric acid to form nicotine sulfate it is considerably safened. Acute nicotine poisoning is characterized by hot burning sensations in the mouth, esophagus and stomach and is followed by salivation, nausea, vomiting and convulsions. Paralysis of the respiratory muscles results in death. Chronic poisoning effects are those of inanition (13). The approximate acute oral LD_{50}[1] toxicity to rats is 50-60 mg./kg. (6).

Suggested treatment for nicotine poisoning due to ingestion is stomach lavage with strong tea or coffee and administration of charcoal or permanganate to detoxify the nicotine. Artificial respiration and oxygen should be administered to maintain breathing (13). Treatment is only necessary for a few hours to a day or two due to rapid detoxification.

Respiratory failure is the most important action of rotenone and pyrethrum on warm blooded animals. Large dermal applications of the two materials have failed to produce fatal results. It would appear that only large oral doses can be fatal to man. Symptomatic treatment is suggested for rotenone, while gastric lavage is suggested for oral ingestion of pyrethrum solutions (to remove the solvent, often kerosene) (13). Approximate acute oral LD_{50} toxicities to rats are: rotenone 132 mg./kg. and pyrethrum 200 mg./kg. (14).

Arsenic compounds act as general poisons to protoplasm and exhibit their effect when water soluble arsenious or arsenic acid is formed. Arsenicals may be toxic when absorbed through the skin or orally ingested. Symptoms of lead arsenate poisoning are those of lead poisoning and the treatment is that recommended for lead poisoning. Charac-

1. Indicates quantity of poison needed to kill 50 percent of a test group.

teristics of acute arsenic poisoning due to ingestion in warm blooded animals are severe diarrhea with a marked loss of body fluids and electrolytes and a consequent damage to vital organs. Death generally occurs in one or two days following an acute poisoning (20). Approximate acute oral LD_{50} values to rats of the two most commonly used arsenic compounds follow: lead arsenate 100 mg./kg. (14), calcium arsenate 20 mg./kg. (14). Indicated treatment includes gastric lavage with large quantities of warm water, saline laxatives and castor oil. Physician in attendance may administer BAL.

DDT has been under investigation as an insecticide since 1939 and has been commercially used in this country since 1946. DDT is produced in greater tonnage than any other insecticide and a good picture of its toxicological effect on vertebrates is known.

"Acute poisoning in man is that expected from the observation of such poisoning in laboratory animals. An early symptom is paresthesia of the lips, tongue and face. Later dizziness and weakness are noted. There is apt to be numbness, tingling and hyperesthesia in the extremities. Tremors about eyelids and face spread to the trunk and extremities; nausea and vomiting may or may not occur. This prodrome is followed (within an hour if the dose is sufficiently large and rapidly absorbed—as from a digestible oil) by a tonic and then a clonic convulsion of a few minutes duration. A period of relaxation with prostration and labored breathing is followed by another convulsion. The cycle repeats itself (a few times only in large doses) until death, recovery, or control by anesthesia or sedation occurs" (15). Except in extremely serious cases of accidental ingestion or when DDT has been taken with suicidal intent recovery becomes apparent and is well advanced in twenty-four hours. An exception is an instance where three persons each ate 20 grams of DDT and exhibited weakness in the hands for five weeks (10). Approximate acute oral LD_{50} value of DDT to rats is 250 mg./kg. Approximate single dermal exposure (24 hours) LD_{50} value of 30% technical DDT to rabbits is above 2820 mg./kg. (14).

"There is no specific antidote for chlorinated hydrocarbon insecticide intoxication and there are no clinical laboratory findings which contribute to the diagnosis (19)." However, suggested treatment for ingested DDT recommends removal of stomach contents by inducing vomiting followed by stomach irrigation. Saline cathartics may be employed. Barbiturates should be used in adequate quantity to control convulsions (19).

DDT is generally considered a safe insecticide to use. No well described case of fatal uncomplicated DDT poisoning is known. Also, no case of chronic DDT poisoning in man has been confirmed. (9). Quantities as high as 285 mg./kg. have been taken by man without fatal results (5) and human volunteers have ingested 0.5 mg./kg. per day for prolonged periods without illness (10). Man is known to store DDT in his adipose tissue, detoxify it in his liver, and slowly excrete it through his urine (6). DDT produces definite histological changes in the liver (10). DDT, in solution, may be absorbed through the skin, respiratory

system and gastro-intestinal tract and is generally considered most hazardous when the solution is of an oily nature.

From a study conducted in a restaurant and institution it was found that an average meal contains 0.31 ppm of DDT (dry weight) and that an average man eats 0.0026 mg./kg. of DDT per day (15). Studies such as the one just mentioned have caused alarmists, such as Biskind (1), to freely criticize the use of DDT and suggest it responsible for recent increases in several diseases of man and animal. No experienced worker in the field supports his views. On the other hand, Hayes, U. S. Public Health Service, feels no hazards exist in our national health scene from present day use of DDT (10). The American Medical Association refutes Biskind's claim in a recent editorial:

"In the light of recent reports, Biskind's claim that the facts regarding chlorophenothane have been concealed, suppressed, denied, and distorted no longer holds true. Too many persons are willing or eager to attribute an increase in certain illnesses or an otherwise unexplainable death to an exposure to some new chemical hazard without matching the patient's signs and symptoms with the known effects of poisonous doses of the chemical or determining the degree of the patient's exposure. Under the current administrative setup, the Department of Agriculture discusses the hazards of handling all new insecticides with the Public Health Service and requests the Food and Drug Administration to evaluate the hazards resulting directly or indirectly from residues on foods. In the case of chlorophenothane, it is safe under ordinary conditions of legitimate use and definitely safer than such insecticides as arsenic, nicotine, and sodium fluoride" (6).

Other chlorinated hydrocarbons vary considerably in their toxicity to man and most are more toxic than DDT. Multiple dermal exposures constitute the most serious hazard involved with their use. Poisoning symptoms appear closely allied to DDT and treatment depends on the use of symptomatic measures. Some toxicity values of the other chlorinated hydrocarbons are presented (14).

	Acute oral Approx. LD_{50} mg./kg. rats	Dermal (Single Exposure—24 hrs.) Approx. LD_{50} mg./kg. rabbits	in dimethyl
Methoxychlor	6000	above 2820 (30% Tech.)	phthalate
Chlordane, technical	457	below 780 (20% Tech.)	phthalate
Lindane	125	above 188 (2% Tech.)	phthalate
Toxaphene	69	below 780 (20% Tech.)	phthalate
Aldrin	67	below 150 (4% Tech.)	phthalate
Dieldrin	87	below 150 (4% Tech.)	phthalate

The organic phosphates represent the newest important group of insecticides. A number of them have been commercially used since the end of World War II. Considerable research energy has been devoted to this group in an effort to develop materials of high insect toxicity and versatility. Great differences exist in the structure and physical proper-

ties of the organic phosphates manifested by differences in volatility, toxicity to warm blooded animals and residual action. The common denominator of the group is cholinesterase inhibition. A large number of phosphate compounds are in use or under development. Principal materials of commercial significance are parathion, TEPP, EPN, Systox (demeton) and malathion.

Early symptoms of parathion poisoning in man are: nausea, headache, abdominal cramps, lacrimation, salivation, giddiness, sweating and blurring of vision. As poisoning advances muscular weakness, diarrhea, vomiting, tightness of the chest and contracted pupils occur. Late stage symptoms are muscular twitching, prostration, pulmonary congestion, convulsions and coma. In the great majority of cases symptoms of parathion poisoning generally appear 2-3 hours after the last exposure and rarely after six hours. If an interval of twelve hours or more exists between the last exposure and symptoms the case is certain to be something other than parathion poisoning. An efficient antidote for poisoning is atropine sulfate. First aid treatment to victims of parathion poisoning indicates immediate administration of two atropine tablets (each 1/100 gr.) orally. If the patient is unable to swallow or retain stomach contents he may dissolve atropine tablets under his tongue. If a physician has not arrived in one hour atropine tablets should be administered again. If the toxicant has been swallowed vomiting should be induced by giving warm salty or soapy water. Contaminated clothing should be removed and the patient's body washed with soap and water. Artificial respiration should be practiced if difficult breathing is apparent. Hospital treatment following first aid steps includes further use of atropine in quantities five to ten times larger than the average therapeutic dose, keeping the patient fully atropinized, the use of oxygen as required and removal of secretions from the respiratory system by aspiration. The acute emergency lasts from one to two days and the patient must be closely observed during this period (9). After recovery from poisoning the patient should avoid exposure to all phosphates until his red blood cell cholinesterase level has returned to normal. He will remain susceptible to small quantities of phosphates until regeneration of red blood cell and tissue cholinesterase is completed. This may be as long as three months (9). Any susceptibility to phosphate poisoning is completely lost after the cholinesterase level returns to normal (19).

Phosphate insecticides may enter the body in quantities sufficient to be toxic through skin absorption, oral ingestion or inhalation of dusts or aerosols. Most poisonings are the result of skin exposures. Considerable debate has focused on the inhalation hazard of parathion. Hazleton reports the inhalation of particulate matter such as dusts and aerosols as highly toxic, but doubts the hazard of vapor toxicity (11). Extensive studies of parathion in the body indicate it is not stored in the tissues, fat or blood (11). It is not passed through milk (11). Hazleton has reviewed the work of several authors that indicate the molecule is detoxified by splitting off the aromatic nitro group which is then in the urine as p-aminophenol and p-nitrophenol (11). Sensitive tests for measuring cholinesterase in human blood have been developed which

serve to warn individuals of the possibility of forthcoming poisoning prior to the appearance of symptoms. To be of value determinations must be made prior to exposure and at regular intervals during exposure. These tests are strongly advocated wherever parathion is handled.

Two extremes of toxicity to man are represented by TEPP and malathion. The only pharmacological action of both compounds is that they inhibit cholinesterase and yet are vastly different quantitatively. TEPP is the most toxic phosphate insecticide used in agriculture and is extremely unstable in the presence of moisture. Its hazard to man is one of single applications or repeated small exposures. No residue hazard exists on treated crops. Malathion is the least toxic phosphate insecticide to human beings commonly used in agriculture and is considered a relatively weak cholinesterase inhibitor. To date no authenticated case of malathion poisoning has been reported. OMPA (Schradan) is an organic phosphate of the systemic class of insecticides designed to enter plant tissues and fluids and poison insects attacking them. In vitro, OMPA is not a cholinesterase inhibitor but must be metabolized before active cholinesterase inhibition is shown (11). The liver of mammals (12) and various insect organs accomplish the metabolism of OMPA (3).

Some toxicity values of representative organic phosphate insecticides are presented (14).

	Acute Oral Approx. LD_{50} mg./kg. rats		Dermal (Single Exposure—24 hrs.) Approx. LD_{50} mg./kg. rabbits
Malathion (95% tech.)	2103	(Hazleton)	12,300 (Guinea pigs)
Demeton	19		24 (Monsanto)
EPN	14.5		30–50 (Undiluted tech.)
Parathion	3		40–50 (Undiluted tech.)
TEPP	1.2		5 (Undiluted tech.)

Sulfur is considered non-toxic to humans. The insecticidal oils, organic thiocyanates in concentrations normally used and specific acaracide compounds, such as Ovotran, are of low toxicity to vertebrates. The dinitro compounds, such as DNOC and DNOCHP, are toxic to man and have been shown to accomplish poisoning by materially increasing metabolic activity and oxygen consumption (17).

Materials which exhibit insect control by highly effective gases are called fumigants and are generally used in specialized situations. A large number of fumigants are recognized with HCN (Hydrocyanic acid or hydrogen cyanide) and methyl bromide being two of the better known.

HCN is a colorless gas at room temperature. It is used in several forms, among those being: as a liquid supplied from steel cylinders, and in a granular or dust form of calcium cyanide that evolves HCN upon contact with moisture in the air. Calcium hydroxide is the residual material left after the HCN has been liberated from the calcium cyanide. Hydrogen cyanide is extremely toxic to warm blooded animals and may be fatally inhaled or absorbed through the skin. It is rapid in action and may cause poisoning without warning symptoms. Symp-

toms that may appear are vomiting, giddiness, faintness, respiratory stimulation followed by depression, convulsions and coma (21). In man, hydrogen cyanide combines with the oxidated enzymes of the blood and prevents body tissues from utilizing oxygen (2). First aid to victims of cyanide poisoning should be prompt and the administration of proper treatment can reverse poisoning in a matter of minutes (21). This involves the conversion of cyanide into a cyanmethemoglobin by inhaled or intravenous nitrites and the oxidation of cyanide to the thiocyanate by intravenous use of sodium thiosulfate (21).

Methyl bromide is a colorless gas at room temperature and is used from sealed containers. It is sprinkled or sprayed or propelled from cans by carbon dioxide. Methyl bromide is toxic to man and inhalation should be avoided. Considerable attention should be directed to safe use of methyl bromide as poisoning is cumulative and symptoms may not manifest themselves for days or several months after exposure (17). Symptoms to man from mild poisoning are headache, double vision, disturbance of equilibrium, dizziness and giddiness. Advanced symptoms of delerium, convulsions and loss of consciousness precede death (2). Two theories exist on methyl bromide's mode of action to warm blooded animals. One contends methyl bromide is converted in the body to methyl alcohol and a bromine salt with the methyl alcohol acting as the toxicant. The other theory suggests methyl bromide as the toxicant itself (18).

Any material capable of controlling insects presents a potential hazard to human life. A great deal of publicity and education on safe handling of insecticides has been done by agricultural advisors and manufacturers. To date, most accidents involved with insecticides in agricultural use have been the result of carelessness, gross neglect or lack of concern for others. It is unfortunate that fatal accidents to careless insecticide users not only take their lives, but create a number of unfavorable press releases that often misinform our consuming public. Sensationalism and notoriety always seem to attach themselves to such accidents. Careless insecticide users jeopardize our modern insecticides by casting a shadow of doubt over the justification of their use.

Individuals are responsible for their own safety and the safety of helpers when using insecticides in agriculture or pest control. Insecticide manufacturers insure the safety of employees by demanding strict industrial hygiene appropriate to the material being produced.

Government and state agencies attempt to protect the health of the consuming public by recommending materials, their application and timing, and limiting the amount of a toxicant that may remain on an edible crop at harvest. It is apparent that the individual responsible for the application of a toxicant is charged with the maintenance of his own health and that of his helpers.

Careful observance of insecticide labels and manufacturers' directions should always be considered a must by the user of insecticides. Generalized safety rules worthy of perennial practice are: avoid skin contact with or inhalation of insecticide dusts or sprays; do not eat or smoke while applying insecticides; always wash spilled insecticides from

body and clothing; wear protective clothing and a respirator when using highly toxic materials; always wash before eating; spray or dust so that the insecticide drifts away from the operator; destroy insecticide containers; advise others of the materials being used; be aware of first aid procedures to be followed should poisoning occur. When poisoning is suspected consult a physician and advise him of the material or materials used.

The public benefits from the use of insecticides in the form of better food, clothing, shelter and health. Mass studies of various areas where insecticide use is heavy have been made and show no deleterious public health picture attributable to insecticides. One such study was made in the Mississippi Delta by Fowler (4) where some authors (1) had attributed an increased incidence of many diseases to heavy insecticide use. After considerable study it was concluded that pesticides could not be found directly or indirectly responsible for the incidence of disease (4). A study of orchardists in the state of Washington by Sumerford (23) supports Fowler's work.

Fatal accidental poisonings due to agricultural pesticides are comparatively few in number compared with other commonly available toxic materials. During 1950-1952 there were 277 fatal accidental poisonings among industrial policy holders of the Metropolitan Life Insurance Company (exclusive of Pacific Coast and Canada) (24). This total broken down appears as (24):

Barbiturates	84
Drugs and Medicine (except barbiturates)	67
Alcohols	57
Unspecified	19
Petroleum Products	16
Lead	13
Insecticides and Rodenticides	11
Alkalis and Acids	10

Insecticides will continue to present health hazards to users as long as powerful and efficient compounds are available to work with. A sensible evaluation of the ramifications involved when handling them will keep poisonings at a minimum.

Common names and abbreviations are referred to frequently. Chemical names of the compounds are listed:

DDT—1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane.

CHLORDANE—1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-meth-anoindene.

LINDANE—gamma isomer of 1,2,3,4,5,6-hexachlorocyclohexane of not less than 99 per cent purity.

TOXAPHENE—$C_{10}H_{10}Cl_8$ chlorinated camphene having a chlorine content of 67-69 percent.

METHOXYCHLOR—1,1,1-trichloro-2,2 bis(p-methoxyphenol)-ethane.

ALDRIN—not less than 95 percent of 1,2,3,4,10,10-hexachloro-1,4,4a,5,
8,8a-hexahydro-1,4,5,8-dimethanonaphthalene.

DIELDRIN—not less than 85 percent of 1,2,3,4,10,10-hexachloro-6,7-
epoxy-1,4,ra-5,6,7,8,8a-octahydro-1,4,5,8-dimethanonaphthalene.

PARATHION—0,0-diethyl 0-p-nitrophenyl thiophosphate.

TEPP—tetraethyl pyrophosphate.

EPN—0-ethyl 0-p-nitrophenylbenzenethiophosphonate.

DEMETON—mixture of 0,0-diethyl-S-ethylmercaptoethyl thiophosphate
and 0,0-diethyl-0-ethylmercaptoethyl thiophosphate.

MALATHION—0,0-dimethyl dithiophosphate of diethyl mercaptosuc-
cinate.

OMPA (Schradan)—octamethyl pyrophosphoramide.

OVOTRAN—p-chlorophenyl p-chlorobenzenesulfonate.

DNOC—4,6-dinitro-0-cresol.

DNOCHP—4,6-dinitro-0-cyclohexyphenol.

HCN—hydrocyanic acid or hydrogen cyanide.

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