Toxicity and Health Aspects in the use of Insecticides

Ministry of the Environment

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TOXICITY AND HEALTH ASPECTS IN THE USE OF INSECTICIDES

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PREFACE

The control of crop-destroying insects has always been necessary to protect man's food supply, but even more so now, with the world's population growing by leaps and hounds. This need has given rise to the development of powerful chemical pesticides. Because of the necessarily toxic nature of these substances, safety is of major importance in their use.

There is an obvious need for chemical pesticides in Canada. Although research on the subject is being carried out, at the moment there is no other means of adequately controlling most of the insects and growths that take a heavy annual toll of our country's agricultural production. Even with the use of pesticides, we are still faced with the loss of large amounts of Farm produce.

Pesticides are used mainly to agriculture to protect crops and livestock. They are used by people, in the city as well as the country, to protect their health, comfort and property. Without pesticides our well-being and the national economy would suffer.

At the same time, if they are not properly used, pesticides can be dangerous to humans, domestic and farm animals, beneficial insects and wild life. However, they can be safe if used for their prescribed purpose and in the proper amounts, as directed by competent authorities.

J.G.K.

INSECTICIDES IN PUBLIC HEALTH

Some of the most dramatic and important uses of pesticide chemicals are in guarding public health.

Millions of people are alive today because of the use of pesticides in suppressing insects and rodents which transmit diseases such as malaria, typhus, yellow fever and encephalitis. Over a ten-year period, according to one estimate, the use of DDT throughout the world saved some 5 million lives and prevented 100 million illnesses.

Reports from the World Health Organization and other public health groups point out the health progress made possible in India, Asia and South America by chemical control of the malaria-carrying mosquito and typhus-carrying body louse. We are less likely to remember the lives which are being saved right here in our own country through chemical control of spotted fever ticks and rat fleas, which carry bubonic plague and murine typhus. Chemical pesticides are also vitally important to public health sanitation, which helps keep our homes, farms and businesses free of disease carriers such as rats, mosquitoes, cockroaches and flies.

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It Can Happen Here

The successful control of the encephalitis (sleeping sickness) outbreak in the United States in 1962 served as a reminder of how dependent we are on the use of chemical pesticides for public health in Canada. Problems of this nature indicate that these epidemics do not occur only in other parts of the world. Equine encephalomyelities, for example, has become a human disease. Transmitted by mosquitoes, this disease has affected thousands of people in Canada and the northern United States in recent years.

Chemistry Contributes To Pest Control

In the past, before the development of the newer insecticides, the destruction caused by insects was as great all over the world as it is seen today in underdeveloped areas. Vivid descriptions of the depredations of locusts and other insects appear in the writings of ancient Greece, the Bible, and the legends of people all over the world. It was not until man began to use insecticides that he had any real success in his never-ending war with his chief competitor for food - the insect. Early insecticides included sulphur, the dried flower of the pyrethrum daisy, the powdered root of the derris plant, whale oil, soap, kerosene, Bordeaux mixture and Paris green.

By the early 1900's, an agricultural chemical industry began to meet the demand for more effective insecticides. Some of these new products came from the chemical industry, some from the gas industry and some from the rapidly developing petroleum industry. Arsenic compounds were widely used. Hydrogen cyanide proved very effective against scale insects, and sulphur dioxide came into use to fumigate stored grains.

The big break-through in the control of insect pests came in the early 1940's.

At that time the new synthetic, or man-made, organic chemicals were put to use in war-torn and pest-ridden areas to save human lives by killing such disease-transmitting pests as ticks, lice and mosquitoes. Among the earliest and most widely known of these synthetic insecticides was DDT. It reached the headlines of the world's newspapers in 1944 when it was used to stop a typhus outbreak in Naples, Italy. Since that time it has been used to combat ticks, fleas, mosquitoes and other disease-carrying insects all over the world. Other synthetic insecticides quickly followed and, like DDT, have proved to be as effective against crop-destroying pests as they are against disease-carrying insects.

Insecticides' Side Effects

Often when a new chemical is put to actual use an effect other than the one intended is discovered. Laboratory research and field testing cannot always provide information on what a chemical's total impact will be. Such is the case with insecticides. Many insecticides are toxic to beneficial species of animals and insects. If these species are destroyed by the improper use of insecticides, a pest problem more serious than the original one may be created. For instance, crop production in some cases has been hindered by the loss of necessary pollinating insects.

Drift is a problem in both the ground and aerial application of insecticides. Under certain conditions, the chemicals can spread over many miles from the site of application. Care must be exercised in choosing the physical form and quantity of insecticide used, the method of application and the prevailing weather conditions. Indiscriminate use of insecticides can cause injury or death to wildlife and fish, or interfere with their natural functions.

Environmental Pollution

Environmental pollution refers to <u>unwanted</u> insecticide chemicals in air, soil, water and vegetation - insecticides which damage desirable species of animals and

plants. In a broad sense, it can also include the accumulation and storage of insecticides in animals and plants.

Small quantities of insecticides are often added to natural bodies of water to control aquatic organisms such as trash fish, mosquito larvae, gnats, algae, snails and weeds. Water pollution can result from the use of excessive amounts of insecticides for this purpose or from the unintentional addition of insecticides through drift, drainage from treated areas, or accidental application over water bodies.

The absorption of insecticide chemicals in relatively low concentrations by the smaller aquatic organisms is complicated by a natural phenomenon known as "biological magnification". When an insecticide proceeds through the food chain - as predator feeds upon predator - the concentration of contaminant is increased.

The more persistent insecticides can remain in the soil for a number of years, thus affecting our ecosystem. Since many of these substances have long active life spans, one careless application can pollute the atmosphere, a stream, or a field for a long time.

How Insecticides Work

When used as insecticides, pesticide chemicals operate in a number of different ways to protect plants from pests. It is important to remember that these pesticides, by and large, are poisonous: they can be used as they are because of a specific high toxicity to insects or because the manner of use can be controlled so as to avoid excessive exposure of man and animals. The following are the ways in which these pesticide chemicals work:

Stomach Insecticides

With this type of insecticide, the insect pest consumes the toxic material while

eating a part of the growing plant. Stomach insecticides are usually sprayed or dusted on the crop for protection from chewing insects such as caterpillars and grasshoppers. Arsenicals and chlorinated hydrocarbons are widely used as stomach insecticides.

Contact Insecticides

Stomach poisons are of limited use against insects such as aphids and mosquitoes which are nourished by sucking liquid from plant or animal tissues. Contact poisons, however, are effective if sprayed or dusted directly on the insect or on a surface upon which the insect will crawl. Nicotine, pyrethrum, and derris are widely used as contact poisons.

Unfortunately, most of these natural substances are effective for only a short period and can be easily washed from the surface upon which they are applied. (Rotenone, obtained from derris, is effective for several days.) Contact insecticides kill insects which they reach, but usually do not remain on the plant long enough to kill insects that come later.

Insecticides Which Work In Several Ways

Other insecticides, such as DDT, chlordane and BHC (benzene hexachloride), act on insects in many ways. These insecticides destroy pests which consume them, touch them, or breathe their vapours. Many of these new synthetic insecticides have the added advantage of remaining on the surface to which they are applied for a relatively long time. Thus, a single application can protect the plant for an extended period.

Systemic Insecticides

The pesticide industry has recently developed materials that act after absorption into the plant instead of by direct chemical action. These materials can be absorbed through the roots after application to the soil, or they can be absorbed through the

leaves. In either case, they protect the plant for extended periods of time, killing insect parasites whether they eat the plant substance or suck the plant juice.

Comparable systemic insecticides are available for use on animals. These insecticides, when fed to the animal or injected into its bloodstream, destroy the insects which attack it. For example, they can kill cattle grubs without harming the steer, its meat, or its hide. Similar systemic insecticides can kill the fleas which plague dogs.

Chemical Sterilants

The latest phase in the progressing science of insect control is the development of steroids and other types of chemicals that make insects sterile. This method strikes at the insect's most effective weapon - its tremendous capacity for reproduction.

A variant of this method of insect control involves the release of sterilized male insects to breed with females, which then lay sterile eggs. Chemosterilants and the sterile male technique not only affect the reproductive capacity of insects, but also greatly reduce their ability to develop resistance to chemical control.

Attractants and Repellents

Attractants are a kind of scientific flypaper. They are used to lure insects or rodents to selected locations where they can be caught, sterilized or killed. The use of attractants to interfere with the normal reproduction of insects offers the promise of drastic reductions in numbers and of more effective control.

Repellents are chemicals which drive insects and other pests away from treated objects. Man has used materials like these for years, on both skin and clothing to drive away flies, mosquitoes, gnats and other insects.

TOXICITY

Interpretation Of Toxicity

Any compound can be toxic if it is absorbed to an excessive degree. The simplest way of expressing a compound's toxicity is by means of its LD_{50} value. This represents the lethal dosage necessary to kill 50% of a very large population of test animals under stated conditions (for example, a single oral dose of aqueous solution). LD_{50} values must be interpreted with care, however, because of certain limitations to the test, discussed below.

First, the health hazard presented by a compound depends more on the way it is used than on its degree of toxicity. In Canada, the majority of fatal and non-fatal poisonings caused by pesticides involve materials which are not very poisonous, but they are available to a great number of people and are sometimes used carelessly. This fact does not lessen the tragedy of needless injury.

Second, it is known that toxicity varies with the age, sex and health of the animals tested, the nutrition They have received, the formulation of the poison, and the route of administration. By necessity, the LD_{50} values are expressed for animals. They can be applied to humans only with great reservation.

Third, an LD_{50} value is a statistic which, in itself, gives us information on the dosage that is fatal to only half of a large test group of animals.

Fourth, LD_{50} values are usually expressed in terms of single dosages only. Thus, these values give little or no information about the possible cumulative effects of a compound.

In spite of these necessary qualifications, LD_{50} values are useful in making objective comparisons of the inherent toxicity of different compounds. Some materials

are so toxic that exposure of the skin to a few drops is sufficient to produce poisoning. Other compounds are harmless enough that a small dose may be ingested without causing any harm.

As a very general guide, the probable lethal single oral dose for a grown person (154 pounds), compared with corresponding metric figures for test animals, can be estimated as follows:

Acute Oral LD_{50} For Any Animal (Mg of Substance Per Kg. Body Weight)	Probable Lethal Oral Dose Technical Material For Human Adult
Less than 5 mg/kg	A few drops
5 - 50	A pinch to 1 teaspoonful
50 - 500	1 teaspoonful to 2 tablespoonsful
500 - 5,000	1 ounce to 1 pint (1 pound)
5,000 - 15,000	1 pint to 1 quart (2 pounds)

TYPES OF TOXICITY

Introduction

Toxic materials may gain entry to the body by:

(1) Eating - This is termed ingestion or oral toxicity.

(2) Breathing - This is termed respiratory or inhalation toxicity.

(3) Skin Contact - This is termed percutaneous or dermal toxicity.

(4) Injection - This is termed parenteral toxicity and is investigated only under experimental conditions. Toxic effects may be described as follows:

(i) Acute - Poisoning produced by a single large dose or exposure.

(ii) Chronic - Poisoning produced by repeated small doses or exposures.

(iii) Subacute - Intermediate between acute and chronic poisoning.

(iv) Cumulative - Poisons may accumulate in the body because the body is unable to rid itself of the material as quickly as it is absorbed. Lead is a classic example of a material which accumulates in the body and produces cumulative poisoning. Chlorinated hydrocarbon insecticides, also cumulative poisons, are stored in the body fat. Cumulative poisoning may result also from materials which do not accumulate in the body but impair its function day by day faster than it can be repaired. Eventually, effects may be produced by a relatively small dose. An example of this type of poisoning is the reduction of cholinesterase (see page) by the organic phosphorous insecticides, or the effects of the anti-coagulant type of rodenticides.

Oral Toxicity

(1) Acute Oral Toxicity - The Oral LD_{50} Dose is that single dose which, when given by mouth, kills 50% of the animals under test. This test should be carried out on specified animals, usually white rats, under standard conditions. The dose is expressed as milligrams of insecticide per kilogram of body weight of test animal (mg/kg).

(2) Subacute Oral Toxicity - This is usually determined by feeding of dogs over a 3-month period and is measured in terms of mg/kg.

(3) Chronic Oral Toxicity - This is generally determined by feeding given concentrations of the insecticide in the entire diet of the animal. Usually, rats are fed over a two-year period (their approximate life span). The doses administered are expressed in parts of insecticide per million parts

of diet (ppm). Various dose levels are fed in order to determine:

(a) "No-effect Level" - This is the largest amount in ppm in the diet which can be given without detectable effects in the animal. The "No-effect Level" is very important - residue tolerances for food for human consumption are generally based on it. A safety factor of 1/100 is commonly used for residue tolerances.

(b) Level which produces physiological, chemical or histologic changes without external appearance of damage.

(c) Level which retards growth.

(d) Level which produces clinical evidence of poisoning.

(e) Level which causes death.

In chronic feeding studies, note is always made of any other effects, such as tumour growth.

Dermal Toxicity

(1) Acute Dermal Toxicity - The Dermal LD_{50} Dose is that amount of insecticide which, when left in contact with the bare skin of test animals for 18 to 24 hours, produces death in 50% of the animals. It is also expressed in mg/kg. Generally, guinea pigs and rabbits are used, and the material is applied by a special cuff which holds it against the skin.

(2) Chronic Dermal Toxicity - This test is not often carried out on experimental animals.

Inhalation Toxicity

(1) Acute Inhalation Toxicity - Generally small groups of animals are exposed to saturated vapours of the insecticide in air for short periods - commonly for 4 hours. The LC_{50} Dose is that concentration which kills 50% of the test animals after 4 hours' exposure. The LT_{50} Dose is the time taken for a given concentration to kill 50% of test animals. Neither the LC_{50} nor the LT_{50} dose is commonly used.

Concentrations are expressed as per cent or ppm of the vapour in air. For particulate matter, for example, dusts and spray mists, the concentration is generally expressed as milligrams of the insecticide per cubic metre of air (mg/cu. m.).

(2) Chronic Inhalation Toxicity - Limited chronic inhalation studies have been carried out with insecticides. Certain figures have been proposed as threshold limit values for insecticide exposure by repeated inhalation. These values refer to air concentrations which would not be expected to produce evidence of toxicity during 8-hour working day exposures over a 40-hour work week. These values are based on experimental data in animals, as well as published data from cases of poisoning in humans, where such information is available. They should be used as guides to the maximum permitted in the air breathed by workers. The threshold limit values are produced by The American Conference of Governmental Industrial Hygienists. They are revised annually. The values for insecticides are listed in Table V. The threshold limit values for insecticides may be compared with those for gases or vapours used as fumigants (Table VIII).

Parenteral Toxicity

(1) Acute Parenteral Toxicity - Acute parenteral toxicity may be determined by injection into different body sites. For example, if the insecticide is injected into the intraperitoneal cavity, the Intraperitoneal LD_{50} Dose refers to that single dose which kills 50% of the test animals when given in this fashion. Similarly, there may be intravenous, intramuscular, subcutaneous and other injection methods, each with a specific LD_{50} term.

(2) Chronic Parenteral Toxicity - This form of toxicity is not commonly determined.

In toxicity testing, evidence of skin and eye irritation are carried out by applying the test material against the skin or instilling measured amounts into the eye. Testing for allergic potential is more difficult, and human volunteers are often used.

Relationship of Toxicity To Persons In Exposure

The most common basis for comparison of the toxicity of insecticides is the oral LD_{50} in white rats. A compound with a high oral toxicity, however, need not necessarily have a high dermal or inhalation toxicity as well.

Individuals applying insecticides may experience exposure, chiefly by inhalation and skin contact. With some of the insecticides, skin contact is more important than inhalation. Acute poisoning by ingestion occurs only as a result of accident or attempted suicide.

Toxicity and Hazard

"Toxicity" is an absolute term. It is measurable to a degree by means of the animal tests mentioned above. The term "Hazard" is not synonymous with "Toxicity" - it is a relative term which indicates the risk involved in using a material. Hazard depends upon many things, including inherent toxicity, physical and chemical properties, conditions of use, and the use concentration. Some very toxic materials, used with proper care, offer very little hazard.

Assessment of toxicity does not necessarily include the ability of a material to produce cancer in test animals or skin or respiratory allergies in magi, but these are of importance in the use of the material. Fire and explosion properties, although they can represent important hazards, are not covered by toxicity testing.

CLASSIFICATION OF INSECTICIDES

1. INORGANIC SUBSTANCES: e.g. arsenicals, lead, fluorides, lime and silica aerogel.

2. ORGANIC SUBSTANCES:

   (1) Mineral Products: (a) Petroleum; e.g. kerosene
   (b) Coal Tar; e.g. naphthalene

   (2) Botanical Products: e.g. Pyrethrum, Derris, Ryania, Nicotine.

3. SYNTHETIC CHEMICALS:
   a. Chlorinated Hydrocarbon Compounds (CH)
   b. Organic Phosphorous Compounds (OP)
   c. Carbamates
   d. Synthetic Pyrethrins

1. INORGANIC SUBSTANCES

The arsenicals have high acute toxicity. They have been used in pest control work for many years and their toxicity is well appreciated. The oral LD_{50} values for some arsenical compounds are as follows; Lead Arsenate: 1,050 mg/kg: Calcium Arsenate: 298 mg/kg; and Paris Green: 100 mg/kg. Arsenicals are persistent chemicals and their continued use may give rise to residue problems.

Sodium Fluoride may still be encountered as a roach and ant powder. It is a very dangerous poison when ingested: the fatal human dose of this material when taken by mouth, is estimated to be about 4 grams. Such baits should be kept out of the reach of young children.

Silica Aerogel contains about 60 to *70%* free Silica in an amorphous form. It kills insects by desiccation. It is not toxic to humans, but care should be taken to prevent prolonged exposure by inhalation.

2. ORGANIC SUBSTANCES

(1) Mineral Products

Petroleum products, particularly petroleum solvents, are used as solvents in many insecticidal formulations, while kerosene alone has been commonly used for killing mosquito larvae. In general, petroleum distillates are not highly toxic. They do, however, present a fire hazard, and prolonged or repeated skin contact with these solvents may lead to dermatitis.

Naphthalene, used in moth control, is obtained from coal tar. It is not considered very toxic; cases of poisoning have occurred chiefly in children who have eaten the material. It should not, however, he used in confined spaces where occupants continuously breathe the vapours, such as a closed bedroom.

(2) Botanical Products

Pyrethrum is a plant extract. It is of low toxicity to humans, though accidental poisoning by ingestion has occurred, but the dust may be irritating when inhaled. In some individuals, pyrethrum has caused allergic respiratory responses similar to those caused by ragweed pollen. It is not a skin irritant. Pyrethrum may be applied in areas where food is handled. It has quick insecticidal action but has the disadvantage of a short residual period. See additional information under "Synthetic Pyrethrins", Page 24.

Derris roots contain Rotenone as the active insecticidal agent. Rotenone is toxic to insects and fish, and swine are unusually sensitive to it. It is of low toxicity to humans, but the fine dust may be irritating to the skin, eyes and respiratory passages of persons applying it. Accidental ingestion is followed by gastrointestinal irritation with nausea and vomiting.

Nicotine is an alkaloid which is extracted from the tobacco. The alkaloid is highly toxic, with an oral LD_{50} of 10 mg/kg. It is fast-acting and penetrates the intact skin readily. Nicotine is commonly used as 40% nicotine sulphate. In this form it is much less toxic and does not penetrate the intact skin.

Ryania is manufactured from the stem of tropical plants. It is of low toxicity to humans.

3. SYNTHETIC CHEMICALS

Much time has been spent on the development of synthetic materials for insecticidal purposes. There are two main groups of these - the Chlorinated Hydrocarbon Insecticides (CHI) and the Organic Phosphorous Insecticides (OPI), although the Carbamate group and the Synthetic Pyrethrums are also of importance. The following describes these four groups:

A. Chlorinated Hydrocarbon Insecticides (CHI)

Introduction

The chlorinated hydrocarbon insecticides have in common the chemical composition implied in the group name. However, beyond this broad similarity, the compounds vary widely in chemical structure and activity. Although much is known about the pharmacology of these materials, their basic mode of action is not known. It is entirely possible that chlorinated hydrocarbon insecticides of significantly different chemical structure have different modes of action. It is certain that there are qualitative as well as quantitative differences in their pharmacologic action.

The following description, based largely on DDT, is applicable to the chlorinated hydrocarbon insecticides as a group. The actions known to be peculiar to specific compounds are described in the separate sections.

The acute oral and dermal LD_{50} values to rats of certain chlorinated hydrocarbon insecticides and derivatives, including those treated in this publication, are given on page 27.

Pharmacologic Action

The chlorinated hydrocarbon insecticides act on the central nervous system, but the exact mechanism of this action either in man or in animals has not been determined. Large doses of these insecticides induce nausea and/or diarrhea. On repeated dosage, the compounds have produced microscopic changes in the liver and kidneys of some experimental animals. This has not been demonstrated clearly in man in connection with uncomplicated poisonings. Somewhat different lesions may be produced in man than animals by a single fatal dose.

The compounds and/or their degradation products are stored in fat; such storage

results either from a single large dose or from repeated small doses. The materials stored in the fat appear to be largely inactive, since the total amount stored in an experimental animal is often greater than the amount which could cause death if all of it were given at one time. The presence of insecticides or their derivatives is usually demonstrated in milk and urine. The compounds stored in fat are eliminated only very gradually when further dosage is discontinued.

Acute Poisoning

Central nervous system and gastrointestinal symptoms predominate in chlorinated hydrocarbon poisonings. These symptoms are: nervous irritability, hypersensitivity to stimuli, muscular tremors, nausea, vomiting, diarrhea, convulsions and coma. Death occurs from respiratory failure. In order to diagnose acute CHI poisoning, it is necessary to have the following information:

1. A history of exposure
2. Neurological symptoms - tremors followed by convulsions
3. Gastrointestinal upset - nausea, vomiting and, commonly, diarrhea.

Chronic Poisoning

Chronic poisoning has been experimentally produced in animals by prolonged ingestion. In such cases, there is a loss of appetite with resulting emaciation. Paralysis and convulsions also occur. Liver and kidney cell damage occur, and sometimes brain cell damage can be detected. Storage of CHI in body fat is a constant feature, but there is no relationship between the amount of storage and the degree of poisoning. As noted previously, the mode of action in poisoning is not understood, but it is obvious from the clinical picture that nerve conduction is impaired, with repetitive firing from a single stimulus.

Treatment

There is no specific antidote for CHI intoxication. If the material has been ingested, prompt vomiting should be induced. The physician should carry out gastric lavage. Saline laxatives (not oil laxatives) can also be administered. If there is skin contact, contaminated clothing should be removed and the skin thoroughly cleansed with soap and water. Tremors and convulsions can be controlled with barbiturates. If the patient is convulsing, a rapid-acting barbiturate, such as sodium pentothal, should be used. It should be given in an amount sufficient to control convulsions, tremors, and the anxiety that may be present. Morphine and adrenaline should not he used. On empiric grounds, a diet low in fat and high in calcium and carbohydrate should be prescribed after apparent clinical recovery.

Residue

The toxicity problem of chlorinated hydrocarbon insecticides is intensified by the persistence of these chemicals in the environment. Residue from just one application of insecticide can remain in the soil and water for many years. If continued application is required, an accumulation problem is created.

The persistence of CHI insecticides has actually been a reason for its use in some cases. As a result, recent surveys of agricultural soils in southern Ontario have uncovered a widespread incidence of residues. The highest concentrations reported in the Province were of DDT and its conversion products in orchard soils. The persistence of these insecticides depends on the insecticide itself, the soil type, soil moisture, soil temperature, winds or air movements, cover crops, soil cultivation, the presence of soil microorganisms, insecticide formulation and the method of application. The chemicals persist longer in soils high in organic matter than in mineral soils. Moisture in soil displaces many CHI from soil particles and makes them vapourize more easily, while high temperatures and microorganisms increase the rate of decomposition. On the other hand, cover crops increase the chemicals' persistence by reducing the rate of

vapourization and the effect of the wind. Residues in the soil are then taken up in smaller concentrations by plant and animal material.

Insecticide residues in the air are the result of the spraying of finely vapourized formulations; the effect of wind on dry, sprayed soils; smoke from the manufacturing process; the burning of supposedly empty containers; and warehouse fires. Insecticides reach water through intentional or accidental direct spraying; with the runoff from treated soils; by percolation through the soil to ground waters; as effluents from insecticide manufacturers; through the careless disposal of containers; and as particles carried in rain. The chlorinated hydrocarbon insecticides are not soluble in water, but adhere to solid particles and depend on water turbulence to be kept in suspension. The problem of biological magnification has its origin mainly in water, where relatively low levels of the chemicals in tiny organisms are concentrated in the higher forms of life as they proceed up through the food chain. The great affinity of chlorinated hydrocarbon insecticides for biological matter makes possible its easy assimilation by plankton and by other types of water and land life, both animal and vegetable.

B. Organic Phosphorus Insecticides (OP)

Introduction

The organic phosphorous insecticides are characterized by:

1. A similar chemical structure (they may all be considered derivatives of phosphoric acid) and
2. A similar primary mode of action.

These insecticides differ widely in their inherent toxicities; in their rates of absorption; in the point of maximal action following absorption; and in their rates of destruction or excretion.

(The acute oral and dermal LD_{50} values for white rats of certain organic phosphorus insecticides are given on page 28.)

Routes of Absorption

Organic phosphorus insecticides are absorbed into the skin as well as into the respiratory and gastrointestinal tracts. Absorption by the skin tends to be low, but, because the insecticides are difficult to remove, such absorption is frequently prolonged. The absorption is somewhat greater at higher temperatures and Is much greater in the presence of dermatitis. Thus, dermatitis can lead to serious poisoning following exposure that would ordinarily cause no inconvenience.

Pharmacologic Action

The organic phosphorus insecticides act as inhibitors of the cholinesterase enzyme, thus allowing the accumulation of large amounts of acetylcholine. Acetylcholine acts as a chemical mediator bridge to the nerve-gland or nerve-muscle junction. If the cholinesterase enzyme is removed, acetylcholine accumulates. As a result, the nerve impulse continues to function and there is constant stimulation.

The cholinesterase contents of various tissues in the same poisoned animal are not equally affected. The level in all tissues, including the brain, can be lowered markedly from the pre-exposure level without seriously affecting normal functioning, especially if the reduction is gradual. Almost as important as the degree of cholinesterase depression is the rate at which it occurs. A sudden slight depression resulting from a rapidly absorbed small dose can lead to incapacitating acute illness, though not to fatal illness. A sudden marked depression from a sufficient dose leads to critical and, frequently, fatal poisoning. However, the blood cholinesterase of man and animals may be gradually depressed to a very low level by repeated small exposures to OP compounds without necessarily producing serious symptoms, or any symptoms whatsoever. Thus, while a very low blood cholinesterase is not always proof

that a clinical illness represents poisoning, critical poisoning usually does not occur in man or laboratory animals without such low enzyme levels. In every *case,* the exposure history, symptoms and clinical findings must be considered carefully, no matter what may be the cholinesterase level.

It is now known that some effects of organic phosphorous insecticides (e.g. headache and irritation of the urinary tract) are not always related directly to low cholinesterase level, but the relative importance of different processes in determining the clinical outcome is not established. In any event, recovery is apparently complete if a poisoned animal or man has time to reform his critical quota of cholinesterase. Experiments with rats show that gradual depression of the blood cholinesterase by repeated, small, tolerated doses does not make the animals significantly more susceptible to a challenge dose. Field experience suggests that the same is true of man. Thus, there is a physiological adjustment to the stress of repeated small, tolerated doses that is at least partially independent of the absolute blood cholinesterase level. However, repeated doses which produce any detectable clinical injury in rats tend not only to reduce cholinesterase levels progressively but to produce cumulative clinical injury also. Thus, if a small second dose of poison is administered before physiological adjustment to the first dose is complete, the effect is partially additive.

Following clinical recovery after an illness caused by one or a few doses, physiological adjustment may be safely assumed to be complete only after the activity of the blood cholinesterase has returned to normal. The recovery rate is generally considered to be approximately 1% per day. Depending on the degree of depression and other factors, the recovery may thus require about three months. This does not mean, of course, that workers who have been poisoned may not return to work much sooner than three months, providing the attending physician is satisfied that his patient is clinically normal and able to carry out all safety measures under the conditions of his employment.

Some unmetabolized organic phosphorous insecticides are able to inhibit cholinesterase and are said to have a direct action while many other compounds are not active until they have been altered by either chemical or enzymatic changes within the body after absorption - the latter are called indirect inhibitors. Direct inhibitors tend to have more prominent local effects and to produce systemic poisoning more rapidly.

Acute Poisoning

The symptoms of acute poisoning from OPI are similar in man and animals. They are chiefly centred in the parasympathetic nervous system and include excess saliva, abdominal cramps, vomiting, diarrhea, pinpoint pupils, a sense of tightness in the chest, and difficulty in breathing. In the case of the other nerve fibres (preganglionic), headache and increased heart rate are experienced. If the poisoning is severe enough, the somatic nerves are involved and irregular muscle contractions with tremors occur. Pulmonary oedema can develop and present a medical emergency. When death occurs, it is the result of respiratory failure.

Chronic Poisoning

There is some question as to whether such a condition can be produced by organic phosphorus insecticides. In experimental animals, excessive secretions, increased bowel activity, general weakness and muscular twitching have been described. The mode of Action with OPI is better understood than with CHI. The OPI inhibit the cholinesterase enzyme, with the results described above under "Pharmacologic Action".

Treatment

If the material is ingested, vomiting should be induced at once and gastric lavage carried out. If clothing and skin are splashed, the clothing should be removed immediately and the skin washed with soap and water. If breathing stops, artificial

resuscitation should be started without delay. Oxygen should be given if it is available, and atropine sulphate should be administered by injection - intravenously, if necessary. For OPI poisoning, doses of 2 mg. (1/32 grain) of this sulphate should be given every 15 minutes until signs of excess atropine administration become apparent. Morphine and adrenaline must not be used.

All patients should be put at rest for 24 hours, no matter how well they feel after treatment. In cases where there is no response to atropine, a drug known as Protopam is used. This drug overcomes the effect of the OPI on the cholinesterase enzyme. It has been used with success in serious cases of poisoning. For this reason, areas in which OPI poisoning may occur should have this material available for emergencies.

Residue

There is no residue problem with the organic phosphorus insecticides, since these compounds decompose rapidly in the soil. However, under a combination of specific conditions, such as very dry soil, these chemicals can last a short while. This is not nearly as serious as the persistence of the chlorinated hydrocarbon insecticides.

C. Carbamate Insecticides

Introduction

Carbaryl is the most commonly used carbamate insecticide. It is manufactured as a 98% concentrate, which is used in preparing dusts, wettable powders and flowable formulations. It has a wide variety of insecticidal uses against pests of fruits, nuts, vegetables, forage crops, cotton, and forest and range land.

Routes of Absorption

Carbaryl is absorbed through all portals of entry into the body, including the

skin.

Pharmacologic Action

The carbamates are reversible inhibitors of cholinesterase. The reversal is so rapid that, unless special precautions are taken, measurements of blood cholinesterase in people or animals exposed to carbamates are likely to be inaccurate, always in the direction of appearing to be normal. The compounds are rapidly metabolized. Concentrates may cause skin irritation as well as systemic poisoning.

Toxicity

In one case, a moderately severe poisoning of an adult person resulted from a single, carefully measured oral dose of 250 mg. (amounting to about 2.8 mg/kg). The smallest dosage that will produce illness in man following prolonged exposure is not known. Because of the rapid metabolism, the dangerous repeated dose may be only slightly smaller than the dangerous single dose. Workers exposed to carbaryl dust (sometimes at concentrations as high as 40 mg/M^3 under abnormal conditions, but usually at lower concentrations) showed a slight depression of blood cholinesterase but no illness. Dogs were acutely poisoned when exposed to dust in a chamber, at a concentration of 75 mg/M^3, for five hours.

In the male rat, the oral LD_{50} is 850 mg/kg and the dermal LD_{50} is 4,000 mg/kg. Carbaryl was fed to male and female rats for 92 days at levels as high as 225 to 237 mg/kg/day without significant effect on food consumption, rate of growth or level of plasma or red cell cholinesterase. Single oral doses at the highest level depressed the plasma and red cell cholinesterases, but the activities of these enzymes returned to normal within sixteen hours.

D. Synthetic Pyrethrins

Introduction

The active ingredients in pyrethrum extract consist of a mixture of four compounds: Pyrethrin I and II and Cinerin I and II. Pyrethrin 1 has the greatest insecticidal activity. Allethrin is a synthetic pyrethrin analogue.

Pyrethrum, Pyrethrins and Allethrin are available commercially In powder or dust form, in a variety of solvent extracts in aerosol form, and in emulsifiable preparations of various concentrations. The usual household spray contains about 0.5% active pyrethrum principles, often combined with synergists. Allethrin has also been used in vaporizers.

Routes of Absorption

Pyrethrins and Allethrin may be absorbed from the gastrointestinal tract and by the respiratory route. They are not absorbed to a significant degree through the skin, however, allergic reactions may result from skin contact.

Pharmacologic Action

Pyrethrum and Allethrin affect the nervous system. The symptoms of poisoning resemble those of Veratrin intoxication, proceeding from excitation to convulsions to tetanic paralysis, except that Pyrethrins cause muscular fibrillation as well. Death is due to respiratory failure. If recovery occurs, it is usually complete. Injury to man from Pyrethrum has most frequently resulted from the allergenic properties of the material, rather than its direct toxicity.

Toxicity

Under practical conditions, Pyrethrum and Allethrin are probably the least toxic to mammals of all the insecticides currently in use. Pyrethrum has been used orally as an anthelmintic in some areas for many years with no apparent ill effects. The approximate oral LD_{50} for white rats of Pyrethrum is 200 mg/kg and of Allethrin, 680 mg/kg.

Rare individual hypersensitive reactions are possible, especially following a previous sensitizing exposure. In one case, Pyrethrum poisoning was the cause of death of a two-year-old child who ate half an ounce (15 g.) of Pyrethrum concentrate. Allethrin and Pyrethrum are rapidly detoxified in the gastrointestinal tract and to some extent in other tissues of warm-blooded animals. They are excreted in the urine. Because of their ready excretion, these compounds exhibit little or no toxicity following repeated exposure.

The threshold limit value for Pyrethrum in air is 5 mg/M^3.

TABLE I: Acute Oral And Dermal LD_{50} Values Of Chlorinated Hydrocarbon Insecticides For Male And Female White Rats.

COMPOUND	ORAL LD_{50} (mg/kg)		DERMAL LD_{50} (mg/kg	
	Males	Females	Males	Females
Chlordane	335*	430*	840*	690*
Chlorobenzilate	1040*	1220	-	-
Dilan	600	425	6900*	5900 *
Endrin	17.8*	7.5*	12	15*
Endosulfan, Thiodan	43	18	130	74
Isodrin	15.5*	7.0*	35*	23*
Kelthane	1100*	1000*	1230*	1000*
Lindane	88	91	1000	900
Methoxychlor	(6000.0)**	-	-	6000*
Perthane	4000*	4000*	-	-
Storbane	(200)**	-	-	-
Thiodan	43	18	130	74
Toxaphene	90*	80*	1075	780

* These values were determined by the Toxicology Section, Communicable Disease Center, United States Department of Health Service, under standardized conditions.

** Sex not specified.

TABLE II: Acute Oral And Dermal LD_{50} Values Of Organic Phosphorus Insecticides For Male And Female White Rats*.

COMPOUND	ORAL LD_{50} (mg/kg)		DERMAL LD_{50} (mg/kg)	
	Males	Females	Males	Females
Carbophenothion	30	10.0	54	27
Chlorthion	880	980	4500	4100
Co-Ral	41	15.5	860	-
DDVP	80	56	107	75
Delnav	43	23	235	63
Demeton	6.2	2.5	14	8.2
Diazinon	108	76	900	455
Dicapthon	400	330	790	1250
Dimethoate *	185	250	>800	-
Di-Syston	6.8	2.3	15	6
EPN	36	7.7	230	25
Ethion	65	27	245	62
Fenthion	215	245	330	330
Futhion	13	11	220	220
Malathion	1375	1000	4444	4444
Methyl parathion	14	24	67	67
Methyl trithion	98	120	215	190
NPD, Aspon ®	-	-	2100	1800
Parathion	13	3.6	21	6.8
Phorate	2.3	1.1	6.2	2.5
Phosdrin	6.1	3.7	4.7	4.2
Phosphamidon	23.5	23.5	143	107
Ronnel	1250	2630	-	-
Schradan	9.1	42	15	44
TEPP(R)	1.05	-	2.4	-
Trichlorfon, Dipterex	630	560	2000	2000

* With the exception of the Dermal LD_{50} for dimethoate, these values were determined by the Toxicology Section, Communicable Disease Centre, United States Department Health Service - under standardized conditions.

TABLE III: Combined Tabulation Of Toxicity Classes.

Toxicity Rating	Commonly Used Term	ROUTE OF ADMINISTRATION			Probable Lethal Dose For Men
		Oral LD_{50} Rats mg/kg	Inhalation LC_{50} Concentration in ppm Causing Death in from 2 to 4 of 6 Rats Exposed for 4 hours	Dermal LD_{50} Rabbits mg/kg	
1	Extremely Toxic	1	10	5	1 grain (a taste)
2	Highly Toxic	1-50	10-100	5-43	1 teaspoon (4 ml)
3	Moderately Toxic	50-500	100-1,000	44-349	1 ounce (30 gm.)
4	Slightly Toxic	500-5,000	1,000-10,000	350-2,819	1 pint (250 gm.)
5	Practically Non-Toxic	5,000-15,000	10,000-100,000	2,820-22,599	1 quart
6	Relatively Harmless	> 15,000	100,000	22,600	1 quart

Source: Hodge, H.C. and Sterner, J.H.
American Industrial Hygiene Association Quarterly
Vol. 10, No. 4, p. 23.

TABLE IV: Threshold Limit Values of Insecticides for 1971, adopted by the American Conference of Governmental Industrial Hygienists.

Substance	Maximum Allowable Concentration in Air mg/M^3
Abate	10.0
Arsenic and compounds (as As)	0.5
Azinphos - methyl - skin (Guthion)	0.2
Carbaryl	5.0
Chlordane - skin	0.5
Chlorinated camphene - skin	0.5
Cyanide (as CN) - skin	5.0
DDT - skin	1.0
Dichlorvos (DDVP) - skin	1.0
Demeton ®- skin	0.1
EPN - skin	0.5
Endrin - skin	0.1
Fluoride (as F)	2.5
Lindane - skin	0.5
Malathion - skin	10.0
Mercury (alkyl compounds) - skin	0.01
Methoxychlor	10.0
Nicotine - skin	0.5
Parathion - skin	0.1
Pentachlorophenol - skin	0.5
Phosdrin (Mevinphos ®) - skin	0.1
Pyrethrum	5.0
Rotenone (Commercial)	5.0
Strychnine	0.15
Systox (see Demeton)	-
TEPP - skin	0.05
Thallium (soluble compounds) - skin (as Tl)	0.1
Toxaphene (Chlorinated camphene)	0.5

TABLE V: Chlorinated Hydrocarbon Insecticides: Acute Oral Toxicity In White Male Rats and Probable Lethal Dose in Man.

Compound	LD_{50} White Male Rats mg/kg *	Toxicity Rating	Probable Lethal Dose For Adult Male 70 kg. (154 lbs)
BHC	1000	Low	1 pint
Chlordane	335	Moderate	1 ounce
Chlorobenzilate	1040	Low	1pint
Dilan	-	Moderate-low	-
Endrin	17.8	High	1 teaspoon
Isodrin	15.5	High	1 teaspoon
Kelthane	1100	Low	1pint
Lindane	88	Moderate	1 ounce
Mirex **	306 ± 71	Moderate	1 ounce
Methoxychlor	6600	Low	1pint
Perthane	4000	Low	1pint
Strabane	250	Moderate	1 ounce
TDE	3000	Low	1pint
Thiodan ®	43	High	1 teaspoon
Toxaphene	90	Moderate	1 ounce

* Source: U.S. Department of Health, Education and Welfare, Communicable Disease Centre, Toxicology Section, Atlanta, Georgia.

** Pesticides Manual, British Crop Protection Council.

TABLE VI: Organic Phosphorus Insecticides Acute Oral Toxicity In White Male Rats and Probable Lethal Dose in Man.

Compound	LD_{50} White Male Rats mg/kg *	Toxicity Rating	Probable Lethal Dose for Adult Male
Baytex, (Fenthion)	215	Moderate	1 ounce
Carbophenothion	30	High	1 teaspoon
Chlorthion ®	880	Moderate	1 ounce
Ciodrin ®	110	Moderate	1 ounce
Co-ral	41	High	1 teaspoon
Cygon ® (Rogor)	215	Moderate	1 ounce
DDVP	80	Moderate	1 ounce
Delnav ®	43	High	1 teaspoon
Demeton (Systox)	6.2	High	1 teaspoon
Diazinon	108	Moderate	1 ounce
Dibrom ®	250	Moderate	1 ounce
Dicapthon	400	Moderate	1 ounce
Dipterex ®	560	Moderate	1 ounce
Disyston ®	6.8	High	1 teaspoon
Dylox	450	Moderate	1 ounce
EPN	36	High	1 teaspoon
Fenitrothion **	660	Moderate	1 ounce
Guthion ®	13	High	1 teaspoon
Imidan	147	Moderate	1 ounce
Malathion	1375	Low	1 pint
Mirex	306±71	Moderate	1 ounce
Meta-Systox ®	65	High	1 teaspoon
Methyl parathion	14	High	1 teaspoon
Methyl trithion ®	98	Moderate	1 ounce
Parathion	13	High	1 teaspoon
Phosvel **	44.5	High	1 teaspoon

continued . . . . .

TABLE VI: (CONT'D)

Compound	LD_{50} White Male Rats mg/kg *	Toxicity Rating	Probable Lethal Dose for Adult Male
Phosdrin ®	6.1	High	1 teaspoon
Phostex	2500	Low	1 pint
Ronnel (Korlan) ®	1250	Low	1 pint
Ruelene	1600	Low	1 pint
Sayfox (Menazon)	900	Low	1 pint
Schradan	9.1	High	1 teaspoon
TEPP	1.0	Extremely Toxic	1 grain
Thimet ®	2.3	High	1 teaspoon

* Source: U.S. Department of Health, Education and Welfare, Communicable Disease Centre, Toxicology Section, Atlanta, Georgia.

** R.N.R., Canada Department of Agriculture, Ottawa, Ontario.

TABLE VII: Threshold Limit Values of Chemicals Used as Fumigants for 1971, Adopted At the Meeting of the American Conference of Governmental Industrial Hygienists.

Substance	Maximum Allowable Concentration in Air	
	ppm	mg/M^3
Carbon Tetrachloride	10	65
Chloropicrin	0.1	0.7
1,2-Dibromoethane - skin (ethylene dibromide)	-	3
1,2-Dichloroethane (ethylene dichloride)	50	200
Hydrogen Cyanide - skin	10	11
Methyl Bromide - skin *	15	60
Phosphine	0.3	0.4

* Notice of Intended Changes for 1971 Adopted by ACGIH.

APPENDIX

Directions For Submitting Blood Samples For Cholinesterase Testing

1. Prepare finger by alcohol swab.

2. Finger prick in usual manner.

3. Draw blood by sucking into the plastic capillary tube provided. This tube has been heparinized in the laboratory. An ordinary rubber tube from a haemocytometer outfit can be used to suck up the blood.

4. About five or six drops of blood are desirable to fill tube to the indicated mark (about ¼ full).

5. Remove rubber tube.

6. Seal ends of the plastic tube. A cigarette lighter flame works well here to soften the ends. Pressure is applied while the plastic is molten to seal the end.

7. Place capillary tube in container with worker's name.

   Put in special chilled container (35-50^{0}F) and send by express prepaid to:

   Occupational Health Laboratory,
   360 Christie Street,
   Toronto 176, Ontario.

8. Samples should be submitted to the laboratory early in the week as the testing takes one day to perform.

9. The laboratory will return your own chilled container express collect.

10. Results will be mailed or telephoned to the physician submitting the sample as indicated by the findings.

Normal Cholinesterase Testing:

Plasma	80-200%
Red Blood Cells	80-120%

Individuals below 50% should be removed from exposure to organic phosphorus insecticides.

Results for individuals with levels under 40% will be given by telephone.

Levels of 20% of normal activity are invariably associated with symptoms of poisoning.

REFERENCES

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3. Insecticide Handbook For Manitoba Pesticide Dealers, Manitoba Department of Agriculture, Winnipeg 1, Manitoba.

4. Dictionary of Insecticides and Related Chemicals, Purdue University, Cooperative Extension Service, Lafayette, Indiana.