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CHAPTER 6

RODENTICIDE TOXICOLOGY

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A rodenticide is a chemical substance or mixture of substances intended for preventing, destroying, repelling or mitigating animals belonging to the Order Rodentia of the Class Mammalia and closely related species.

Many rodenticides once used for rodent control are no longer considered suitable — some because of ineffectiveness and high cost while others because of hazards associated with their use. Among the rodenticides restricted in the Philippines due to toxicity hazard (Magallona, 1980) are: arsenic trioxide, phosphorus, thallium sulfate, 1 - Naphthyl thiourea (ANTU), Sodium fluoro acetate (1080), fluoroacetamide (1081), strychnine, and gophacide. Because most rodenticides are generally poisonous to all vertebrates including man and domestic animals, precautions should be exercised on their use so that safety for humans, livestock and environment is given prime considerations.

This chapter discusses the nature, modes of action, toxicity and other characteristics of rodenticides and some practical considerations on safety and handling of rodenticides. Rodenticides are divided into five functional categories according to their primary effects or use patterns. Rodenticide characteristics have been reviewed by Savarie (1981). Only the most widely known and used, as well as some restricted rodenticides, are reported herein.

INORGANICS

Five inorganic chemicals can be used as acute rodenticides, namely: zinc phosphide, arsenic trioxide, thallium sulfate, phosphorus and barium carbonate.

Zinc phosphide. Zinc phosphide is a non-specific poison used against a variety of rodents. It is the first chemical to be registered in the U. S. for incrop use against rats damaging sugarcane (Hood, 1972). In the Philippines, many farmers still use this poison with cereal baits. The toxicity of zinc phosphide is caused by the highly toxic gas phosphine (PH_3), formed when zinc phosphide reacts with water and hydro chloric acid in the gastrointestinal tract. Phosphine produces characteristic poisoning symptoms in the liver and lung: Gastrointestinal irritation and hemolysis giving rise to hemolytic icterus (bile entering blood stream) and the blocking of the kidney function. Secondary poisoning has been observed in cats feeding on rats that consumed 5% zinc phosphide bait.

Arsenic trioxide (As_2O_3). Also known as white arsenic and arsenous acid, this is a very effective non-specific rodenticide because it does not have much odor or taste. It was one of the oldest rodenticides widely used at one time.

Death is believed to be due to acute irritation of the gastrointestinal tract resulting in bloody diarrhea and secondary shock. An antidote (given intramuscularly) for low dose level of arsenic poisoning is 1, 2 diphthio-propanol. There is secondary poisoning hazard with this rodenticide. Presently, it is not allowed for use in the Philippines because of toxicity considerations.

Thallous sulfate (Tl_2SO_4). More commonly known as thallium sulfate, this is a non-specific poison highly toxic to all animals. Baits containing thallium are highly effective against all species of rodents, but this desirable property is negated by its primary and secondary toxicity effects to non-target species. Symptoms of acute poisoning include gastrointestinal irritation, muscle paralysis and death by respiratory failure. There is a long latent period between ingestion and symptom appearance. It takes 1 to 6 days for the victim who took high lethal doses to die. It is also a chronic poison and can be absorbed through the intact skin. There is no effective antidote for thallium poisoning. This chemical is also included in the list of prohibited pesticides in the Philippines.

Phosphorus. The yellow or white form of phosphorus is non-specific and highly toxic. Doses of 10 mg/kg and lower are commonly lethal to birds and mammals. This form spontaneously ignites in air and must be kept in water. It cannot be dry-mixed in baits but is formulated as a greasy paste spread on appropriate baits. Shortly after ingestion, a toxic dose elicits severe gastrointestinal irritation, cardio-vascular failure, convulsions, coma, and finally death. Phosphorus does not have an effective antidote and its use is prohibited in the Philippines.

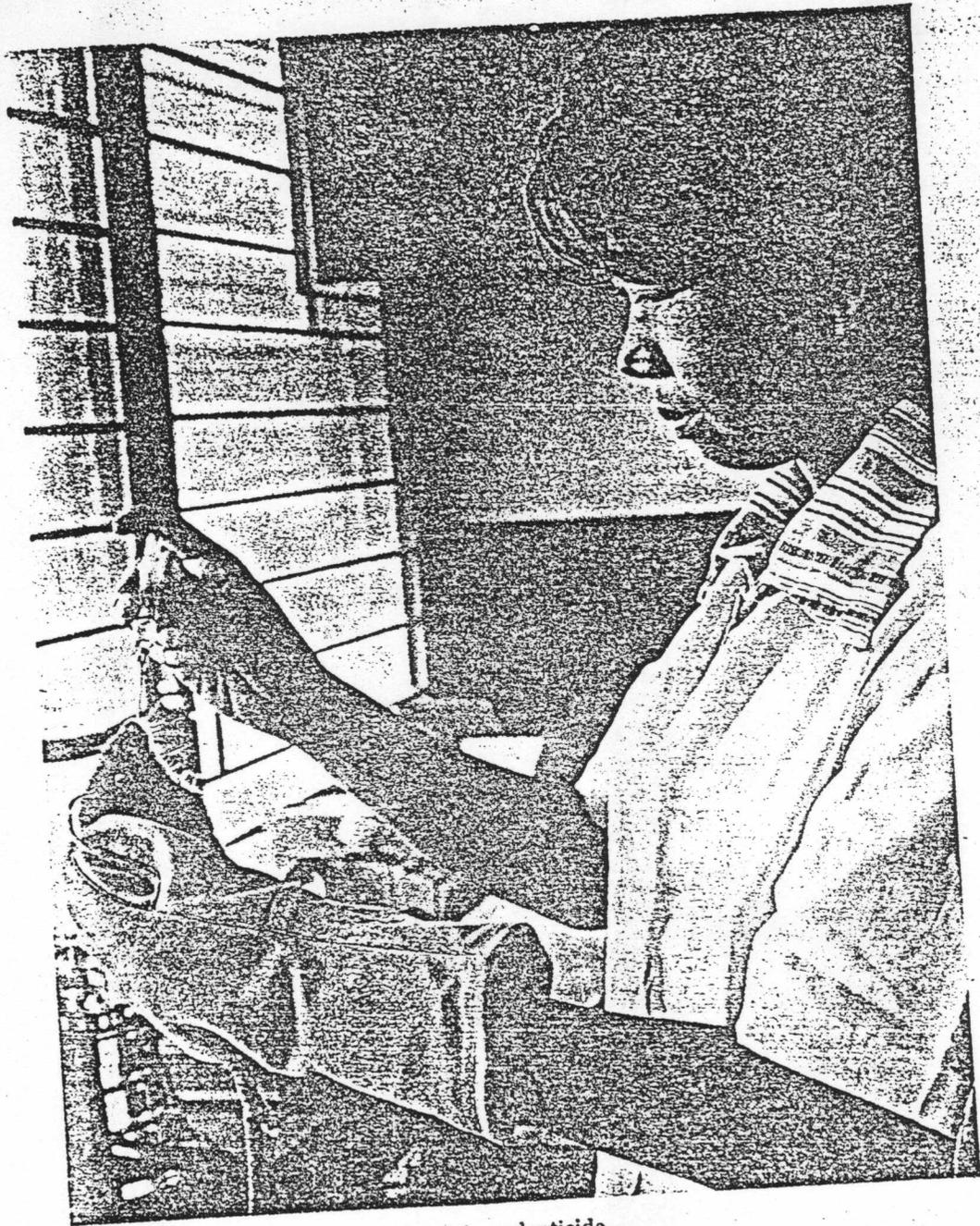
Barium carbonate ($BaCO_3$). It dissolves in the stomach to release the free barium ion, which causes an intense stimulation to all types of muscles. Poisoning symptoms in rats are highly variable and may appear as soon as 2 hours or be delayed for 48 hours; most of the mortalities occur in 2 to 3 days. Vomiting, diarrhea, and hemorrhage are caused by the action of barium on the gastro-intestinal musculature. Death results from cardiac failure and respiratory arrest.

Red Squill. Red squill (*Urgunaea maritima*), also known as sea onions, is a plant belonging to the lily family. Glycosides are the principal active ingredients, and one of them, scilliroside, has an acute oral LD_{50} * of 0.7 mg/kg in male Norway rats and 0.43 mg/kg in females. In rodents, red squill

* LD_{50} — The lethal dose required to kill 050% of the target population.



Gavaging



Gavaging rat to determine oral LD₅₀ of a rodenticide.

produces death through central nervous system (CNS)-convulsions. It is a selective rodenticide because it induces vomiting in non-target species such as dogs. Rats cannot vomit to get rid of the poison.

Strychnine. This compound is a non-specific poison highly toxic to both mammals and birds. It is a potent convulsant and is rapidly absorbed from the gastro intestinal tract. Convulsive dizziness commonly appear within 5 to 30 minutes after ingestion. The usual cause of death is respiratory failure.

Strychnine is rapidly detoxified and excreted and does not usually cause secondary poisoning. However, target species usually die quickly from strychnine and may affect scavengers that feed on dead rats. Its use is prohibited in the Philippines.

Aliphatic Fluorines. Sodium fluoroacetate (1080), fluoroacetamide (1081) and methyl fluoro acetate are the most potent rodenticides known, being toxic to all animals in doses under 1 mg/kg. Their modes of action are identical. The compounds enter the citric acid cycle exactly as acetate does, resulting in the formulation of fluoro-citric acid which blocks the enzyme aconitase, thereby disrupting the Tricarboxylic acid (TCA) cycle. Since this cycle is of basic importance to all tissues, widespread functional changes occur in all organs, most particularly the heart and the central nervous system.

These changes cause tetanic convulsions and cardiac irregularities and ultimate failure in poisoned animals. Poisoning is rapidly fatal and there is no known antidote. This poison is prohibited in the Philippines.

ANTU. Antu (1-naphthalenythiourea) has a relatively high degree of selective toxicity for rats and dogs. Susceptible animals such as Norway rat and dog die from massive pulmonary edema and pleural effusion into the pleural cavity around the lungs. This results in anoxia and ends in respiratory failure. Repeated sub-lethal doses in rats lead to the development of tolerance so that resistance to several doses is developed. The World Health Organization (WHO) is recommending against its use.

Phosacetim. Phosacetim or gophacide is the only synthetic organophosphate chemical used as a regular rodenticide. It is an anti-cholinesterase inhibitor. Poisoning symptoms associated with phosacetim apparently develop slowly in rodents, enabling them to consume lethal doses.

Norbomide. This rodenticide has a high level of toxicity against rats, but not against other animals including mice and birds. Its toxicity in several rat species varies from 10-50 mg/kg of body weight *R. r. mindanensis* (10-25 mg/kg). Oral administration of lethal dose produces mortality within 30 minutes to several hours. Lethal manifestations of norbomide are caused

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by intense vasoconstriction which is irreversible and is not altered by such drugs as sodium nitrate isoproterenol epinephrine, or atropine. Circulation in the heart and skeletal muscle becomes impaired and death results from ischemia of vital organs and tissues such as the heart and the respiratory center in the medulla of the CNS.

The rapid onset of action of norbormide is probably the reason why baits containing it are not well accepted by rats. Microencapsulation has not increased bait consumption and mortality. The results of tests made so far suggest that the most likely use of norbormide would be for the control of Norway rats and mice (Redfern et al. 1975).

Calciferol. Calciferol (vitamin D₂ compound) is a non-specific toxicant with high cumulative effects, introduced primarily against anti-coagulant resistant rats and mice. It was intended for use in combination with warfarin. A high level of calciferol in the bait induces dangerously high blood calcium levels, while warfarin produces vitamin K deficiency. Calciferol disrupts calcium metabolism and produces hypercalcemia by promoting calcium resorption from bowels and intestinal absorption. Calcium salts are deposited in soft tissues such as the kidneys, blood vessels, heart and lungs. Symptoms of toxicity such as anorexia, diarrhea and thirst usually develop about 2 days after ingestion, but death can be delayed for as long as 7 days. There is no specific antidote to calciferol poisoning.

CHRONIC RODENTICIDES

There are two classes of chronic or anticoagulant rodenticides — the coumarins and the indandiones. They have several properties that are distinct from the acute toxicants. Toxic symptoms are delayed for several days; rodents must consume lethal doses before they stop feeding on baits. This eliminates the problem of bait shyness commonly encountered with acute toxicants and pre-baiting is unnecessary.

Savarie (1981) reviewed the effects of coumarin and indandione derivatives as these rodenticides have qualitatively similar functions as exemplified by warfarin. Additional features of other compounds are discussed elsewhere. Warfarin functions as an anti-vitamin K is essential for the synthesis of blood-clotting factors in the liver known as II (prothrombin), VIII, IX and X. Oral anticoagulants depress the formation of these factors; thus, inhibiting the formation of the fibrin clot in the blood. Toxic manifestations after ingestion of oral anticoagulants are delayed for several days because it takes time for the circulation of clotting factors in the blood.

The use of warfarin baits and other anti coagulants tested in the laboratory (Pauk and Hirata, 1976) have been implicated in deaths of dogs, cats and hogs. Mongoose fed with rats killed by anti-coagulants died or had an

elevated coagulation time, an indication of high potential secondary toxicity of these compounds. The effect of secondary poisoning or potential primary hazards on non-target species under field condition have not been determined.

Coumarins. Coumarin derivatives used extensively as rodenticides and often referred to as first generation coumarins are: warfarin, coumafuryl, coumachlor and coumatetralyl. In general, these compounds require multiple feedings causing death and they were the primary methods of control in the 1950s in many countries. However, resistance to warfarin was discovered in wild Norway rats and mice in Europe and the United States. Cross-resistance to the other coumarins and indandiones was also observed.

Three coumarin derivatives were subsequently developed to control warfarin-resistant rodents: Difenacoum, brodifacoum and bromadiolone. They are known as the second generation coumarins. These compounds are highly potent with LD_{50} 's of less than 5 mg/kg in wild Norway rats and even other rats of the genus *Rattus*. They are highly effective after a single feeding. Difenacoum produces effective control in several species including house mice, *R. norvegicus*, *R. r. mindanensis*, *R. exulans*, *Arvicanthis niloticus*, *Bandicota bengalensis*, *Nesokia indica* and *Tatera indica* (Savarie, P.J. 1981). Brodifacoum is the brominated derivative of difenacoum. It is more toxic to rats and mice and has a potency factor of about 10 times greater than that of difenacoum. It has wide activity against the commensal rodents *R. norvegicus*, *Mus musculus*, *R. mindanensis*, *R. losea*, *Bandicota bengalensis* and *B. nemrivaga* (Dubock, 1979). A 100% kill has been obtained on warfarin-resistant rats fed with brodifacoum baits. Bromadiolone also has unique rodenticide properties. It is highly toxic to rodents in single oral dose. This compound has been claimed to be effective against warfarin-resistant rats.

Indandiones. The commonly used indandione rodenticides are pindone, pival, diphacinone and chlorophacinone. Small multiple doses of indandiones act like the coumarins but when administered in large single doses, indandiones are lethal in 2 to 12 hours without appreciable effects on blood clotting. Labored breathing, muscular weakness, pulmonary congestion, venous engorgement, and hyperexcitability are toxic signs after large single doses of indandiones. These symptoms or toxicity are not seen in rodenticide applications.

Antidote for anticoagulant poisoning. Vitamin K, preferably aqueous vitamin K (phytonadione), is the antidote for anticoagulant rodenticide poisoning. It is given subcutaneously or intramuscularly at 10 to 25 mg doses; intravenous route may be needed in severe bleeding (Magallona 1980).

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In severe poisoning, fresh whole blood transfusion may be required to supply accessory coagulation factors and vitamin C (100 mg several times a day) may be a useful adjunct in therapy. Oral ferrous sulfate may be used to treat secondary iron deficiency anemia.

FUMIGANTS

Fumigants are non-specific acute toxicants that are effective as gas. Some of the most frequently applied fumigants are cyanide, carbon monoxide, and methyl bromide. The Fertilizer and Pesticide Authority restricts use of methyl bromide and HCN generating compounds to Licensed Pest Control Operations only.

Calcium cyanide and sodium cyanide react with moisture in the air and soil to liberate the highly toxic gas called hydrocyanic acid also known as hydrogen cyanide and prussic acid. This toxic gas is the most rapidly fatal of all poisons and affects all animals. It is rapidly absorbed and distributed to all body cells depriving them of oxygen. It exerts its effect through the inactivation of the cytochrome oxidases, without which all cell energy transfers cease. The symptoms and signs of poisoning are the effects of the functional failure of organ systems such as convulsions and cardiac failure of organ systems with death occurring in a matter of minutes.

Carbon monoxide is highly toxic in low concentration to all animals. It acts by combining with the hemoglobin to form a stable compound, thereby reducing the oxygen carrying capacity of the blood. Death is due to tissue anoxia with depression of the respiratory center. It is hazardous because it has no odor or color to warn of dangerous concentrations.

Methyl bromide is a heavy gas which has no warning odor. It is colorless, odorless, and highly volatile liquid and toxic to the CNS. Inhalation of its vapors produces symptoms such as headache, dizziness, mental confusion, and convulsions. High concentrations result in acute pulmonary congestion and death.

REPELLENTS

Thiram, aldrin, dieldrin, and endrin are some repellents used against rodents. The repellent properties of thiram are effective against rodents, birds, rabbits and deer. It has a relatively low toxicity to mammals and its action is probably irritation of skin and tissue (Savarie, 1980). Thiram and endrin formulated together is a very effective repellent for seeds but its effect could be due to the toxicity of endrin. This formulation is highly toxic to birds and rodents. A carbamate compound has been developed for application to electrical cables to make them resistant to gnawing by rodents.

HANDLING AND STORAGE

In his book, Magallona (1980) reviewed the role of the Philippine Fertility and Pesticide Authority in pesticide registration, distribution and safe handling.

Like all pesticides, rodenticides should be stored in a cool dry place away from people especially children, animals, food, and feeds. Before using any rodenticide, always read the directions and precautions printed on the label. Never eat or drink while mixing or preparing bait. Most rodenticides are packed in cartons and once these cartons are emptied, they may be burned or buried.

RAT CONTROL EXPERIENCE

Rat control in the Philippines is based on the use of anticoagulant rodenticides. The first rodenticide used was Masagana 2000. It was developed by the members of the National Institute of Research and Development (NIRD) and the method of application was developed by the NIRD and researchers (Magallona et al. 1980). PC (Phosphorocoumatel) is a Rodent Control Agent.

These rodenticides are used in the field and continued use has resulted in sustained rodent control and ecological balance.

Table 7-1

Common
 Warfarin
 Coumatel
 Coumachlor
 Chlorophacinone

Diphacinone

*Also registered