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PROBLEMS AND RECENT ADVANCES IN THE DEVELOPMENT OF RODENTICIDES

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ABSTRACT

The cost of developing rodenticides has increased substantially during the past 10 years because of inflation and the need to supply voluminous data to fulfill requirements for registration. Chemical companies have concentrated their research efforts on materials for use against commensal rodents, primarily the Norway rat and house mouse, because there is greater chance of making a profit from these chemicals than from those developed for use against rodents that damage agricultural crops. Perhaps the greatest stimulus for the development of rodenticides was brought about by the discovery in Great Britain and the United States of rats that are resistant to warfarin. Rodenticides such as calciferol (vitamin D_2), RH-787, difenacoum, brodifacoum, and bromadiolone were developed, at least in part, because of their demonstrated effectiveness against anticoagulant resistant rats and mice. Since 1965 an improved red squill preparation and norbormide have been evaluated as rodenticides, but neither has passed government requirements for effectiveness.

INTRODUCTION

Pesticides in the United States are regulated by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), administered by the Environmental Protection Agency (EPA). This Act is very comprehensive and imposes stringent test guidelines on the manufacturers of pesticides. All chemicals for pesticide application - - toxicants, fumigants, chemosterilants, and repellents - - are included, and the active ingredient of a pesticide is defined as any substance or mixtures thereof that "will prevent, destroy, repel, or

mitigate any pest . . ." Detailed test requirements are provided by the Act for testing of efficacy against target species, and for safety to man, nontarget domestic species, and wildlife (including amphibians, reptiles, and fish). Depending on the intended use of a pesticide, as many as 53 separate toxicological tests may be required to satisfy safety requirements.

Since 1972, when FIFRA and amendments to it have been implemented, research costs for developing a pesticide from the laboratory to the market have increased 300 percent (St. Aubin, 1977). Most pesticides are developed by private companies that expect to make a profit from their investments in research and development; however, the high costs of development may hinder research, particularly for rodenticides whose animal sales volume is much lower than that for insecticides or herbicides. In the late 1960's the chance of an experimental chemical attaining marketing potential ranged from one to 5,000 to one in 36,000 (von Rumker *et al.*, 1970). Today, when pesticides must be safer, more selective, and less persistent, these odds are undoubtedly higher. In 1969 it was estimated that an average annual sales volume of $900,000 was necessary for a company to justify development of a rodenticide. Depending on the intended use of a pesticide, the costs for development may approach $4,000,000. The time required for registration of a pesticide has increased from two to five years in the 1960's to seven to 10 years today. Inasmuch as patent laws protect a company for 17 years, only seven to 10 years remain for regaining research and development costs.

Historically, the development of rodenticides has depended on empirical methods involving screening techniques such as oral dosing and feeding studies. No major effort has been made to understand the basic physiological, biochemical, or toxicological effects of rodenticides on target or nontarget species. As compared with the organophosphorus and carbamate insecticides developed for agriculture, there has been a paucity of studies of the relationship between the chemical structure and activity of rodenticides. The absence of these basic studies has stymied efforts to develop new chemicals for the numerous pest species that are of major concern. Because of its universal distribution and problems that it causes, more is probably known about the wild Norway rat than about any other rodent pest. However, acceptance and toxicity problems are typically encountered when a rodenticide developed for these rats is applied against species such as *Sigmodon* and *Microtus*.

Since the 1950's warfarin has been the most used rodenticide throughout the world. Its effectiveness and safety are well documented, but like any other chemical it can be hazardous to man and nontarget species if it is misused. When rats resistant to warfarin were discovered in Great Britain (Boyle, 1960) and the United States (Jackson and Kaukeinen, 1972), attempts were made to replace it with other rodenticides. However, it was shown that rats resistant to warfarin were also resistant to the other commonly used anticoagulants such as pindone, diphacinone, and chlorophacinone (Lund, 1972).

The objective of this paper is to present data on chemicals that have been evaluated as rodenticides since 1965. Emphasis is on those that have been developed for marketing; however, with the hope of stimulating research interest some chemicals will be discussed because they have unique rodenticidal properties. Unless noted otherwise, data in the text and tables come from studies conducted at the Denver Wildlife Research Center (DWRC). The scientific names of animals mentioned in the text or tables are given in Appendix 1, and the chemical names and sources of the rodenticides in Appendix 2.

ASSESSMENT OF CHEMICALS

Red Squill

Although red squill is probably the oldest rodenticide used today, attempts to increase its effectiveness are still being pursued. Scilliroside, a glycoside, is the active ingredient of red squill; a preparation of red squill known as stabilized scilliroside was shown in laboratory free-choice feeding tests to be more effective against wild Norway rats than the older product known as fortified red squill (Maddock and Schoof, 1970). In these feeding tests the stabilized preparation killed 60 percent of the test rats (2/10 males, 10/10 females) whereas the fortified product killed none. Maddock and School also reported that excellent control was obtained in 17 of 20 premises (dairies, hog farms, chicken ranches) treated with bait containing 0.015 percent stabilized scilliroside active ingredient (a.i.).

Using the EPA laboratory test protocol (no prebaiting; paired-preference) for acute rodenticides, researchers at the DWRC observed 25 percent mortality in Norway rats (0/10 males, 5/10 females) exposed to bait containing 0.015 percent a.i. stabilized scilliroside. However, when rats were prebaited for two consecutive days and then offered the 0.015 percent bait, with an alternate source of food, the mortality was 100 percent (8/8 males, 8/8 females). These two tests demonstrate the extreme variations that can be obtained with different test procedures. Unfortunately EPA does not recognize the validity of prebaiting tests as proof of efficacy, and the stabilized scilliroside product has not been registered in the United States.

Norbormide

Norbormide, which is selectively toxic to rats (Roszkowski *et al.*, 1964), was "discovered" during routine pharmacology screening studies designed to detect anti-inflammatory and anti-appetite drugs for use in human clinic medicine. Its acute toxicity to other animals such as dog, mouse, cat, and chicken is greater than 1,000 mg/kg. Toxic effects of norbormide are manifested by an intense peripheral vasoconstriction that probably involves ischemia of vital organs and ultimately death. Vasoconstriction does not occur in resistant animals. It was introduced with high expectations for controlling wild Norway rats, but field investigation indicated acceptance problems, particularly in roof rats (Maddock and Schoof, 1967).

In attempts to increase its acceptability, norbormide was microencapsulated (Cornwell, 1970). Theoretically, rats should consume more of an encapsulated product and hence, mortality should be increased. However, Cornwell did not observe this effect. Although more of the bait containing one percent microencapsulated norbormide was consumed, mortality was not increased. One reason for this failure may be that digestion of the capsular wall was thus preventing the absorption of lethal amounts of norbormide.

In acute oral toxicity tests, the DWRC has found that microencapsulated norbormide is as toxic as the technical material (Table 1). However, feeding tests with a bait containing one percent active ingredient norbormide in a microencapsulated form were not promising. Rats were prebaited for three nights before being offered the treated bait, but even under these conditions 100% mortality was not obtained (Table 2). The

consumption of exceedingly high doses by two surviving ricefield rats clearly shows that increased bait consumption does not result in increased mortality.

Table 1. Acute oral toxicity of microencapsulated norbormide in rats.

Common name	Sex	Lot. No.	LD_{50}, mg/kg (95% confidence limits)
Wild Norway	F	AC 675-4:1	12.5 (6.3-25)
Ricefield	F	AC 675-4:1	21.0 (12.5-35)
Ricefield	F	676-10:1	35.4 (18.4-68)

Table 2. Feeding test results with microencapsulated norbormide in rats.

Common name	Sex	Lot No.	Average LD_{50}'s consumed	Mortality
Wild Norway	F	AC 675-4:1	6.3	4/5
Ricefield	F	AC 675-4:1	22.6*	3/5
Ricefield	F	676-10:1	5.2	4/5

* Average LD 50's consumed for three rats that died = 8.0; average $LD_{50's}$ consumed for two rats that survived = 44.6

NK-15561

A relatively new acute rodenticide, NK-15561, was discovered by Japanese workers during the screening of many thiourea derivatives (Tokumitsu *et al.*, 1973). Oral dose of NK-15561 causes convulsions in rodents in one to three hours and death within 1.5 to three hours. Laboratory feeding tests with twenty-five baits were effected in wild Norway and roof rats and Japanese field voles. Aversion to the treated bait was noted in sublethally dosed animals — a common effect when acute rodenticides are used. It was reported that NK 15561 was very effective against Norway rats and field voles in field trials.

In laboratory free-choice feeding tests at DWRC (Table 3), consumption was low, and probably reflected the development of sublethal symptoms. Survivors ate only negligible amounts of treated bait on subsequent test days. Four Polynesian rats (one male and three females) did not eat the treated bait.

Table 3. Results of the free-choice feeding of rats with 2% NK-15561.

Common name	Sex	Form of bait*	Mortality	Treated bait eaten (g) Mean (range)	Chemical consumed mg/kg Mean (range) By dead	By survivors
Wild Norway	M	G	5/5	0.6(0.3-0.9)	32(13-65)	------
	F	G	3/5	0.4(0.1-0.7)	30(20-51)	32(5,59)
Ricefield	M	G	4/5	0.4(0.1-1.1)	41(8-83)	17(----)
	F	G	3/5	0.4(0.1-0.8)	47(22-82)	31(6,56)
Polynesian	M	G	1/3	0.2(0.0-0.5)	47(----)	65(0,131)
	F	G	1/3	0.1(0.0-0.2)	53(----)	28(0-74)
Wild Norway	M	O	5/5	2.3(0.9-4.8)	114(42-294)	------
	F	O	1/5	1.0(0.1-2.2)	133(----)	47(9-78)

* Granules (G) are the commercial product obtained from the manufacturer; oatmeal (O) = 90% oatmeal, 5% glycerol, and 5% Alcolec S.

Phosacetim

It is rather surprising that of the thousands of organophosphorus chemicals that have been synthesized, only one, phosacetim (Gophacide), has ever been evaluated as a practical rodenticide. It is an acetylcholinesterase inhibitor that is slowly activated *in vivo*, but not *in vitro* (Dubois *et al.*, 1967). The usually fast onset of action of organophosphates probably precludes the ingestion of enough bait to cause mortality; however, the poisoning symptoms associated with phosacetim apparently develop slowly, enabling rodents to consume lethal doses. There is a wide variation in its acute toxicity to animals. Lethal doses ranged from five to 75 mg/kg in several mammals such as pocket gophers, Norway rats, deer mice, and jackrabbits (Richens, 1967; Thompson, 1972). Field tests have resulted in excellent control of the pocket gopher (Ward *et al.*, 1967) and kangaroo rat (Schroeder, 1967). The susceptibility of birds to toxic doses ranges

from less than 2.5 mg/kg in magpies to greater than 1,700 mg/kg in domestic chickens. Secondary poisoning symptoms have been observed in golden eagles when they consumed carcasses of animals killed by phosacetim. Some eagles were severely weakened, but they all recovered. The occurrence of poisoning symptoms in eagles is one reason why this chemical never obtained registration status in the United States. In contrast, coyotes displayed no toxic manifestations when fed poisoned animals (Ward *et al.*, 1967).

UK-786

UK-786 is a remarkably species-specific toxicant for Norway rats. Its acute oral LD_{50} in male albino rats and male albino mice is 6.6 mg/kg and 1,160 mg/kg, respectively (Morrison *et al.*, 1968). Savarie *et al.*, (1973) determined the selective toxicity of UK-786 to Norway rats by administering it orally to birds (bobwhite quail, pigeon, red-winged blackbird, house sparrow) and mammals (rabbit, deer mouse, gerbil, ricefield rat, wild Norway rat, albino rat, Polynesian rat, and albino mouse). Only wild and albino rats were susceptible. Its LD50 in wild Norway rats was 8.4 mg/kg in males and 8.9 mg/kg in females. In contrast, the LD_{50} exceeded 120 mg/kg in male ricefield rats and was 354 mg/kg in male Polynesian rats. The LD_{50}'s for all birds were greater than 100 mg/kg, and usually greater than 50 mg/kg. The acceptance of UK-786 was determined in rats by offering bait with concentrations of 0.125 to 2.0 percent. No mortalities occurred in Polynesian and ricefield rats. Although acceptance was low, 80 percent mortality was recorded with the two percent bait in wild Norway rats. The supplier of UK-786 has not indicated a desire for its further evaluations. It probably would not be economical to develop a chemical for use against a single species such as the Norway rat.

Calciferol

In 1973 a product containing calciferol (vitamin D_2) and warfarin was marketed in England that could be used to formulate a bait containing 0.1% calciferol and 0.025% warfarin. High levels of vitamin D_2 in the diet cause death from hypercalcemia, and warfarin causes anticoagulant poisoning by blocking vitamin K metabolism. Rationale for using the two ingredients was that, since their mode of action was through different biochemical mechanisms, the development of resistance to either ingredient would be less. Baits containing only calciferol are toxic to rats and mice (Greaves *et al.*, 1974) and successful field trials have been conducted with calciferol plus warfarin against warfarin-resistant wild Norway rats (Rennison, 1974) and against house mice (Rowe *et al.*, 1974). The effectiveness of calciferol as a rodenticide offers the possibility that other vitamin D derivatives, such as vitamin D_3 and its hydroxy analog 1α-hydroxycholecalciferol, potential rodenticides (Makita *et al.*, 1976).

RH-787

A series of acute rodenticides designated by code as RH-945, RH-908, RH-787, which is also known as pyrinuron, were described by Peardon *et al.* (1972) and Peardon (1974). The toxicity of these chemicals to animals is shown in Tables four, five and six. Data submitted by the supplier indicated that RH-945 was selectively toxic to rodents and relatively nontoxic to birds. However, the DWRC findings for Norway rats and albino mice indicated that RH-945 was not very toxic. Acute oral LD_{50}'s (mg/kg) made available

Table 4. Acute oral toxicity of RH-945 in animals.

Common name	No. tested, sex M	No. tested, sex F	Dose (mg/kg)	Deaths or LD_{50}
Bobwhite quail	3	1	500	0
Starling	2	2	500	0
Red-winged blackbird	2		500	0
House sparrow	2	2	500	0
Brown-headed cowbird	2	2	500	0
Deer mouse	12		30.0	LD_{50}
		20	26.0	LD_{50}
		16	34.5	LD_{50}
Mouse, albino	32		7.5-960	0/4 at 7.5, 16, 60, and 960; 1/4 at 30, 120, 240, and 480
Rat, albino	31		15-480	0/3 at 15 and 30; 0/7 at 60; 2/7 at 120; 1/7 at 240; 0/4 at 480
Rat, wild Norway		9	30-120	1/3 at 30, 60, and 120
			42.0	LD_{50}
Rat, black			200	0
Rat, Polynesian			200	0
Jackrabbit	4	4	14.7	LD_{50}
Ground squirrel	1	1	62	0

Table 5. Acute oral toxicity of RH-908 in animals.

Common name	No. tested, sex M	No. tested, sex F	Dose (mg/kg)	Comments*
Bobwhite quail	4		90	LD_{50} (E)
		4	90	LD_{50} (E)
Coturnix quail	4		90	LD_{50} (E)
		4	90	LD_{50} (E)
Starling	1	1	500	No deaths
House sparrow	3		356	LD_{50} (E)
		3	500	No deaths
Brown-headed cowbird	3		178	LD_{50} (E)
Deer mouse	6		22.3	LD_{50}
		6	31.7	LD_{50}
Gerbil	6		3.8	LD_{50}
Rat, ricefield		12	2.2	LD_{50}

* E = estimated

from the supplier were 16-21 for Norway rats and 13 for albino mice. No apparent reasons for this big discrepancy are known. Later evaluations by other investigators in the United States also revealed large variations in the toxicity of RH-945 to wild Norway rats (Marsh and Howard, 1975). The LD_{50} in deer mice compared favorably with that reported by the supplier, and excellent control was obtained in free-choice (paired-preference) feeding tests with deer mice (Table 7).

Although the LD_{50} was greater than 500 mg/kg in the five species of birds tested, two secondary feeding tests with RH-945 in raptors produced mortality and symptoms of poisoning. In the first test jackrabbits were administered an oral lethal dose (94 mg/kg) and fed to two golden eagles. Both eagles died after each consumed about half of a carcass. In the second test, jackrabbits killed by an oral dose of 18 mg/kg were fed to one great-horned owl, one barn owl, and one red-tailed hawk. After consuming portions of the carcasses, both owls died and the red-tailed hawk showed toxic symptoms, but survived. Since RH-945 was never registered for marketing, these data are of academic interest only, but they do show that wide variations can exist in the toxicity to non-target species of birds.

Table 6. Acute oral toxicity of RH-787 in animals.

Common name	No. tested, sex M	F	Dose (mg/kg)	Deaths or LD_{50}
Bobwhite quail	1	1	500	0
Caturnix quail	1	1	500	0
Starling	1	1	500	1 (M)
House sparrow	1	1	500	0
Brown-headed cowbird	1		500	0
Deer mouse	8		87.2	LD_{50}
		8	87.2	LD_{50}
Gerbil	6		43.7	LD_{50}
Rat, F_1 wild Norway	9		11.1	LD_{50}
		12	14.0	LD_{50}
Rat, F_1 ricefield		9	22.3	LD_{50}
Rat, F_1 Polynesian	12		28.1	LD_{50}
		12	17.7	LD_{50}
Rat, black			19	LD_{50}

RH-908 was never extensively evaluated because research efforts were directed toward the developmentof RH-787. In general, RH-908 is more toxic than either RH-787 or RH-945; concentrations as low as of 0.1 percent killed 80 percent of the deer mice tested (Table 7). It is effective against Norway, roof, Polynesian, and African white-tailed rats, and field tests with a 0.75% bait were very effective on ground squirrels (Marsh and Howard, 1975).

Although detailed studies on the mode of action of RH-787 have not been published, it can be classified as a vitamin antimetabolite because it inhibits niacin metabolism (Anon., 1975; Deckert *et al.*, 1977). Onset of action is relatively slow, and several hours are usually required before animals die. Like RH-945, it exhibits a wide range of toxicity between target and nontarget animals; however, no discrepancies in its toxicity to Norway rats have been reported. Paired-preference feeding tests with two percent baits have been very effective in Norway, roof, and cotton rats, and house and deer mice. Laboratory and field tests with one percent baits have proven to be effective for the control of pine voles (Byers, 1976). In addition to the acute toxicity data listed in Table 6,

Table 7. Bioassay test results for RH-945, RH-787, and RH-098 in deer mice.

Chemical	Concentration (%, w/w)	Wheat Seeds accepted (%)	Mortality M	Mortality F	Total Mortality (%)
RH-945	1.0	45	5/5	5/5	100
	0.5	61	4/5	5/5	90
	0.25	77	2/5	4/5	60
	0.1	98	0/5	1/5	10
	0.05	100	0/5	1/5	10
RH-787	1.0	42	2/2	3/3	100
	0.5	68	1/2	2/3	60
	0.25	96	0/3	1/2	20
	0.1	100	0/2	0/3	0
RH-908	0.5	33	2/2	3/3	100
	0.25	67	3/4	1/1	80
	0.1	80	3/3	1/2	80
	0.05	96	0/2	0/3	0
	0.025	99	0/1	0/4	0

$LD_{50's}$ (mg/kg) for other animals are: Norway rat - - 4.75 roof rat - - 18; cotton rat - - 20 to 60; chicken - - 710; pigeons - - greater than 1,780; dogs - - greater than 500; and rhesus monkeys - - 2,000 to 4,000. Secondary poisoning symptoms with RH-787 have not been demonstrated. In one study in which mice were killed with a large oral dose of RH-787 and fed to cats and dogs, the cats and dogs developed no symptoms of poisoning (Peardon, 1974).

After extensive evaluations in the United States, the EPA registered two formulations. One contains two percent RH-787 in a bait for control of Norway rats, roof rats, and house mice. The second is a 10% tracking powder for house mice.

Gliftor

A rodenticide called gliftor is being used for control of rodents (*Microtus* species) in the Soviet Union. Gliftor is a mixture of two liquids - - 1, 3-difluoro-2-propanol (DP, the active inpredient) and 1-chloro-3-fluoro-2-propanol. Gliftor has an evaporation rate higher than that of water (Granovskii *et al.*, 1971), and inhalation of its vapors can cause disorders of the central nervous system and cellular components of the blood in experimental animals (Tkach *et al.*, 1971). There is considerable variation in its toxicity among species. The acute oral LD_{50} in albino mice is 330 mg/kg, and treatment of adult male or

female mice results in increased mortality of the offspring (Tattar, 1973). Its intraperitoneal LD_{50} (mg/kg) is 165 in mice; 96 in rats; and 7.6 in rabbits (Ukach, 1974). Oral doses of 9 mg/kg or less are lethal to species of *Microtus* (Pegelman and Ivanov, 1973).

The mechanism of action has not been discussed, but from its chemical structure it is conceivable that (DP) could be metabolized into fluoroacetic acid by the following steps:

$$FCH_2CHOHCH_2F \rightarrow FCH_2CH_2OH \rightarrow FCH_2COOH$$

(DP) 2-flouroethanol (fluoroacetic acid)

It is well known that fluoroacetic acid is very toxic to animals. The wide range in toxicity of gliftor perhaps depends on whether animals have the biochemical mechanisms to convert it to fluoroacetic acid.

At the DWRC laboratory, feeding tests in male albino rats with a bait containing one percent DP as the sole source of food resulted in 90% mortality in two to five days. Animals were prebaited for one and offered and treated bait on the second and third days. As compared with prebait consumption, the consumption of treated bait dropped 77 on the first day and almost one hundred on the second days. The poor acceptance of treated bait on the first day indicated that DP is not palatable, or that sublethal symptoms develop rather quickly. Symptoms of toxicity were observed after the first feeding of treated bait.

Difenacoum and Brodifacoum

Within the past four years, three anticoagulants have been developed that may have important implications for the use of chronic rodenticides. The historical development of two of these chemicals, difenacoum and brodifacoum, can be traced back to comparative anticoagulant studies conducted in warfarin-resistant rats in which it was found that coumatetralyl was more effective than warfarin (Greaves and Ayres, 1969). In what can be considered as a basic approach to the study of the warfarin-resistant problems, it was observed by Hadler and Shadbold (1975) that chemical modifications of the 4-hydroxy coumarin side chain might produce chemicals that would be effective against resistant rats. As a result of their investigations, 25 chemicals were synthesized and both difenacoum and brodifacoum were shown to be very effective in normal and anticoagulant resistant rats.

Difenacoum and brodifacoum are very effective single dose rodenticides in wild Norway and ricefield rats (Table 8). Brodifacoum has a potency factor about 10 times greater than that of difenacoum.

In 1975 the DWRC conducted feeding tests with resistant wild Norway rats supplied by Dr. Alan Bowerman, New York State Rodent Control Bureau. The resistant rats had survived feeding tests in which they consumed 15 to 28 mg/kg of warfarin. Non-resistant rats were obtained from a colony maintained at the DWRC. Individually caged rats were offered a single cup containing 30 g of oatmeal bait treated with 0.005% difenacoum for six consecutive nights. Cups were replenished daily with fresh bait and food consumption was recorded. Two groups of rats consisting of eight nonresistant and eight resistant rats were tested. Each group comprised four males and four females. There was 100% mortality in both groups within five to eight days after exposure to the treated bait.

Table 8 Acute, single oral LD_{50} (mg/kg) of difenacoum and brodifacoum in rats.

Common name	Sex	Difenacoum LD_{50}	Difenacoum (Days to Death)	Brodifacoum LD_{50}	Brodifacoum (Days to Death)
Wild Norway	Male	2.5	3-6	0.28	4-7
	Female	3.5	6-10	0.22	5-10
Ricefield	Male	7.0	5-10	0.28	6-7
	Female	2.5	4-15	0.39	5-9

The nonresistant rats consumed 6.5 to 14.3 mg/kg of difenacoum, and the resistant rats 7.1 to 14.0 mg/kg. These data show that difenacoum is very effective against resistant rats, especially when one considers the high doses of warfarin that did not kill the resistant rats.

Hadler *et al.* (1975) also reported that difenacoum was very effective in Norway rats, but their data indicated that it might not be potent enough for the control of resistant mice.

Rodenticide characterisctics of difenacoum were summarized by Bull (1976). Both laboratory and field trials demonstrated that it produces effective control in several pest species, including house mice and wild Norway, ricefield, Polynesian, and Nile rats. Difenacoum baits offer a large margin of safety for domestic animals such as dogs, cats, and chickens, and its secondary toxicity is probably no greater than warfarin to nontarget species. Vitamin K1 is an effective antidote. Laboratory feeding tests have shown that difenacoum is effective against the lesser bandicoot rat, the short-tailed bandicoot rat, and the Indian gerbil (Greaves and Rehman, 1977).

Bromadiolone

Bromadiolone also has unique rodenticide properties. Chemically it is similar to both difenacoum and brodifacoum, and it is also highly toxic to rodents in single oral doses. Its acute oral LD_{50} for both male and female wild Norway rats is 1.4 mg/kg; mortalities occur in four to eight days. Bromadiolone is also claimed to be effective in warfarin-resistant rats, but it has not been tested against resistant rats at the DWRC.

A paired-preference feeding test in wild Norway rats was very effective with a commercial bait containing 0.005 percent (Table 9). The one male that survived the test ate 15 g of treated bait on the fourth test day, but only small amounts (average of less than 0.3 g) on later days. Except for the fourth day, when only treated bait was consumed, untreated bait consumption was 20 to 15 g per day. It would appear that this animal "cued" onto the treated bait and developed bait shyness.

Bromadiolone is being considered for registration by the EPA and is being marketed in France.

Table 9. Results of six-day free-choice feeding tests of wild Norway rats with 0.005% bromadiolone in oat groats baits.

Sex	Mortality	Time to death (days)	Bait eaten, g, mean (range)		Chemical consumed, mg/kg, mean (range)
			Treated	Untreated	
Male	9/10*	6-8	53.87 (16.7-70.9)	19.03 (4.2-54.9)	7.49 (3.6-11.1)
Female	10/10	6-10	51.04 (34.6-65.2)	13.13 (5.7-28.4)	9.92 (7.8-14.4)

*The sole survivor ate 15 g of treated bait containing the equivalent of 3.6 mg/kg bromadiolone on the 4th test night, but insignificant amounts on earlier or later days.

SUMMARY

Within the past 10 to 15 years, several rodenticides have been added to the armamentarium of chemicals that can be used to control damage caused by vertebrate pests. Some formulations of older rodenticides were improved, but major research was also conducted to develop new chemicals. A red squill formulation known as stabilized scilliroside was demonstrated in both laboratory and field tests to be more effective than the older product known as fortified red squill. In attempts to increase the acceptability of norbormide, it was microencapsulated; however, this technique did not increase its effectiveness. Relatively new acute rodenticides include NK-15561, phosacetim, UK-787, RH-787, and gliftor. The use of phosacetim has been discontinued. NK 15561 is used in Japan, and RH-787 is registered in the United States. UK-786 was tested only in the laboratory, where it was found to be highly toxic to only Norway rats. Gliftor was developed in the Soviet Union and is toxic to voles. Calciferol was developed to be incorporated into warfarin baits to kill anticoagulant resistant rats. The use and need of a calciferol-warfarin combination is being replaced by the newer anticoagulants difenacoum, and brodifacoum, and bromadiolone, which are effective against anticoagulant-resistant rats. Although it takes several days for the animals to die, these three anticoagulants are effective in single doses.

Appendix 1. Common scientific names mentioned in the test or tables.

Common Name	Scientific Name
Birds	
Pigeon	*Columbia livia*
Chicken	*Gallus domesticus*
Bobwhite quail	*Colinus virginianus*
Coturnix quail	*Coturnix coturnix japonica*
Great-horned owl	*Bubo virginianus*
Barn owl	*Tyto alba*
Red-tailed hawk	*Buteo jamaicensis*
Golden eagle	*Aguila chrysaetos*
Magpie	*Pica pica*
Starling	*Sturnus vulgaris*
Red-winged blackbird	*Agelaius phoeniceus*
Brown-headed cowbird	*Molothrus ater*
House sparrow	*Passer domesticus*
Mammals	
Wild Norway rat	*Rattus norvegicus*
Roof (black) rat	*R. rattus*
Ricefield rat	*R. r. mindanensis; R. argentiventer*
Polynesian rat	*R. exulans*
Nile rat	*Arvicanthis niloticus*
House mouse	*Mus musculus*
African white-tailed rat	*Mystromys albicandatus*
Lesser bandicoot rat	*Bandicota bengalensis*
Short-tailed bandicoot rat	*Nesokia indica*
Cotton rat	*Sigmodon hispidus*
Deer mouse	*Peromyscus sp.*
Japanese field vole	*Microtus montebelli*
Pine vole	*M. pinetorum*
Kangaroo rat	*Dipodomys ordii*
Gerbil	*Meriones unguiculatus*
Indian gerbil	*Taferia indica*

Pocket gopher	*Thomomys* sp.; *Geomys* sp.
Ground squirrel	*Spermophilus* sp.
Rabbit, domestic	*Oryctolagus cuniculus*
Jackrabbit	*Lepus californicus*
Cat	*Felis catus*
Dog	*Canis familiaris*
Coyote	*Canis latrans*
Rhesus monkey	*Macaca mulatta*

Appendix 2. Listing of Chemicals.

Common or Trade Name[R]	Chemical Name	Source
Red squill, MGK F-1901	3β, 6β-6-acetyloxy-3-(β-D-glucopyranosyloxy)-8,14-dihydroxybufa-4,20,22-trienolide	McLaughlin Gormley King Company 8810 Tenth Avenue, N. Minneapolis, MN55427 USA
Norbormide, Shoxin[R] Raticate[R]	5-(α-hydroxy-α-2-pyridylbenzyl)-7-(α-2-pyridylbenzylidene)-5-norbornene-2,3-dicarboximide	Pitman-Moore, Inc. Washington Crossing, NJ 08560 USA
NK-15561, Kayanex[R]	methylene-bis(1-thiosemicarbazide)	Nippon Kayaku Co., Ltd. New Kaijo Bldg., 2-1, 1-Chome Marunouchi, Chiyoda-Ku, Tokyo, Japan
Phosacetim, Bayer 38819, DRC-714, Gophacide[R]	0,0 bis (p-chlorophenyl) acetimodoylphosphoramidothicate	Farbenfabriken Bayer A. G. Leverkusen, West Germany
UK-786	5-(N-piperidino)-10-11-dihydro-5H-dibenzo (a.d.)-cycloheptene	Pfizer, Ltd. Sandwich, Kent England
Calciferol (vitamin D_2	24-methyl-9,10-secocholesta-5,7, 10(19), 22-tetraene-3β-ol	Sorex (London) Ltd. Fulton House, Empire Way Wembley, England
Warfarin, Sorexa CR[R]	3-(α-acetonylbenzyl)-4-hydroxy-coumarin	
RH-787,	N-3-pyridylmethylN'-p-nitro-phenyl urea	Whitmoyer Laboratories, Inc. 1 Gibraltar Plaza Horsham, PA 19044 USA
Difenacoum, Ratak[R]	3-(3-p-diphenyl-1,2,3,4-tetrahydro-naphth-a-yl)-4-hydroxycoumarin	Imperial Chemical Industries Plant Protection Division Fernhurst, Haslemere, Surrey, England

Brodifacoum, PP-581, WBA 8119, Talon[R]	3-[3-(4'-bromo[1-1'-biphenyl]-4-yl-1,2,3,4-tetrahydro-a-naphthalenyl)-4-hydroxy-2H-1-benzopyran-2-one	ICI United States Inc. Agricultural Chemicals Division P.O. Box 208, Goldsboro, NC 27530 USA
Bromadiolone, LM-637, Super Caid[R]	3-[3-(4'-bromo[1,1'-biphenyl]-4-yl)-3-hydroxy-1-phenylpropyl]-4-hydroxy-2H-1-benzopyran-2-one	Chempar Chemical Co., Inc. 260 Madison Avenue New York, NY 10006 USA

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