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DEVELOPMENT OF AN ANTICOAGULANT RESISTANCE MONITORING PROGRAM FOR PHILIPPINE RATS

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Key Words: anticoagulants, monitoring program, Philippines, resistance, rats.

A study to develop a suitable method for screening anticoagulant resistance in rats and compounds known to counter the development of resistant rats elsewhere was conducted on two local pest species.

A 25-day no-choice feeding test using 0.025% warfarin bait for *Rattus rattus mindanensis* and a 30-day no-choice feeding test for *R. argentiventer* were established as a method of screening warfarin-resistant rats. Should resistance develop among these species, this method may be used to screen resistant rats. The animal would be considered resistant if it survives 14 days after the treated bait is withdrawn.

Bromadiolone [hydroxy-4', coumarinyl-3') -3-phenyl-3, (bromo-4, biphenyl-4')-1-propanol-] at 0.005%, brodifacoum [3-(4'-bromo 1-1' biphenyl)-4yl- 1, 2, 3, 4, tetrahydro-1-naphthalenyl)-4 hydroxy-2H-1-benzopyran-2-one] at 0.002% and warfarin [3-(α-acetonylbenzyl)-4-hydroxy coumarin)] at 0.025% resulted in similar mean number of days to death 5.6, 6.5, and 5.9 days, respectively. The first two compounds have potential use in the Philippines to kill anticoagulant-resistant rats.

The information gathered from this study served as a guideline in this proposed anticoagulant resistance monitoring program for these rat species in the Philippines.

INTRODUCTION

Anticoagulant rodenticides have already been used worldwide before they were introduced in the Philippines. Their use in the country became popular when a delivery system for anticoagulants called sustained baiting was developed.

Sustained baiting with anticoagulant rodenticides was designed specifically for use in tropical crops like rice (Sanchez and Reidinger, 1980), corn (Sanchez et al., 1976), coconut (Reidinger and Libay, 1980) and pineapple-coconut intercrop (Hoque, 1982). The method has become part of the required crop protection technology since 1973 and has been rapidly accepted by Filipino farmers.

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Intensive use of anticoagulants in the country, however, may lead to resistant rat populations. This happened in Europe (Boyle, 1960) and in the United States (Jackson and Kaukeinen, 1972) where anticoagulants were used intensively for a decade or so. Prevention of resistance, however, requires a system that will regulate resistance in a population within an acceptable range. Apparently the first attempt at a national system for the regulation of anticoagulant resistance was done in the United States. Animals from different countries collected were sent to either of the two anticoagulant resistance laboratories and screened for resistance using the standard feeding test of the World Health Organization (Brooks and Bowerman, 1975; Frantz and Padula, 1980). If the frequency of resistance among urban rats were 10% or more, they advised not to use anticoagulant rodenticides until the prevalence of resistance dropped to 5% or less.

The prevalent increase of resistant rats has prompted a search for alternative compounds. Recent compounds include brodifacoum, an anticoagulant rodenticide that can be used as an acute toxicant against both resistant and non-resistant rats. This rodenticide has been tested in the laboratory (Redfern et al., 1976; Rowe and Bradfield, 1976) and in the field (Rennison and Dubock, 1978). Bromadiolone is a similar type of compound which is also capable of controlling warfarin-resistant rats and mice (Meehan, 1978).

Inasmuch as sustained baiting with anticoagulants is thus far the best control method developed to protect Philippine crops from rats, it would be beneficial to use anticoagulants as long as possible. However, we need to develop techniques that can be used for an efficient monitoring program based on periodic sampling and testing of rat populations to detect resistance.

This study was then conducted to develop a suitable method of screening anticoagulant-resistant rats on two local pest species, *Rattus rattus mindanensis* (Mearns) and *R. argentiventer* (Robinson and Kloss), and to test compounds known to counter the development of anticoagulant resistance in rat populations elsewhere for effectiveness on local species. The information gathered will be needed to develop a system to regulate resistance within acceptable ranges and monitor anticoagulant resistance in Philippine rats.

MATERIALS AND METHODS

R. r. mindanensis were collected from ricefields in Muñoz, Nueva Ecija, and Sta. Cruz, Laguna (Luzon) and *R. argentiventer* from Butuan, Agusan del Sur (Mindanao). *R. r. mindanensis* specimens were grouped in holding cages by sex while *R. argentiventer* specimens were grouped similarly but were held in colony rooms since they survive better this way. Both species were maintained on "creep pellets" (a local feed for domestic animals) and water provided *ad libitum* for at least 3 weeks before the tests. Non-gravid female and male adult rats which appeared healthy were placed in individual

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cages (17 cm x 24.5 x 17.5 cm) for at least one week before any test was initiated. Animals were maintained at room temperatures ranging from 21.1 to 26.7 C and a dark period of 9 to 10 hr.

Length of Feeding Period

Preparation of bait materials and the selection of number of days that the rats are exposed to baits were based on a WHO (1972) report with some modifications. Baits were prepared by dispersing technical warfarin in talcum powder and then mixed into an appropriate amount of rice, giving a final concentration of 0.025% in the bait. Feeding test of 0.025% warfarin was chosen for two reasons: 1) this is the concentration of anticoagulant baits used to control Philippine rats, and 2) *R. argentiventer* and *R. r. mindanensis* co-exist but are often confused with each other. Thus, 0.025% warfarin concentration in baits is assumed toxic to both or either species in the field.

Groups of 20 rats consisting of equal numbers of males and females were assigned at random to each of the feeding periods: 2, 4, 6, and 9 days for *R. r. mindanensis* and 2, 4, 6, and 8 days for *R. argentiventer.* Replicate feeding tests were conducted for each species until a total of 40 animals were subjected to each feeding period. Animals were offered untreated rice for 2 days before they were given the treated bait. Individual animals were given 15 g of the treated bait daily throughout the assigned feeding period with no alternate food. Prepared baits were removed from cages at about 8:00 a.m. every day and replaced at about 4:00 p.m. to reduce feeding pattern variability among animals. Individual consumption was measured daily by weighing the unconsumed food (including air-dried spillage) and subtracting it from the total amount of food provided by the previous evening. After the selected feeding periods, anticoagulant baits were replaced with creep pellets. Observations for mortality were generally made every 12 hr. for at least 28 days after each feeding test was started. Each dead animal was necropsied to detect symptoms of poisoning such as a usually pale liver or internal hemmorhage.

The relationship between mortality and duration of feeding on anticoagulant bait was analyzed by probit analysis (Finney, 1971). Separate analyses were made on the mortalities between sexes, and between two trials for each species. When no significant differences were found between sexes, the data from both sexes in each species were summed within each feeding period for further analyses. A t-test was also used to compare mean bait consumed and poison ingested by dead and surviving animals.

Feeding Test of Three Rodenticides

One week before the test, the animals were weighed, placed in individual labelled cages and fed whole rice and water *ad libitum.* Twenty healthy

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adult male *R. r. mindanensis* were assigned randomly to each of the other three treatments. A control group was fed with plain rice and the other groups were fed with rice baits containing 0.002% brodifacoum [3-(4'-bromo 1-1' biphenyl) -4y1- 1, 2, 3, 4, tetrahydro-1-naphthalenyl) -4 hydroxy -2H-1-benzopyran-2-one], 0.005% bromadiolone [hydroxy-4', coumarinyl-[3-(α-acetonylbenzyl) -4- hydroxy coumarin]. The desired amount of each toxicant was dispersed in talc until a homogeneous mixture of toxicant and talc was attained to form a concentrate. This concentrate was then mixed with one part poison (by weight) to 39 parts of rice until a uniform coating of rice surfaces was attained. The animals were given the formulation for 3 consecutive days and the warfarin for 10 days; the control group was fed with untreated rice until all treated animals died. Baits were replaced with creep pellets after the animals had completed their selected feeding periods. Individual consumption was measured each day and daily records were kept on mortality until all animals given the treated baits have died. Before analysis, data in this test were transformed first into logarithm using completely randomized design. Means were compared using Duncan's multiple range test.

RESULTS AND DISCUSSION

Length of Feeding Period

Table 1 summarizes the toxicity of 0.025% warfarin baits on *R. r. mindanensis* and *R. argentiventer* at different feeding increments. There seemed to be great individual variations in the response of the test animals. Both species seemed to have similar susceptibility to the poison as shown by low amounts of bait fatal to the animals. Variations were also noted on their degree of tolerance to the poison as shown by the different amounts of bait consumed by surviving animals. Great variability was apparent on the number of days before animals died after feeding on the bait. This ranged from 2 to 4 days regardless of the length of time that they were exposed to the bait.

The amount of bait consumed by *R. r. mindanensis* that survived in the test ranged from 8 to 76 g and poison ingested ranged from 11 to 138 mg/kg. Animals that died significantly consumed more baits than those that survived at 2 days ($p > 0.001$). Animals that died ingested higher amount of poison ($p < 0.001$) except at 2 days feeding. *R. r. mindanensis*, whose status as a true *R. rattus* or its sub-species has been questioned, was similar to R. *rattus* in its variability of response to 0.025% warfarin treatment (Greaves et al., 1976). A dosage of 7.4 to 48.2 mg/kg was lethal to *R. rattus* during a 10-day feeding on 0.005% warfarin (Bentley and Larthe, 1959), whereas 14 to 182 mg/kg was lethal to *R. r. mindanensis* during a 9-day exposure to 0.025% warfarin bait.

R. argentiventer that died during the tests consumed 11 to 53 g bait and ingested 14 to 92 mg/kg toxicant. Dead animals significantly consumed

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Table 1. Toxicity of 0.025% warfarin baits to two species of rats exposed to different feeding periods. Forty animals with equal numbers of males and females were used for each feeding period.

Feeding Period (days)	Total Bait Consumed				Total Poison Consumed (mg/kg)				Days to Death		Percent Mortality
	Dead		Survivors		Dead		Survivors				
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	
					Rattus rattus mindanensis						
2	21.9	11-30	19.7	8-30	31.1	14-60	30.1	11-52	5.5	3-11	40
4	36.2	10-63	31.5	8-62	54.2	22-144	48.9	25-80	6.4	4-12	62
6	39.3	15-94	38.6	12-76	64.5	21-116	38.6	22-138	6.6	4-17	82
9	49.0	11-134	19.2	16-23	78.4	14-182	33.9	27-41	7.1	3-16	95
					Rattus argentiventer						
2	16.2	12-20	15.4	11-20	34.1	11-54	33.3	19-62	4.3	3-9	50
4	25.7	12-45	29.9	13-37	57.3	28-99	59.1	14-82	4.7	2-6	72
6	26.8	12-53	18.2	11-23	65.5	15-182	45.8	26-76	5.0	2-14	85
9	28.6	111-49	22.7	23-38	64.7	27-117	58.5	27-99	5.6	3-9	92

more baits than the survivors at 6-day ($p < .002$) and at 8-day ($p < .001$) feedings. Likewise, dead animals ingested higher amount of poison ($P < .05$) except at 4-day feeding. Doses fatal to *R. argentiventer* were as low as 11 to 28 mg/kg and for those which survived as high as 62 to 99 mg/kg. Buckle et al. (1980) observed a similar trend in *R. argentiventer* in Indonesia. Slightly higher mortalities were observed in the *R. argentiventer* tested here than in the study of Buckle et al. (1980).

Table 2 shows lethal feeding periods (LFPs) of 50, 95, and 98 and their respective 95% fiducial limits. Different LFPs between species did not vary significantly as shown by the overlapping fiducial limits. Slope of the line was 2.7 (s.e. ± 0.056) for *R. r. mindanensis* and 2.3 (s.e. ± 0.056) for *R. argentiventer.* Chi-square for *R. r. mindanensis* was 1.21 and 0.21 for *R. argentiventer* which shows that both species have homogeneous populations.

For *R. r. mindanensis* with 95% fiducial limits, LFP_{50} was 2.7 days (2.7 to 3.5), LFP_{95} was 14.5 days (7.9 to 22.4), and LFP_{98} was 15.1 (9.6 to 24.0). LFP_{50} and LFP_{98} were slightly lower than those of *R. rattus* (Bentley and Larthe, 1959). Based on WHO (1972) instructions to establish length of feeding period for screening resistant rats, *R. r. mindanensis* then had to be fed for 25 days. The result showed a lower LFP_{50} for *R. r. mindanensis* than *R. rattus* (Greaves et al., 1976). This meant a shorter feeding time for *R. r. mindanensis* before 50% of the animals died as compared to *R. rattus* with an LFP_{50} of 6.4 days.

For *R. argentiventer* with 95% fiducial limits LFP_{50} was 2.1 days (1.4 to 3.1), LFP_{95} was 15.4 (8.6 to 27.4) and LFP_{98} was 16.1 days (8.9 to 29.4). These LFPs were diferent from those obtained by Buckle et al. (1980). The LFP_{95}, LFP_{98} and the upper fiducial limits of the *R. argenti-*

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venter tested in the Philippines were much higher than those of the rats tested in Indonesia. Taking the upper 95% fiducial limits for LFP_{98} would mean 30 days feeding period corresponding to 14.4 LFP_{50s} or 1.7 times longer than the LFP_{98} obtained by Buckle et al. (1980) in Indonesia.

Animals in this study died 2 to 4 days earlier than the *R. argentiventer* tested by Buckle et al. (1980). This seemed to show that *R. argentiventer* in the Philippines is more susceptible to 0.025% warfarin than the species in Indonesia (Buckle et al., 1980).

Table 2. Estimated lethal feeding period (days) of adult rats exposed to different durations of feeding on 0.025% warfarin bait. Eighty males and 80 females were used for each feeding period.

Percentage Mortality	Estimated Lethal Feeding Period (Days) *R. r. mindanensis* Mean	95% Fiducial Limits		*R. argentiventer* Mean	95% Fiducial Limits	
50	2.7	2.1	3.5	2.1	1.4	3.1
95	14.5	7.9	22.4	15.4	8.6	27.4
98	15.1	9.6	24.0	16.1	8.9	29.4

Feeding Tests of Three Rodenticides

Table 3 summarizes the results of a no-choice feeding test of 0.002% brodifacoum, 0.005% bromadiolone and 0.025% warfarin to susceptible *R. r. mindanensis*. All animals that fed on baits containing any of the toxicants died. No significant difference was observed on mean number of days to death, (5.6 days for brodifacoum, 6.5 days for bromadiolone, 5.9 days for warfarin). Bromadiolone and warfarin were lethal as early as the third day and brodifacoum one day later. It took 9 days to effect 100% mortality on brodifacoum; 14 days on bromadiolone; and 15 days on warfarin. No appreciable changes were noted on mean intakes of animals when they were shifted to the treated bait. Animals consistently consumed high amount of bait even up to the third day of baiting.

R. r. mindanensis fed with bait containing 0.002% brodifacoum all died 9 days earlier than those of resistant *R. rattus* (13 days) and 10 to 17 days for the non-resistant *R. rattus* (Redfern et al., 1976). This could have been due to the longer feeding time (3 days) in this study. It took a shorter period to effect mortality in *R. r. mindanensis* (4 days) than the *R. rattus* of Redfern et al. (1976) (5 and 6 days, respectively for the resistant and non-resistant animals).

Initial mortality from brodifacoum treatment was one day later than from the other compounds. This delayed effect of brodifacoum may give animals additional time to ingest a lethal dose before the poison produces its effect. Moreover, a shorter period is needed to effect 100% mortality once a lethal dose has been ingested by the animal. There was no apparent change in daily bait intake of rats fed with brodifacoum, indicating that this toxicant can be used in a continuous field baiting program like other anti-coagulants inasmuch as animals do not seem to show aversion to the poison.

The overall effect of 0.005% bromadiolone was similar to that of the other two compounds in terms of bait consumption and days to mortality. The animals in this test reacted similarly like the non-resistant *R. rattus.* Mean days to death for *R. r. mindanensis* was 6.5, slightly lower than that of *R. rattus* which was 8.5.

Table 3. Performance of three rodenticides during a no-choice feeding test on Rattus rattus mindanensis. *Animals were given untreated plain rice for 2 days followed by the treated bait. Control animals were fed with plain rice during the test. Results presented here are the means of 20 adult males per treatment.*

Treatment[1] and Concentration (%)	Mean Daily Bait Intake			Total Amount of Active Ingredient Lethal to Animals (mg/kg)			Days to Death	
	Untreated	1st day	3rd day	Mean		Range	Mean	Range
Brodifacoum 0.002	10.7	11.5	11.0	4.4	2	6.1	5.6	4-9
Bromadiolone 0.005	9.5	9.6	10.5	9.8	3.5	15.6	6.5	3-14
Warfarin 0.025	10.3	9.8	10.2	78.6	33.2-	108.3	5.9	3-15
Control	9.4	9.6	11.8	—	—	—	—	—

[1]Brodifacoum and bromadiolone baits were offered for 3 days and warfarin for 10 days. All animals that were fed with the toxicants died.

Lethal dose for *R. r. mindanensis* was 3.5 to 15.6 mg/kg and 7.3 to 13.1 mg/kg for *R. rattus.* These results apparently show that *R. r. mindanensis* is as variable as *R. rattus* in its response to 0.005% bromadiolone. *R. r. mindanensis* fed with bromadiolone bait started to die on the third day like the warfarin-treated animals, but it took longer (14 days) to effect 100% mortality compared to brodifacoum (9 days). In both toxicants, animals fed with this compound did not show apparent aversion towards the bait as can be seen from the consistently high amounts of bait consumed by the animals. With these results, the rodenticide can be used in multiple baiting against *R. r. mindanensis.*

Results of feeding tests on warfarin were the same as those observed by Hoque and Reidinger (1980) in terms of days to death and total amount of poison to effect mortality. However, a slightly lower mean days to death (5.9) was obtained in this study than in previous tests (10.1 days).

RECOMMENDATIONS

This study was conducted as a reaction to reports about genetically resistant rat populations in countries that have used anticoagulant rodenticides for over a decade (Boyle 1960; Jackson and Kaukeinen, 1972). Baseline information were gathered to develop a system that will help monitor anticoagulant resistance on Philippine rats. The difficulty is that anticoagulant resistance in rat populations within the Philippines is unknown and the methods for detecting resistance in the two species studied here were developed in lieu of animals with known resistance. What was needed was a technique to monitor resistance level in rat populations and an alternative for farmers to counteract the build-up of resistant populations.

A model with three major components was developed from Odum (1971) to illustrate the proposed monitoring system for the Philippines (Figure 1). Controlled quantity refers to the resistance in a given rat population. The screening method used in this study is included in the sensor part of the model. The effector includes the various methods and rodenticides available to protect crops. Inasmuch as sustained baiting is the best method developed thus far to protect crops from rats, it will be beneficial to use chronic anticoagulants for as long as necessary.

Theoretically, resistance (the controlled quantity) is always present in a given rat population, but the extent is unknown in the Philippines. It is therefore important to know what percentage of resistance can be tolerated in terms of damage to crops or how many damaging animals can be tolerated in the field. These have always been an issue among biologists. To state some of the observations of people in the field might shed light on these questions.

Davis (1972) found that urban Norway rats recover more rapidly if the population is reduced 50 to 70% but slower with a 90% reduction. In the Philippines, Sumangil (1978) reported that a rat population that was reduced from 60 to 70% can easily recover in a year, whereas it would take 2 years for a rat population to recover after a 90% reduction. According to Davis (1972) and Sumangil (1978) relief from rat problems was often felt in areas where a reduction of 90% has been accomplished. Taken in context does this mean that the residual 10% of the population can be tolerated to inflict damage?

Studies at the National Crop Protection Center (NCPC), University of the Philippines at Los Baños, have not yet shown a direct relationship between population and damage. Brooks and Bowerman (1975) recommended a 10% level of resistance as the cut-off point at which chronic rodenti-

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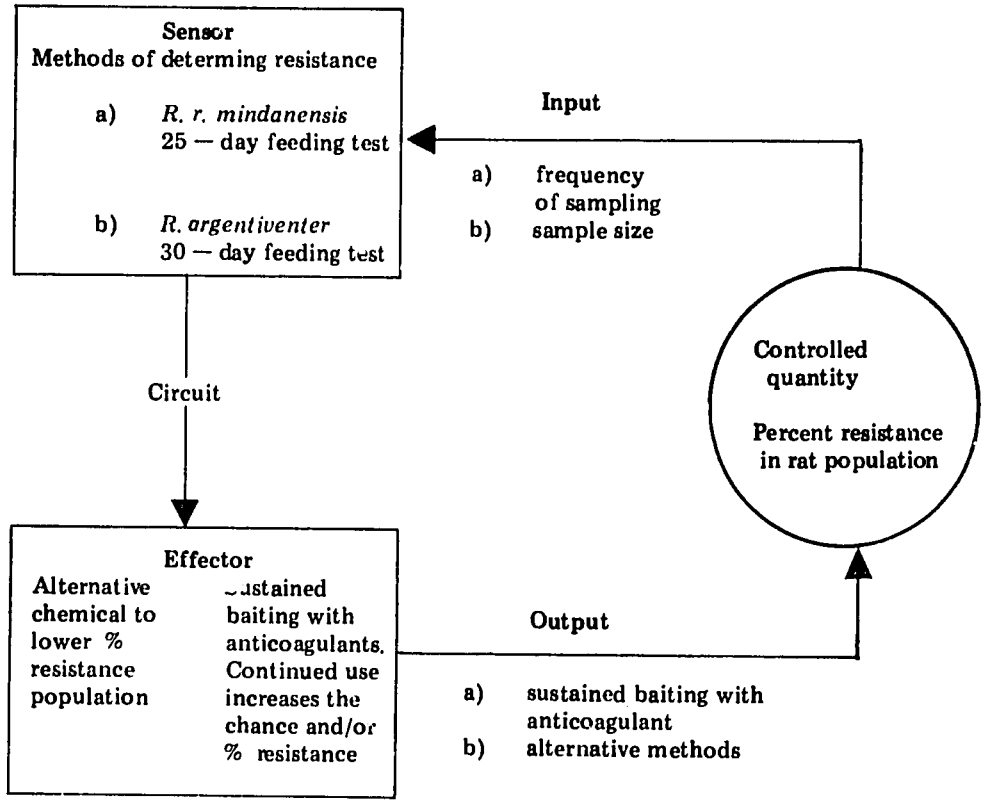

Fig. 1. Schematic diagram of a proposed anticoagulant resistance monitoring system for the Philippines (after Odum's 1971 cybernetic model).

cides should not be used until resistance level decreases to 5%. This recommendation was based on an urban location and this may make a big difference in crop areas.

The inputs needed to feed the sensor include sample size and frequency of sampling. Annual sampling of no less than 40 animals should be conducted in areas which may represent a town or barrio where anticoagulants have previously been in constant use. The NCPC and the 12 regional crop protection centers under the aegis of the Bureau of Plant Industry, strategically located all over the country, may serve as sensing centers. Before laboratories are established, personnel should be trained on the rudiments of the method for screening resistant rats. NCPC can provide training and quality control to standardize procedures and minimize variability of results. The future resistance laboratories should be equipped with basic equipment such as individual rat cages, colony cages, weighing scale, feeding cups, water bottles, and others.

The sensor for *R. r. mindanensis* is the 25-day no-choice feeding tests using 0.025% warfarin. *R. argentiventer* should be subjected to a 30-day feeding test using the same chemical and concentration. Should resistance develop among these species, animals that survive 14 days after the poisoned

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bait is withdrawn may be considered resistant. During the next few years, resistance may still be very low but with intensive use of anticoagulants, resistant populations are expected to develop. However, it would be best to start monitoring resistance now as the data generated might serve as a basis for improving the design and finding a more precise sampling technique.

Per cent level of resistance in a given rat population determines the output from the effector. This indicates whether the existing effector, the sustained baiting with anticoagulants, is still "safe" to use or cause a switch to an alternative method, like chemicals that can drastically lower level of resistance. If percentage of resistance is high (maybe 5% or more), this may call for technical assistance from the government in applying the emergency control measures to lower or eradicate pockets of resistant rat populations.

The rodenticides that were tested on *R. r. mindanensis* in the laboratory may be used as alternatives since they are able to kill resistant rats. However, delivery systems for these chemicals have yet to be studied before they can be recommended as part of the crop protection technology for farmers. Ideally these other rodenticides should be used alternately so that resistance will oscillate within the tolerable level and thus permit resumption in the use of anticoagulants.

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