March 1974

A NEW SERIES OF SELECTIVE RODENTICIDES

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ABSTRACT: A new series of target-specific, single-dose rodenticides has been discovered by Rohm and Haas Company (Peardon, 1972; Peardon et al., 1972). One compound, RH-787, best exemplifies the balance of desirable qualities of a good rodenticide. It is effective against a broad spectrum of pest rodents, has a desirable margin of safety in non-target animals, is well accepted in baits, causes no secondary hazard problems and is effective against "Warfarin-resistant" (anticoagulant-resistant) rats. This material will become commercially available upon receipt of registration from the EPA.

The ideal single-dose (acute) rodenticide has been characterized as one which is highly effective against a broad spectrum of pest rodents, has a wide margin of safety in non-target animals, is very readily accepted in baits, does not induce "bait shyness", does not cause secondary hazard toxicity in pets or raptors, and is effective against Warfarin-resistant (anticoagulant-resistant) rats. It should also be stable to allow good shelf-life, be economical to manufacture and be easy to use. This is a lot to ask of one rodenticide, but it is believed that one or more of our new compounds very closely meet these criteria.

Single-dose rodenticides were widely used for rodent control for many years until the early 50's when Warfarin, a non-specific anticoagulant type poison requiring multiple feedings, was introduced. It gained prominence and for more than 20 years now Warfarin and other anticoagulants have been widely used. Currently, however, widespread development of genetic resistance to the entire gamut of anticoagulants is mounting. In Denmark and Great Britain Warfarin-resistance and cross resistance to other 4-hydroxy-coumarins and 1,3-indandiones is so prevalent that it virtually excludes the use of anticoagulants (Gratz, 1973). Resistance has also been reported in the U.S. and other countries and is continuing to spread (Jackson and Kaukeinen, 1972). Therefore, there is most decidedly a place for a good single-dose rodenticide now and the Rohm and Haas discovery is considered to be particularly timely and important.

While a number of compounds in this series are very good rodenticides, the activity can best be illustrated by talking in depth about one compound, coded RH-787. Biological efficacy and toxicity trials carried out by Rohm and Haas will be covered. Many other trials have been carried out by workers here and abroad and it can only be said that these results confirm our work. Workers in the U.S. include Mr. Rex E. Marsh and his colleague, Dr. Walter E. Howard, Department of Animal Physiology at the University of California in Davis; Dr. William B. Jackson, Environmental Studies Center at Bowling Green State University in Bowling Green, Ohio; Dr. Frank Horsfall, Jr., (Emeritus), Virginia Polytechnic Institute and State University, Blacksburg, Virginia; Dr. Peter J. Savarie, U.S.D.I. at Denver, Colorado; Mr. Richard E. Griffith, Jr., U.S.D.I. at Twin Falls, Idaho; and Dr. H. Wayne Hilton, Hawaiian Sugar Planters' Association in Honolulu, Hawaii.

In laboratory trials, the test used after preliminary activity has been established is the "paired preference test". In this test the rodents are given a completely free-choice between an unpoisoned basal ration and the same feed containing a specified quantity of the rodenticide. Initially this test is used to titrate efficacy by using groups consisting of 4 animals of a given species individually caged at varying dose levels. Seventy-five percent mortality must be achieved in this test to be considered an effective dose. Each species of target animal must be tested before the effective dose level can be established. Species tested by our group include Norway rats (Rattus norvegicus), roof rats (Rattus rattus), cotton rats (Sigmodon hispidus), house mice (Mus musculus), and deer mice (Peromyscus sp.).

When the dose level has been determined, each species must be tested at that level in the "paired preference test' using 20 animals; 10 male and 10 female. However, 90% mortality must be obtained to pass this test. The 2% RH-787 level passed this test against all 5 species, Tables 1 and 2.

Table 1. Efficacy Studies in Rats.

Animal	No. of Animals*	Dosage (%)	Efficacy (%)
Paired Preference Tests			
Norway rats	20	2	100
Roof rats	20	2	80
Roof rats	20	2	90
Cotton rats	20	2	90
Tank Tests			
Norway rats	20	2	95
Roof rats	20	2	100
Cotton rats	20	2	90
Albino rats	20	2 (Final Bait)	100
Albino rats	20	2 (From 40% Conc.)	90

*Ten males and 10 females in each group.

Table 2. Efficacy Studies in Mice.

Animal	No. of Animals*	Dosage (%)	Efficacy (%)
Paired Preference Tests			
House mice	20	2	100
Deer mice	20	2	100
Tank Tests			
House mice	20	2	90
Deer mice	20	2	100
House mice	20	2 (Final Bait)	90
Albino mice	20	2 (From 40% Conc.)	65
Albino mice	20	2 (From 40% Conc.)	100
Tracking Powder Tests			
House mice	16	10	100
House mice	20	10	100

*Each test group contains equal numbers of both sexes.

Next, each species was tested separately using the "tank test". The "tank test" is very similar to the "paired preference test" in that the test animals are given an equal and free-choice of unpoisoned and poisoned rations, 20 animals (10 male and 10 female) are used, and 90% of the animals must be killed to pass the test. The major difference is that all 20 animals are caged together bringing into play the dynamics of group interaction. Rats especially are cunning creatures and can quickly associate anything suspicious about their food and ill feeling, and become very selective in what they eat. No suspicions were aroused with RH-787. The 2% level of RH-787 passed when tested against each of the 5 target animals, Tables 1 and 2.

All the tests described thus far were conducted using the standard EPA ration consisting of the following:

Crude ground corn	65%
Steel cut oats	25%
Mazola corn oil	5%
10-X confectioners sugar (Jack Frost)	5%

The final formulation developed must be tested against rats to show that it also will pass the "tank test". A ration was formulated to be used as bait, tested against rats using 2% RH-787, and 100% kill was obtained, Table 1. We also tested our 40% concentrate formulation and passed the "tank test" with 90% kill, Table 1. With this accomplished, the next step is field testing. For U. S. registration, the EPA requires a number of tests be conducted in each of five widely separated regions of the U.S. using each species for which claims of effectiveness are to be registered. Field work has been started and good results have been obtained to date.

RH-787 is quite target specific. While highly active against pest rodents, RH-787 does not appear to pose a hazard to non-target animals. Here again tests must be conducted directly on each target animal to obtain LD_{50} levels. This is done by individually dosing large numbers of animals by stomach intubation to establish a level which kills 50% of the animals. This means animals must be handled physically including live wild roof rats, Norway rats and all the other pest rodents to be tested. This caused considerable concern to those working with the animals until the "light-proof bag" method was described (Redfern, 1971). Tests in our laboratory indicate a wide margin of safety exists between target and non-target animal LD_{50} levels. While the LD_{50} for Norway rats was found to be 4.75 mg/kg, Table 3, it was found to be 710 mg/kg in chickens, > 1780 mg/kg in pigeons, > 500 mg/kg in dogs, and between 2000 and 4000 mg/kg in Rhesus monkeys, Table 4. The latter would tend to indicate it would not be toxic to humans under use conditions, but we have no human data to substantiate this statement.

Table 3. Toxicity Studies in Rats and Mice.

Animal	Sex	Formulation	LD_{50} (mg/kg)
Albino rats	M	Technical	12.3
Norway rats	M	Technical	4.75
Roof rats	M	Technical	18.0
Cotton rats	M & F	Technical	20-60
Albino rats	M	40% Concentrate	36.0
Albino rats	M	2% Final Bait	580
Albino mice	M	Technical	84
House mice	M	Technical	98
Deer mice	M	Technical	10-20
Albino mice	M	40% Concentrate	220
Albino mice	M	10% Tracking Powder	1050
Albino mice	M	2% Final Bait	4120

Table 4. Toxicity Studies in Non-Target Mammals, Birds and Fish.

Animal	Sex	LD_{50}
Guinea Pigs	M	30-100 mg/kg
Voles	M & F	205 mg/kg
Rabbits	M	> 300 mg/kg
Dogs	M	> 500 mg/kg
Monkeys	-	2,000-4,000 mg/kg
Chickens	M	710 mg/kg
Pigeons	M & F	> 1,780 mg/kg
Bluegill	-	1,000 mg/l. No Effect
Rainbow Trout	-	1,000 mg/l. No Effect
Fathead Minnow	-	1,000 mg/l. No Effect
Channel Catfish	-	1,000 mg/l. No Effect

RH-787 is relatively slow acting. It takes several hours to kill a rat or a mouse after a lethal dose has been ingested. This is a desirable feature in a rodenticide for several reasons. Several hours allows sufficient time for normal feeding so a lethal dose is ingested. Bait-shyness does not develop since no ill effects are associated with the bait. It also gives the animal ample time to return to his burrow before he dies. Although there should be little need for an antidote, work on an antidote is in progress and the delay in action would allow time for treatment if accidentally ingested. Rats have been protected from several times a lethal dose and work is continuing on the mode of action. Information on the antidote and mode of action will be released at a later date.

RH-787 should not be hazardous to handle. While the RH-787 technical material was toxic to target animals (rats) by inhalation, there was no dermal or eye irritation in rabbits. Nor was there acute dermal toxicity (LD_{50} > 4000 mg/kg) in rabbits. These data suggest that formulations of RH-787 should not be hazardous to man when handled according to recommendations.

Secondary hazards should not be a problem with RH-787. Mice for these trials were killed with a 3X LD_{100} dose of RH-787. Mouse carcasses were quick-frozen to prevent decomposition, ground and fed to cats and dogs previously fasted for 24 hours. In our trials, no adverse effects were observed in either cats or dogs, Table 5.

Table 5. Secondary Hazard Toxicity.

Animal	Dosage	Results
Cats	Mice - 3X LD_{100}	No Effect
Dogs	Mice - 3X LD_{100}	No Effect

RH-787 has an advantage over commercially available single-dose rodenticides in a balance of desirable features. In addition, it has an advantage over commercially available anticoagulants in that it kills comparatively fast, saving labor and ultimately money. It also has a distinct advantage over anticoagulants in its ability to kill anticoagulant-resistant rats.

In summary, a number of compounds in the series were active as rodenticides. The characteristics are best exemplified by RH-787 as follows:

1. It is a single-dose rodenticide.
2. It is effective against a broad spectrum of pest rodents.
3. It has a wide margin of safety in non-target animals.
4. It is accepted in bait formulations.
5. It does not cause bait shyness.
6. It does not cause secondary hazards.
7. It is safe to handle.
8. It has good shelf 1ife.
9. It is economical.
10. It is easy to use.
11. It is relatively slow-acting.
12. An effective antidote should become available.
13. And, it is effective against "Warfarin-resistant" (anticoagulant-resistant) rats.

This material will become commercially available upon receipt of registration from the EPA.

I wish to thank Dr. Jackson for permission to include a statement on "Warfarin-resistance" and Mr. J. E. Ware, Mr. R. D. Parsons, and many others at Rohm and Haas for their part in obtaining the data presented.

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