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RACUMIN PLUS , A NEW PROMISING RODENTICIDE AGAINST RATS AND MICE

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ABSTRACT: Coumatetralyl (Racumin) has been known since 1957 as a multiple dose anticoagulant and has been used successfully over many decades. In the seventies and especially the eighties, rats developed an increased resistance to anticoagulants in certain regions of Central Europe. Also, the addition of vitamin K to animal feed (especially to chicken feed) has reduced the efficacy against rats and mice in farm buildings. Combinations of anticoagulants with different types of vitamin D are generally described to increase the efficacy of action against rodents. It was found that especially the combination of coumatetralyl with cholecalciferol (vitamin D3) could overcome the above mentioned problems. Cholecalciferol causes hypercalcemia and, therefore, has a different mode of action compared to anticoagulants. The combination of these active ingredients leads to an obvious increase in efficacy against rodents, even under difficult conditions. The formulation with optimal rodenticidal efficacy contains 0.04 % coumatetralyl and 0.025 % cholecalciferol mixed in rolled oats.

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INTRODUCTION

Anticoagulants are the most important rodenticides worldwide. Multiple dose anticoagulants have been in use since the early 1950s. In the 1970s the so called "single dose anticoagulants" were evaluated. Besides this mode of action, the hypercalcemia-causing agents calciferol and cholecalciferol came into use, particularly for the control of mice.

In the 1970s and 1980s rats developed an increased resistance to anticoagulants in certain areas worldwide (Greaves 1985, 1986; MacNicoll 1982). Also, vitamin K containing feed (e.g., maize and chicken feed) caused severe problems in some places.

This paper describes a combination of coumatetralyl and cholecalciferol which overcomes these problems.

METHODS

Study Animals

The tests were carried out with two strains of the Norway rat *(Rattus norvegicus)* and the house mouse *(Mus musculus)*.

The albino strain of *R. norvegicus* belongs to the WISTAR strain. The wild rats are from a laboratory breeding in our institute. The parental generation of these rats was captured in the environment of Leverkusen (Germany).

Choice Tests with Albino Rats

Pairs of rats housed together in type III macrolon cages were offered 50 g of the test formulation and 50 g of the premix formulation (e.g., rolled oats or shredded wheat) every day for six consecutive days. The sides from which the food variants were offered were switched daily, to compensate for any "side" influences. The quantities of feed eaten were determined each day by weighing. Drinking water was available *ad libitum.*

Choice Test with Wild Rats

Norway rats housed individually in metal cages were offered 30 g of the test formulation and 30 g of the premix formulation every day for four consecutive days. The sides from which the food variants were offered were switched daily, to compensate for any "side" influences. The quantities of feed eaten were determined each day by weighing. Drinking water was available *ad libitum.*

Choice Test According to the Guidelines of the German Registration Authorities (BBA Braunschweig. Germany) with Albino or Wild Rats (BBA 1983)

The tests were carried out in small pens which consist of three chambers in tandem arrangement connected by small loop-holes. Each chamber is one square meter in size. One chamber serves as a "living room" for the rats and contains a nestbox with hay and cellulose as nesting material. The second chamber is empty and serves as a runway and the third chamber contains the test bait, the untreated feed and the water source. The drinking water is available *ad libitum.*

The rats were acclimatized to the pens for two days. Over this period they were fed with a standard diet (altromin O). Over the following four days they received 100 g of the test formulation and 100 g of the premix formulation. The sides from which the food variants were offered were switched daily, to compensate for any "side" influences. The quantities of feed eaten were determined each day by weighing.

The choice tests with *Mus musculus* (wild strain) were carried out using similar methods.

Active Ingredients and Bait Formulations Coumatetralvl (Table 1)

Coumatetralyl has been known since 1957 and belongs to the class of "multiple dose" anticoagulants. Its efficacy is characterized by a highly cumulative effect. In comparison to the so-called "single dose" anticoagulants the LD_W of coumatetralyl for rats is high (16.5-30 mg a.i./kg body weight). After consumption over five consecutive days it increases considerably to 5 x 0.3 mg/kg b.w. The house mouse is far less susceptible than the Norway rat to an acute dose of

Table 1. LD^ of Coumatetralyl and Cholecalciferol against rats and mice.

	acute LD_{50} (mg a.i./kg body weight)	
	Norway rat	House mouse
Coumatetralyl	16.5-30	2000-4000
Cholecalciferol	43.6	42.5
	subacute LD_{50} (mg a.i./kg body weight)	
	Norway rat (after 5 days consumption)	House mouse (after 18 days consumption)
Coumatetralyl	5 x 0.3	18 x 3.5
Cholecalciferol	--	--

coumatetralyl (2000-4000 mg/kg b.w.). However, when given over a longer period, e.g., over 18 consecutive days, the LD_M is reduced to 18 x 3.5 mg/kg b.w.

The mode of action of anticoagulants, e.g., Coumatetralyl, is described well by Meehan 1984 and Schnorbach 1993.

Cholecalciferol (Table 1)

Cholecalciferol has an acute to subacute mode of action. Applied in physiologically high doses, cholecalciferol (vitamin D3) shows good rodenticidal properties. Cholecalciferol is responsible for the transport of calcium from the feed through the intestinal membranes into the blood. In addition, it is involved in the bone formation. In unphysiologically high doses it leads to a massive disturbance of the calcium exchange system. Calcium concentrates itself in the blood and various organs (e.g., kidneys, heart, lungs and the vascular system). Kidney failure is generally the cause of death.

The LDJO in Norway rats is 43.6 mg/kg b.w. and 42.5 for house mice. Further information on cholecalciferol is given in Greaves 1974, Lund 1988, Marshall 1984 and Schnorbach 1993.

Bait Formulations

Under European conditions, baits based on debittered oat flakes or roughly shredded or broken wheat proved to be most successful. The tests were carried out with these basic foodstuffs.

RESULTS AND DISCUSSION

Laboratory Tests

Combinations of anticoagulants with different types of vitamin D are generally described to increase the efficacy of action against rodents (Hadler 1973).

It was found in our laboratory that, in particular, the combination of coumatetralyl and cholecalciferol could overcome the inefficacy of anticoagulants caused by resistance or vitamin K-containing food (Fuhrmann 1991, Lund 1991, Schnorbach 1992). A number of combinations of 0.02 to 0.04% coumatetralyl and 0.01 to 0.1% cholecalciferol have been tested (Tables 2 to 6). Due to its subacute delayed mode of action coumatetralyl (0.04%) cannot achieve 100% mortality after one day of feeding (Table 2); 0.1 % cholecalciferol alone is also not suitable to control a rat population with only one day of feeding, and often the poor acceptance is a result of bait shyness (Table 3). However, the combination of both active ingredients results in the same acute effects with delayed actions as we are accustomed to seeing in cases of single-dose anticoagulants. In contrast to these anticoagulants, the symptoms start earlier after consumption of Racumin plus. In combination with cholecalciferol, the amount of coumatetralyl should not be less than 0.04% but the percentage of cholecalciferol can be diminished to 0.025% or even 0.01% to avoid bait shyness (Prescott et al. 1992) (Tables 4 to 6).

The combination with optimal rodenticidal efficacy (coumatetralyl 0.04%/cholecalciferol 0.025%) was thoroughly tested in the laboratory and outdoors under the name "Racumin plus" in several bait formulations based on rolled oats, roughly shredded wheat or broken wheat. Some representative results are shown in the following sections.

In a choice test carried out according to the BBA guidelines (BBA 1983) Racumin plus was accepted well by rats in comparison to untreated rough shredded wheat (Figure 1). The feeding behavior was typical for single-dose rodenticides with delayed action. However, in comparison to single-dose anticoagulants the time to death was two to four days. After two days feeding, the amount of consumed bait declined sharply and from the fourth day on the rats stopped feeding. The first rats died on the third day and after six days we reached 100% mortality. Similar results are shown in Figure 2 with a wild strain of the house mouse. The bait consumption declined sharply after the second day. The mortality started after three days and ended with 100% on the eighth day.

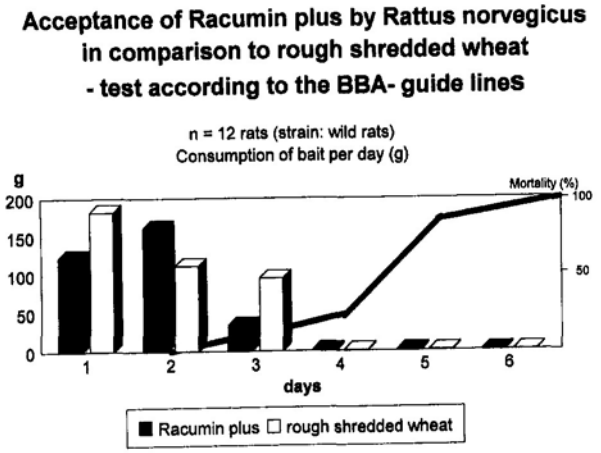


Figure 1. Acceptance of Racumin plus by *Rattus norvegicus* in comparison to rough shredded wheat-test according to the BBA-guidelines.

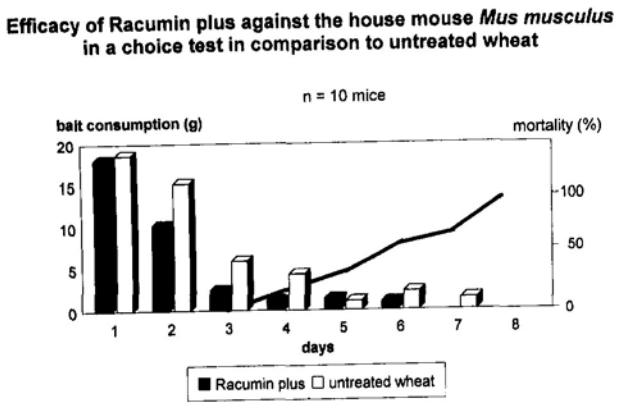


Figure 2. Efficacy of Racumin plus against the house mouse *(Mus tnusculus)* in a choice test in comparison to untreated wheat.

Table 2: Efficacy of a Racumin ready to use bait (0.0375 % coumatetralyl) against *Rattus norvegicus*.

length of feeding (days)	a/w	food-consumption (g)	active ingredient mg/kg b.w.	mortality	delayed mortality min-max	delayed mortality average
1	a	x = 11.8 s = 1.7	x = 26.8 s = 4.1	6 / 10	5 - 12	8.2
1	w	x = 22.3 s = 8.2	x = 35.4 s = 8.6	20 / 48	3 - 8	5.0
2	a	x = 15.1 s = 3.3	x = 34.9 s = 7.8	5 / 10	5 - 8	6.0
2	w	x = 35.8 s = 16.9	x = 68.0 s = 25.5	7 / 8	2 - 12	7.0
5	a	x = 29.1 s = 5.5	x = 66.5 s = 14.2	10 / 10	4 - 10	6.2
5	w	x = 34.2 s = 11.2	x = 72.0 s = 32.9	10 / 10	4 - 8	6.3

x = average; s = standard deviation
a = albino strain of *Rattus norvegicus*
w = wild strain of *Rattus norvegicus*

Table 3. Efficacy of a Muritan ready to use bait (0.1 % cholecalciferol) against *Rattus norvegicus.*

length of feeding (days)	a/w	food-consumption (g)	active ingredient mg/kg b.w.	mortality	delayed mortality min-max	delayed mortality average
1	a	x = 7.9 s = 3.0	x = 40.3 s = 16.2	11 / 20	3 - 14	5.2
1	w	x = 16.5 s = 5.8	x = 71.6 s = 23.3	8 / 10	2 - 12	6.8
2	a	x = 12.5 s = 3.5	x = 61.9 s = 17.5	10 / 10	3 - 6	4.0
2	w	x = 18.9 s = 9.2	x = 100.2 s = 47.3	8 / 10	4 - 9	7.0

x = average; s = standard deviation
a = albino strain of *Rattus norvegicus*
w = wild strain of *Rattus norvegicus*

Aging at room temperature over two years did not affect the acceptance and efficacy of Racumin plus in comparison to a sample which was frozen at minus 25°C over the same period (Figure 3).

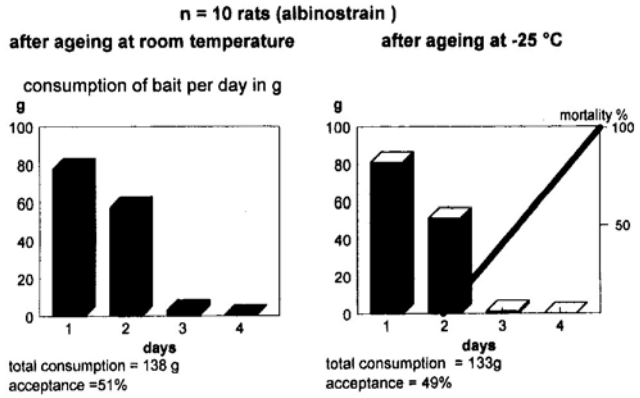


Figure 3. Acceptance of Racumin plus by *Rattus norvegicus* after 24 month aging.

In the Munsterland area (Germany), Norway rats were captured in farms with severe rat problems caused in part by anticoagulant resistance. After an •acclimatization period of four weeks, 27 rats were tested against coumatetralyl and 10 surviving individuals were observed for another eight weeks. They were then fed with Racumin plus and died within two weeks (Figure 4). Due to this promising result, field tests were carried out with Racumin plus in three farms of the Munsterland area with resistance problems (Figure 5). The extent of the rat infestation was ascertained with untreated rolled oats. After one week the oats were exchanged for Racumin plus. The bait was well accepted in the beginning. From the third week on, the consumption of bait decreased sharply and there were no further signs of rat infestation. After a period of seven weeks untreated rolled oats were again offered to determine the efficacy of the treatment. The renewed feeding activity was a result of reinfestation from surrounding farms which were also heavily infested by rats.

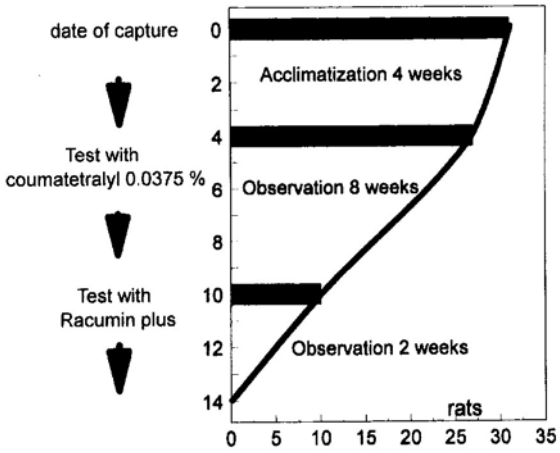


Figure 4. Efficacy of Racumin plus against coumatetralyl-resistant Norway rats.

In a chicken farm near Leverkusen (Germany), where anticoagulants were not effective because of vitamin K-containing feed, a control program was conducted with Racumin plus. Bait acceptance and control of the rats was viewed positively by the farmer. Rats which were captured before the test did not show signs of resistance against anticoagulants after an incubation period of several weeks, indicating that the antidote content in the chicken feed was the real problem at this farm.

Table 4a. Efficacy of a ready to use bait based on 0.02% coumatetralyl and 0.05% cholecalciferol against *Rattus norvegicus.*

length of feeding (days)	a/w	food-consumption (g)	mortality	delayed mortality min-max	delayed mortality average
1	a	x = 15.5 s = 2.5	12 / 12	3 - 6	4.3
1	w	x = 19.2 s = 8.3	11 / 12	3 - 5	3.9
2	a	x = 15.8 s = 8.3	12 / 12	3 - 7	3.7
2	w	x = 27.9 s = 9.4	12 / 12	3 - 4	3.4

x = average; s = standard deviation
a = albino strain of *Rattus norvegicus*
w = wild strain of *Rattus norvegicus*

Table 4b. Laboratory test according to the BBA guidelines: Ready to use bait (0.02% coumatetralyl/0.05% cholecalciferol) against untreated rough shredded wheat.

	consumed bait g/7 days	mortality	delayed mortality min-max	delayed mortality average
1. Test				
bait	98.3	7 / 8	3 - 5	3.7
untreated wheat	216.6			
	low bait shyness			
2. Test				
bait	86.0	10 / 10	3 - 5	4.6
untreated wheat	255.0			
	low bait shyness			

Table 5a. Efficacy of Racumin plus (0.04% coumatetralyl/0.025% cholecalciferol) against *Rattus norvegicus*.

length of feeding (days)	a/w	food-consumption (g)	mortality	delayed mortality min-max	delayed mortality average
1	a	x = 14.6 s = 1.9	6 / 6	2 - 4	3.0
1	w	x = 21.4 s = 9.1	12 / 12	3 - 9	5.1
2	a	x = 20.7 s = 2.4	6 / 6	2 - 3	2.7
2	w	x = 31.5 s = 11.2	12 / 12	3 - 5	4.0

x = average; s = standard deviation
a = albino strain of *Rattus norvegicus*
w = wild strain of *Rattus norvegicus*

Table 5b. Laboratory test according to the BBA guidelines: Racumin ready to use bait (0.04% coumatetralyl and 0.025% cholecalciferol) against untreated rough shredded wheat.

	consumed bait g/7 days	mortality	delayed mortality min-max	delayed mortality average
1. Test				
bait	320.0	12 / 12	3 - 6	4.7
untreated wheat	390.3			
	no bait shyness			
2. Test				
bait	144.6	10 / 10	2 - 5	4.1
untreated wheat	322.4			
	no bait shyness			

Table 6a. Efficacy of a ready to use bait based on 0.04% coumatetralyl/0.01 % cholecalciferol) against *Rattus norvegicus.*

length of feeding (days)	a/w	food-consumption (g)	mortality	delayed mortality min-max	delayed mortality average
1	a	x = 15.6 s = 1.4	6 / 6	3 - 5	3.8
1	w	x = 18.9 s = 6.2	6 / 6	5 - 7	5.7
2	a	x = 24.8 s = 2.6	6 / 6	3 - 4	3.7
2	w	x = 29.7 s = 3.5	6 / 6	4 - 5	4.2

x = average; s = standard deviation
a = albino strain of *Rattus norvegicus*
w = wild strain of *Rattus norvegicus*

Table 6b. Laboratory test according to the BBA guidelines: Ready to use bait (0.04% coumatetralyl and 0.01% cholecalciferol) against untreated rough shredded wheat.

	consumed bait g/7 days	mortality	delayed mortality min-max	delayed mortality average
bait	175.4	10 / 10	3 - 6	4.4
untreated wheat	179.1			
	no bait shyness			

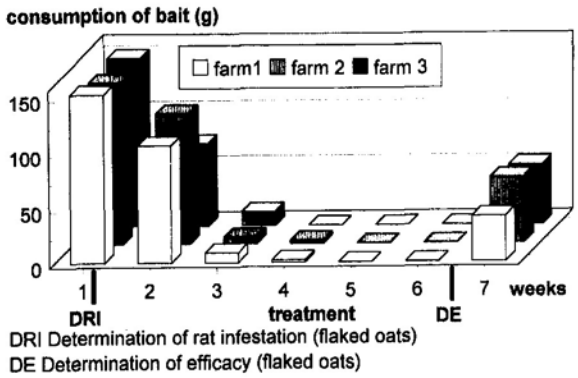
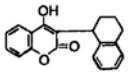
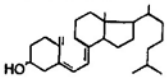


Figure 5. Field test with Racumin plus in three farms **(Miinsterland, Germany)** with anticoagulant-resistant rats ***(Rattus norvegicus).***

Table 7 gives a short summarized characterization of the two active ingredients coumatetralyl and cholecalciferol. Coumatetralyl exhibits good efficacy against rats and does not show development of any bait shyness because of its delayed action. As a multiple dose anticoagulant it is relatively safe for the user. The low efficacy against mice is improved by cholecalciferol. Problems due to resistance to anticoagulants or vitamin K-containing feed can also be overcome by cholecalciferol.

Fast-acting cholecalciferol may cause bait shyness in higher doses (more than 0.05%). The combination with coumatetralyl allows a reduction of the cholecalciferol concentration to avoid bait shyness. Accidental poisoning with cholecalciferol can be treated symptomatically with dexamethasone or furosemide. The treatment with Calcitonin is problematic because of its short half-life of less than 15 minutes in the human body. The described combination of the multiple dose anticoagulant coumatetralyl with the hypercalcemia-causing agent cholecalciferol in an attractive bait formulation is a good agent for modern rodent control even under difficult conditions caused by resistance problems or antidote containing foodstuffs.

Table 7. Characterization of coumatetralyl and cholecalciferol.

	Coumatetralyl	Cholecalciferol
chemical name	3 -(alpha-tetralyl) -4-hydroxycumarin	(3 beta,5 cis, 7 trans)-9,10-secocholesta-5,7,10(19)-trien-3-ol
structural formula		
active ingredient group	4-hydroxycumarin	Vitamin-D-complex
mode of action	anticoagulant	hypercalcemia
benefits	good efficacy against rats no bait shyness safe application	no resistance problems effective against rat and mice
disad-vantages	less effective against mice in some places resistance-problems	causes bait shyness in doses> 0.05%
antidote / sympto-matic therapy	Vitamin K	Dexamethasone Furosemide (Calcitonin)

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LITERATURE CITED

BBA 1983. Richtlinie fur die Priifung von Nagetierbekampfungsmitteln gegen Wanderratten. Richtlinien fiir die amtliche Priifung von Pflanzenbehandlungsmitteln. Biologische Bundesanstalt fiir Land- und Forstwirtschaft Berlin, Braunschweig (Germany). 9 - 3.2, Mai 1983, 13 pp.

FUHRMANN, R. 1991. Labor-und Freilandstudien zur Wirksamkeit eines Kombinationsrodentizids mit den Wirkstoffen Coumatetralyl und Cholecalciferol gegen Coumatetralyl-unempfindliche Wanderratten, *Rattus norvegicus*. Diplomarbeit, Fachhochschule fiir Technik, Sigmaringen, 149 pp.

GREAVES, J. H., R. REDFERN, and R. E. KING. 1974. Some properties of calciferol as a rodenticide. J. Hyg., Camb. 73:341-351.

GREAVES, J. H. 1985. The present status of resistance to anticoagulants. Acta zool. fenn. 173: 159-162.

GREAVES, J. H. 1986. Managing Resistance to Rodenticides *in* Pesticide Resistance, Strategies and Tactics for Management (Committee on Strategies for the Management of Pesticide Resistant Pest Populations, ed.) National Academy Press, Washington, DC, pp 236-244.

HADLER, R. M. 1973. Rodenticides Mittel. Ward Blenkinsop & Co. Ltd., Wembley, Middlesex UK, DE2310636, filed March 2, 1973, published September 20. 1973.

LUND, M. 1988. Nonanticoagulant rodenticides *in* Rodent Pest Management (I. Prakash, ed). CRC Press Inc. USA. pp 331-340.

LUND, M. 1991. Laboratory test with RACUMIN COMBI on bromadiolone-resistant brown rats. Danish Pest Infestation Laboratory, Report No. 63-1991. 4 pp.

MACNICOLL, A. D. 1982. Rodent resistance. A review of studies on warfarin resistance in rats and mice. MAFF/ADAS Agricultural Science Service Research and Development Report "Pesticide Science 1981." Reference Book 252 (81): 38-43. H.M.S.O., London.

MARSHALL, E. F. 1984. Cholecalciferol: A unique toxicant for rodent control. Proc. 11th Vertebrate Pest Conf., California, 1984, pp. 95-98.

MEEHAN, A. P. 1984. Rats and Mice. The Rentokil Library, Felcourt, East Grinstead. 385 pp.

PRESCOTT, C. V., M. EL-AMIN, and R. H. SMITH. 1992. Calciferols and bait shyness in the laboratory rat. Proc. 15th Vertebrate Pest Conf., California, 1992, pp. 218-223.

SCHNORBACH, H. -J. 1992. Ein neues Rodentizid: Ratten und Hausmause wirksam bekampfen. Der praktische Schadlingsbekampfer 44 (11): 262-266.

SCHNORBACH, H. -J. 1993. Rodenticides: Classification of Active Ingredients and Modes of Action with Special Reference to Anticoagulants. Dimensione Pulitio, 2 (7): 37-46.