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WARFARIN RESISTANCE REVISITED

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ABSTRACT: Roughly 50 years ago, the Wisconsin Alumni Research Foundation developed warfarin, the first anticoagulant rodenticide. This product was something close to that desired elusive "magic bullet" of pest management. Warfarin effectively killed rats and mice, required multiple feedings, and had a good margin of safety for non-target species. The widespread adoption of anticoagulants somewhat changed the conduct of rodent control with a shift in interventions toward toxicants and away from education and physical measures. The discovery of warfarin resistance in the United States in *Rattus norvegicus* in 1971, and later in *Mus musculus* and *Rattus rattus*, heralded in another shift in rodent pest mitigation. This shift was the development of more toxic anticoagulant products capable of killing with one or a few feedings and with concomitantly greater risks to non-target species. Development of the more toxic products both anticoagulant and non-anticoagulant continues today, although there is an increasing trend favoring comprehensive approaches (i.e., integrated pest management [IPM]) which: emphasize educating clients and reducing causative conditions; diminishing the role of toxicants; and, when necessary, using products of the least practical toxicity. In this paper, the concept of counteracting anticoagulant resistance is blended with the sometimes necessary use of anticoagulant rodenticides as part of IPM. Nationwide data from the former New York State Department of Health Rodent Control Evaluation Laboratory (in cooperation with the Centers for Disease Control's former Urban Rat Control Program) are examined regarding warfarin resistance in *Rattus norvegicus*. In samples from two dozen project cities, population resistance levels ranged from 1.6% to 76.2% using the standard World Health Organization (WHO) testing criteria. However, most survivors (i.e., resistant rats) of the initial test succumbed upon one or more re-exposure(s) to warfarin using the same WHO testing protocol. The results are surprising and have implications on interpreting the phenomenon of anticoagulant rodenticide resistance and on the pragmatic designing of rodent management programs.

KEYWORDS: rodenticides, anticoagulant resistance, warfarin, Norway rat, baiting strategies, IPM

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INTRODUCTION

A new class of rodenticides became available in the 1940s with the introduction of warfarin by the Wisconsin Alumni Research Foundation, Madison, Wisconsin. The advantage of warfarin (and closely related hydroxycoumarin compounds) was that it was effective in killing rats and mice with a relatively low dose when consumed regularly over a period of several days. Further, a large amount of warfarin bait consumed at one time would not effectively kill; thus, this new rodenticide had a built-in safety factor regarding non-target species such as cats, dogs, and children. Proper baiting procedures should prevent access to baits by non-target species, and certainly should prevent the repeated ingestion necessary for intoxication. In essence, warfarin was a product that was close to that elusive "magic bullet" of pest management. An unfortunate outcome of this discovery was that rodent control became largely an issue of chemical intervention with less emphasis placed on public health education, housekeeping, storage practices, sanitation, and exclusion (proofing and stoppage). Not surprisingly, anticoagulants have been the most preferred rodenticides since World War II.

The identification of warfarin resistance in the United States (known in Europe since 1958) in *Rattus norvegicus* in North Carolina in 1971, and later in *Mus musculus* and *Rattus rattus* (Jackson et al. 1985), heralded in another

shift in rodent pest mitigation. This shift was the industry's increased interest in the development of more toxic anticoagulant products (e.g., brodifacoum, bromadiolone) capable of killing with one or a few feedings. Unfortunately, the more potent anticoagulants also have greater risks to non-target species. Development of the more toxic products, both anticoagulant (e.g., difethialone) and non-anticoagulant (e.g., bromethalin), continues today. While not remarkable in thoroughness nor consistency, there is an increasing trend in some sectors of the pest management industry favoring comprehensive approaches (i.e., integrated pest management [IPM]) which: emphasize educating clients and reducing causative conditions; diminishing the role of toxicants; and, when necessary, using chemical products of the least practical toxicity (Frantz and Davis 1991). Of course, concomitant with changes in the industry are necessary changes in the public's perception of what to expect in an IPM program.

In this presentation, the authors reexamine the definition of "anticoagulant resistance" in Norway rats (*Rattus norvegicus*) and how rodent control programs might counteract anticoagulant resistance. In fact, warfarin products themselves may be more useful than was thought during the heyday of "super rat" preachments. Nationwide warfarin resistance data are examined from the New York State Department of

As resistant animals were identified by the standard screening procedure, they were assigned to one of three retest interval groups (RIG)—or recovery interval groups—depending on the interval between the last day an animal received warfarin bait in the screening test and the first day it was to receive its second laboratory exposure to warfarin in the first retest (retest₁) procedure. The three retest interval groups were defined as follows:

Retest Interval Group (RIG)	Days Since Last Received Warfarin Bait	
	Limits	Range Used
<1 month	15-27	15-27
1-2 months	28-59	28-50
>6 months	180-730	196-633

Once an animal was in the time range of its assigned RIG, it was again tested (i.e., re-tested) by the same procedure as in the standard warfarin resistance screening (see Figure 1). Note that procedural differences occur just prior to Retest Selection due to the necessary timing requirements of the RIGs. That is, in the <1 month group, the authors wanted to retest at 15 days whenever possible; but there was not sufficient time for a nine day post-test, seven days on Lab Chow before pre-test₂, and a two day pre-test₂—a total of 18 days. Therefore, the three steps were merged; in essence, the post-test₁ remained nine days, and pre-test₂ remained two days, but the time between these steps was reduced to four days. If, for some reason, an animal did not meet basic test criteria (body weight, health, etc.) (see Frantz and Padula 1980) at that time, it was held for another week or up to 16 days. After 16 days, the animal was reassigned to a RIG with a longer interval between screening and retest. Rats assigned to the other two RIGs which did not meet criteria were treated similarly.

Many animals surviving the retest₁ were placed back on a Lab Blox diet, held 12 days, returned to Lab Chow for nine days (seven days + two day pre-test), and then retested repeatedly (e.g., retest₂, retest₃, retest₄, etc.) until they died (to be reported elsewhere). For all retests after the first, the interval between warfarin exposures was fixed at 30 days. Note that some animals surviving the first retest (retest₁) were removed from this study for use in other tests requiring resistant rats.

RESULTS AND DISCUSSION

In the <1 month category, 52 rats from mixed sources (excluding Chicago) were retested with 59.6% (31/52) mortality; 18.0% (11/61) mortality resulted when this test was repeated with Chicago-trapped rats (see Table 1). In the second category of 1 to 2 months (see Table 1), 61.2% (30/49) of the mixed-source rats died, whereas 14.7% (10/68) of the Chicago rats died. Repeating this test (1 to 2 month RIG) with 17 of the F₁ Chicago offspring resulted in a mortality of 5.9% (1/17). In the third RIG category of >6 months (see Table 1),

47 mixed-source rats were retested with 83.0% (39/47) mortality; only six Chicago-trapped rats were retested and one died (16.7%).

While test results beyond retest₁ will be discussed elsewhere, it is worth noting that few mixed-source rats survived retest₃. That is, most animals of mixed-source origin (excluding Chicago) tested from each of the three RIG categories succumbed upon their fourth exposure to warfarin bait in no-choice tests. Chicago-trapped rats in the <1 month, 1 to 2 month, and >6 month groups commonly survived retest₃, retest₁₀, and retest₃, respectively. Thus, some Chicago rats survived 11 lethal doses of warfarin rodenticide, the last 10 of which were consumed at 30 day intervals.

From these data, it appears that mortality for most rats is not significantly affected by the recovery time interval (RIG) for at least the categories of <1 month and 1 to 2 months. The high mortality among mixed-source rats in the >6 month category may be age related. For Chicago rats in this latter category, not enough data are available for analysis. Source (geographic origin), however, is clearly important. Upon first retest, Chicago rats have a significantly greater probability of survival than those animals from mixed sources.

Thus, the most significant finding of these data is that "resistant" (as by standard WHO screening measures) Norway rats from many geographic locations are likely to die upon re-exposure to warfarin, the very product which is used to identify or define their resistance. That is, in a baiting program with warfarin it appears that it should be possible to continue to effectively use warfarin bait if a time period of at least two or more weeks without warfarin exposure is allowed between baiting cycles. In fact, the two-week hiatus would be a good time to complete more sustaining, non-toxic interventions such as public health education, housekeeping, storage practices, sanitation, and exclusion (proofing and stoppage). Even in the Chicago area, or other areas that might be identified with similar anticoagulant resistance characteristics, rats will not be "resistant" to such non-toxic interventions that are a significant part of a properly conducted IPM program.

While it should be somewhat easier for rats to consume a normally lethal dose of warfarin in the field situation because of the higher warfarin concentration (.025% in most commercial baits vs .005% in no-choice laboratory tests), bait acceptance might be negatively affected by the higher warfarin concentration and by the availability of other food materials (Jackson et al. 1975). Thus, the need for interventions to limit food resources (e.g., sanitation) is underscored. The uninterrupted use of warfarin baits over long periods of time should be discouraged because such practices would select for resistance (behavioral or other).

A second issue of importance raised by these data is how to define the "resistance" of rats being utilized in efficacy tests of rodenticidal products designed to kill warfarin resistant rats. If a product is tested against "resistant" rats from many geographic areas, the efficacy results become unclear when more than half of such rats might have succumbed to warfarin as shown with the mixed-source test group. Repeated baiting cycles using warfarin (with 30-day intervals of no warfarin) might well

Table 1. Results of resistant^a wild Norway rats' (*Rattus norvegicus*) second exposure (no-choice feeding test) to .005% warfarin bait.

Source of Rats	Time Interval to Retest ₁ (months ^b)	Rats Retested (Number)	Mortality at Retest ₁ (Percent)
Mixed Wild-Trapped ^c	<1	52	59.6
	1-2	49	61.2
	>6	47	83.0
Chicago Wild-Trapped	<1	61	18.0
	1-2	68	14.7
	>6	6	16.7
Chicago Lab-Bred ^d	1-2	17	5.9

^aAs determined by the standard warfarin screening test (Brooks and Bowerman 1973 and 1974)

^bNumber of months since exposed to warfarin bait

^cExcluding Chicago Wild-Trapped rats

^dF₁ offspring of Chicago Wild-Trapped rats

effectively reduce most rat populations without the adverse consequence of increased risk for non-target species intoxication.

CONCLUSIONS

These data raise interesting questions regarding the significance of the warfarin resistance "problem" and how to effectively conduct efficacy tests for products designed to counteract warfarin resistance. Although many details remain to be clarified, these studies support the need to emphasize a non-chemical strategy for rodent control efforts. Environmental sanitation and rat proofing would go far to eliminate food and harborage resources and thus curb breeding activity—affecting all animals in the population as demonstrated decades ago by Davis (1950), Holloway (1947), Orgain and Schein (1953), and others. Elimination of the food alternatives would also increase bait acceptance whenever the chemical strategy is necessary. Under environmentally improved conditions, it should be possible to kill resistant animals in most localities with the standard anticoagulants (including warfarin) and adjusted baiting schedules, rather than switching to rodenticide baits which have a higher risk to humans, pets, livestock, and/or wildlife.

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LITERATURE CITED

- BROOKS, J. E., and A. M. BOWERMAN. 1973. Anticoagulant resistance in wild Norway rats in New York. *J. Hyg., Camb.* 71: 217-222.
- BROOKS, J. E., and A. M. BOWERMAN. 1974. An analysis of the susceptibilities of several populations of *Rattus norvegicus* to warfarin. *J. Hyg., Camb.* 73:1-7.
- DAVIS, D. E. 1950. The mechanics of rat populations. *North Amer. Wildlife Conference* 15:461-466.
- FRANTZ, S. C., and C. M. PADULA. 1980. Recent developments in anticoagulant rodenticide resistance studies: Surveillance and application in the United States. Pages 80-88 in *Proc. 9th Vertebrate Pest Conference*, J. P. Clark, ed., Univ. of California, Davis.
- FRANTZ, S. C., and D. E. DAVIS. 1991. Bionomics and integrated pest management of commensal rodents. Pages 243-313 in *Ecology and management of food-industry pests/FDA Tech. Bull. 4*, J. R. Gorham, ed. Assoc. of Official Analytical Chemists, Arlington, VA.
- HOLLOWAY, A. H., JR. 1947. A study of the structural-sanitary characteristics of urban residential areas in respect to their support of rodent populations. M.S. Thesis, Johns Hopkins University, Baltimore, MD. 100 pp.
- JACKSON, W. B., A. D. ASHTON, S. C. FRANTZ, and C. PADULA. 1985. Present status of rodent resistance to warfarin in the United States. *Acta Zool. Fennica* 173: 163-165.

- JACKSON, W. B., J. E. BROOKS, A. M. BOWERMAN, and D. E. KAUKKINEN. 1975. Anticoagulant resistance in Norway rats—as found in U.S. cities¹ - Part II. *Pest Control* 43 (5): 14,16,18, 20, 22-24.
- ORGAIN, H., and M. W. SCHEIN. 1953. A preliminary analysis of the physical environment of the Norway rat. *Ecology* 34(3):467-473.
- WHO. 1970. Provisional instructions for determining the susceptibility or resistance of rodents to anticoagulant rodenticides. WHO Tech. Rep. Ser. No. 443:140-147.