Richard Poche Scimetrics Limited Corp.

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To:
DPR's Public Comment Portal
https://cdpr.commentinput.com

Subject: Proposed Anticoagulant Rodenticide Mitigation Measures

In response to your Informal Public Workshop on September 24, 2025, we herewith submit following comments:

1. **Importance of Rodent Control**

Ever since the dawn of humanity rodents spread diseases such as plague, leptospirosis, Lyme disease, salmonellosis, rat bite fever, murine typhus, and many others (Meehan 1984). In addition, rodents inflict billions of dollars in economic damage to crops, irrigation systems, homes, and community property. The high reproductive rates of most rodents require a continuous system of control to keep their populations reduced.

The dramatic increase in the human populations with expanding large cities create ideal habitats for invasive species such as the Norway rat, roof rat, and house mouse. These invasive rodents stowed away on ships of the early settlers to North America coming from various parts of the globe. Not only were these invasive species destroying food and water supplies along the way, but diseases such as plague formerly endemic to Eurasia were introduced to the US. These pests rely on humans to provide food and shelter to live in close association with humans. Their genetics are programmed to live in association with man. Poor or no rodent management systems can lead to catastrophic food shortages and disease transmission to humans, wildlife, and domestic animals. Today, global warming has already had an impact on diseases. Rodents are survivors and populations will increase exponentially if left unchecked.

The founder of Scimetrics has over 50 years of laboratory and field experience with rodenticides and other means of rodent research from some 60 countries. After researching all forms of rodent control over that time and seeing firsthand the impact rodents have had in many countries, Scimetrics Limited Corp. was established in 1999 with its mission to develop FGARs to provide customers with reduced-risk products. The first compound we began working with was warfarin. Today, many of our products include an added insecticide to kill fleas and ticks on the rodent, which aids in the reduction of disease transmission.

PO Box 1045 • Wellington, Colorado 80549-1045
970-482-1330 Phone • 970-482-1885 Fax
www.kaputproducts.com

2. The Anticoagulant Overview

Warfarin was developed in the US for rodent control in 1948. The compound was formally approved for human use by the FDA to treat blood clots and associated blood disorders in 1954. An estimated 15 million Americans take warfarin daily to control various forms of blood clotting issues.

The US Environmental Protection Agency (EPA) was at the center of FGAR and SGAR registration approvals since that responsibility was transferred to them from the USDA after its creation on December 2, 1970. A major scientific revelation at the time was the discovery of warfarin resistance within the US. The initial awareness began in the 1972 after a publication by Jackson and Kaukeinen (1972) documented warfarin resistance to Norway rats in North Carolina. The research was theorized two years later by Books and Bowerman (1974) and generated a prevailing thought that resistance was widespread in the US. The discovery created immediate concern within the industry, public health agencies, and the EPA.

About that time SGARs were being developed to address the perceived increase in FGAR rodent resistance in Europe. SGARs were very effective against rodents that were considered resistant to warfarin, although at the time, no one considered the possible implications of SGAR widespread use. The extensive testing in US did not use DNA resistance surveys since the technology was not available at that time. The warfarin resistance dilemma communicated a mixed message to the end-users because rodent control quickly required an SGAR bait and it was assumed FGARs could not get the job done. Perceived resistance pockets varied geographically, and the thinking was that SGARs would be the solution no matter where a rodent problem existed in the US.

Resistance theories were based on flawed testing. Frantz, and Madigan (1998) first reported concern over the WHO test protocol, which had been adopted by the EPA to determine if warfarin resistance rodent labeling claims were to be used on SGARs. Briefly, that testing involved presenting a 0.005% warfarin-treated meal diet (1/5 the nominal 0.0250% concentration) to Norway rats in a no-choice test for six consecutive days and observing mortality. Any survivors were considered warfarin resistant based on the amount of bait consumed. In the Franz and Madigan study, surviving rats from their initial exposure to warfarin were maintained in the lab for a 30-day period then run through the same test again. The percent mortality in the repeat test averaged about 70%. If the surviving rats in the initial test were categorized as warfarin-resistant, then all the rodents in that study should have survived.

Basically, the test protocol was flawed yet it resulted in numerous resistance claims on the product labels. The concept was further examined by Poché and Poché

(2012) with various FGARs. See attached publication "Rodenticides: Warfarin, still a good management tool".

Furthermore, Poché (1998) examined the gut bacteria in rodents as a possible mechanism to help degrade low- dose warfarin after consumption. The warfarin dose absorbed was less than anticipated and resulted in an incurred evaluation and survival of rats as "resistance". At the time much research on human drugs was receiving attention because the effects of bacteria in the intestinal tract contributed to the breakdown of some human drugs (Hill 1995).

By the early 1980's, the use of FGARs declined dramatically and baiting with SGARs increased exponentially. SGARs began to gain attention because rodents were quickly eliminated. Brodifacoum was the first EPA-approved SGAR. This was despite the fact that EPA was aware of secondary toxicity issues from studies conducted with brodifacoum in China, Indonesia, Myanmar and Sudan in 1983. To obtain a "single-feed" label claim SGAR development had to adhere to an EPA Test Protocol that required presenting baits to rodents for a 24-hour period then observing mortality. If mortality achieved 90% or better, then the product sponsor was able to use the claim "kills a rodent in a single feeding".

In the regulatory product registration process, for an SGAR to obtain a label claim "Kills warfarin-resistant rats" data were generated following the WHO testing guidelines and data submitted and approved by the EPA. That is, the surviving rats were used in a test to prove efficacy for whatever SGAR the rodent is exposed to. The surviving rats in the screening had tolerance to 50 ppm warfarin over a 6-day exposure. These studies were not related to DNA resistance although the results were interpreted as such. Poché discussed this in 2010 (see references). Studies, conducted at Genesis Laboratories, addressed the issue by trapping Norway rats from Chicago, a known epicenter of warfarin resistance. A breeding colony was established and maintained for approximately 10 years (Poché 1998). A series of studies following the WHO protocol revealed that improved and higher purity warfarin available today was and still is very efficacious in eliminating Norway rats.

3. Combining seven anticoagulants into one group

Evaluating FGARs and SGARs in the same manner is unscientific when considering the vast differences in toxicity, half-life in tissues, environment effects, and effects on non-target animals. This is not a catch-all basket for rodent control. For example, how can DPR consider the brodifacoum half-life in plasma of 91.7 days as equal to warfarin, which is approximately 30 hours? Different active ingredients have different effects on target animals. The EPA in its discussion of ecological effects states "Information available to EPA on the acute avian toxicity of warfarin indicates that the

pesticide is practically nontoxic to game birds. In subacute studies, warfarin is moderately toxic to practically nontoxic to upland game birds and waterfowl" (EPA R.E.D. Facts Warfarin 1991).

All anticoagulants have different chemical profiles and should be evaluated that way. The potential for bioaccumulation among all anticoagulants cannot be considered equal. Adjustments to risk mitigation proposals and regulations should be made to account for those differences among the group of FGARs and SGARs.

Numerous studies on warfarin were submitted to the EPA to provide data on non-target wildlife toxicity. The following studies were submitted to the EPA to support the evidence: Mach and March (1997), Carlet and Mach (1997), Poché and Mach (2001), Baroch (2004), Davidson (2010), Poché (2010), Mach (1998) Poché (2011), Poché and Poché (2012, Poché et al (2018) Poché et al 2019(a) and Poché (2019b), These citations are in the References section of this letter.

4. Bait concentrations for anticoagulant formulations

For FGARs and SGARs in the US, concentrations may vary depending on the product formulation. For example, Scimetrics has effective baits for California Ground Squirrels formulated with 0.0025% diphacinone (EPA Reg. Nos. 72500-11 and 72500-24), while the California Department of Food and Agriculture is using a bait formulated with 0.01% chlorophacinone (EPA SLN No. CA 890024), i.e. a 4 x higher concentration than Scimetrics' products. A similar product produced by the State contains 0.01% diphacinone.

DPR should evaluate each rodenticide formulation based on the active ingredient, its concentration, half-life in tissues, and residue level in carcasses, which results in different toxicological effects. A dose makes the poison, depending on how much chemical is added (see Paracelsus, 1538) in Ottoboni, 1991). "All things are poison and nothing is without poison. It is the **dose** only that makes a thing not a poison". This is also evident with human drugs.

Lowering the dose reduces the amount of active ingredient per acre, reduces tissue residues in target field rodents, and lowers the risks to wildlife and domestic animals. The dose level of the bait can have significant difference in potential non-target species mortality.

5. Limitation of Duration of Baiting / Pulsed Baiting

The California Central Valley is currently in the midst of a severe field rodent outbreak. We also frequently hear from California residents complaining about an

explosion in ground squirrel populations due to the restrictions put in place with California assembly bills AB1322 and AB2552. Unfortunately, the decision to pass these bills was not based on science, but emotions and political lobbying by various groups. California Ground Squirrels and other rodents cause considerable damage to property, for example, home foundations, electric boxes, attics, food supplies.

A major drawback of pulsed baiting is that rodents will come back with a vengeance due to their high reproductive rates. A maximum of 3 x 35 days of baiting leaves 260 days of non-baiting, which is enough time to have a major rodent infestation due to high reproductive rates.

Pulsed baiting is a good "marketing ploy" to sell the idea of increased safety. However, compounds with extended half-lives and high toxicity will not be "safer"in the end. In addition, collecting all anticoagulant baits per site by day 35 puts an undue burden on pest control companies and operators.

6. **Conclusion:**

Rodent control is complex, and it is important to consider all tools in the tool box for a successful rodent management program. This includes the use of rodenticides. Many of the already implemented regulations in California and the newly proposed restrictions to rodenticides will contribute to fewer people being able to access products. Negative impacts of the already existing restrictions are higher expenses and reduced effectiveness of rodent control, rise in rodent populations leading to increased disease transmission to humans, and an increase in property damage. Further restrictions will increase the problems exponentially, including use of more toxic products, non-registered products being imported into the US illegally, and increase in misuse of baits.

We ask DPR to do a more thorough evaluation of the different rodent baits available on the market, and to consider the toxicity categories of each of the seven anticoagulants and their concentration levels.

We thank the DPR for considering our comments.

Sincerely,
Richard Poché
President
Scimetrics Limited Corp.

PO Box 1045 • Wellington, Colorado 80549-1045
970-482-1330 Phone • 970-482-1885 Fax
www.kaputproducts.com

Scimetrics
Limited Corp.

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RODENTICIDES: WARFARIN, STILL A GOOD MANAGEMENT TOOL

Part 1: First and Second Generation Anticoagulants

Richard M. Poché and David M. Poché, Genesis Laboratories, Inc., Wellington, Colorado, USA

Keywords: anticoagulant, rodenticide, warfarin resistance, antidote, commensal rodents

David and Richard Poché

Introduction

Rodents have been a menace to man for generations inflicting billions of dollars of crop and commodity damage each year. Rats and mice serve as reservoirs of numerous diseases transmitted to humans, such as plague, leptospirosis, Lyme disease, and rat bite fever (Gratz 2006). Millions of people died during the middle ages because of the spread of plague by rat in Europe.

Rodent control products have been developed over the centuries including traps, glues, and chemical methods (rodenticides). Initial acute, or fast acting products were introduced and contained chemicals having no antidotes, such as arsenic, ANTU (α-naphthylthiourea), sodium monofluroacetate, strychnine, and norbormide. It was not until the late 1950s that rodent control was dramatically changed by the development and marketing of warfarin. The chemical is classified as an anticoagulant, or blood-thinner, and inhibits the production of vitamin K within the rodent, resulting in death over several days.

After warfarin's initial success, other anticoagulants were added to the marketplace, including coumatetralyl, chlorophacinone, pindone, and diphacinone. The compounds came to be known as 'first generation anticoagulants'. These novel rodenticides quickly reduced the use of acute rodenticides which have no antidotes.

Beginning in the early 1980s the more toxic 'second generation' chemicals were introduced into the marketplace, including brodifacoum, bromadiolone, and difethialone. The use of the chemicals soon began to diminish the use of the less toxic first generation group. This took place because of the perceived genetic resistance developed in US rodents. The lower dose baits were seen as the newest rodent management success story.

As early as 1958 there were reports of warfarin resistance in Scotland in the Norway rat (*Rattus norvegicus*) (Boyle, 1960). After prolonged use of warfarin in the US, resistance was documented (based on WHO criteria) and published (Jackson & Kaukeinen, 1972). Consequently, more toxic anticoagulants were synthesized to overcome the genetic resistance reports. The rodent control industry over a period of only a few years, moved from the first to second-generation rodent baits. The marketing strategy was to: 1) implicate first generation rodenticides as ineffective against rats and mice and, 2) argue that the newer baits could kill rodents in a 'single feeding' (2nd generation rodenticides) compared to the 'multiple feeding' required by the 1st generation products. In the professional pest control industry, the goal was to convince the technician that more bait would be required with the less toxic products. It was economically cost effective to use less bait in a rodent control program. It was a good marketing idea, but in reality the story had its flaws.

Warfarin Resistance – fact or fiction

More reports began to surface from Europe with rodent genetic resistance not only to warfarin, but also bromadiolone, coumatetralyl, and difenacoum (Pelz, 2001). The same year Norway rats were observed to be resistant to warfarin, difenacoum, bromadiolone, and coumatetralyl, but not to brodifacoum and difethialone (Lodal, 2001).

A reason behind this resistance development was thought to be possible overuse of anticoagulants, the basic warfarin resistance gene had emerged (Pelz, 2001). Studies in the US indicated that anticoagulant resistance was 'widespread' which led to the promotion of second-generation anticoagulants (Jackson & Ashton, 1992). Others suggested the issue of warfarin resistance was exaggerated and potentially was a minor problem in the US. It was proposed that rodents may exhibit a tolerance to low doses of warfarin because of the ability of the gut flora to produce sufficient vitamin K to counter the effects of the compound (Poché, 1998).

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The industry standard for warfarin resistant screening involved the use of a protocol developed by the World Health Organization (WHO, 1982). Wild Norway rats were fed a diet containing 0.005% warfarin for 6 consecutive days in a no-choice design. If the rat consumed an accumulated amount of 12 mg/kg warfarin over the 6-day period and survived, it was classified as resistant.

Dosing rats at 1/5th (0.005%) the EPA recommended concentration of 0.025% warfarin resulted in consistent survival of about 50% of the Norway rats collected from Chicago (Poché 1998). This approach was taken a step farther by re-subjecting surviving rats to the same test 30 days later (Frantz & Padula, 1998). The results were similar with 50% of the Norway rats surviving. If this is a case of genetic resistance, 100% of the rats should have survived, because the animals were deemed resistant in the first test. This process was duplicated multiple times by the authors with the same results: surviving 'warfarin resistant' Norway rats when retested succumbed to the chemical. There was a 30-day latent period so all warfarin and its metabolites had been either excreted or metabolized.

This perceived resistance to warfarin in the US, should be more accurately termed, 'tolerance to low doses of warfarin'. To what extent vitamin K produced by the rats intestinal flora was antidotal enough to counter the effects of the anticoagulant remains to be studied. Studies in humans demonstrated the role of microflora in metabolizing compounds (Manning *et al*, 1988). Flora in the gut of animals has a significant impact on metabolizing compounds (Hill, 1995). This breakdown of first generation rodenticides is part of the reason they pose reduced risk to non-target animals. That issue will be addressed in a subsequent article.

The 'pockets' of resistance as reported from Chicago and Baltimore were studied (Jackson & Ashton, 1992). Norway rats tested in Colorado all succumbed to warfarin at 0.005% after a 6-day exposure. Rats from Chicago subjected to the recommended 0.025% warfarin bait concentration consistently succumbed to the product (100% mortality) (Poché 1998). This is possibly due to geographical differences in Norway rat microflora.

In Europe, Endepols *et al* (2003) studied an area previously thought to be occupied by bromadiolone-resistant rodents. In that instance, the inability to reduce rat numbers had nothing to do with genetic resistance at all. Rather, the insufficient use of properly placed bait stations contributed to inadequate control. Proper baiting techniques ensured a sufficient reduction in rodent numbers. Local authorities had previously concluded that 0.005% bromadiolone bait was not sufficient to control rats and mice, when in fact there was inadequate coverage of bait stations, allowing for constant reinvasion of rodents from neighboring areas. This misinterpretation of field results is not uncommon and has contributed to the misconception that first-generation anticoagulants are ineffective.

Recent work from Uganda in *Rattus spp* has revealed that in a region where no rodenticides have been used, the so called 'resistance gene' is common in the species (Diaz *et al.*, 2010). The issue of warfarin resistance in rodents remains to be completely studied using modern methods.

Single-feeding claims on product labels

In evaluating 20 years of laboratory anticoagulant efficacy data at Genesis Laboratories it was surmised that all anticoagulants have a similar lethality pattern. The time from initial ingestion of bait until death does not differ statistically between first and second generation anticoagulants.

This argument is not made to refute the fact that second generation anticoagulants may kill a rodent in a single feeding, but deals more with the misinterpretation of the statement. The average person reading a rodenticide label with the statement 'kills in a single feeding' will assume the rodent will eat the bait once then, die. Similarly, most pest control professionals believe that second generation baits are faster acting and require less product. In reality, this is not the case. Studies on the biology of Norway rats and house mice (*Mus musculus*) have revealed that they may visit food sources some 80 and 200 times, respectively, during a 24-hour period. With both species, consumption takes place at about 88% of the visits (Meehan, 1984). In the real world, a 'single-dose bait' does not exist.

The single-feed claim test protocol developed by the EPA stipulates a rodenticide exposure for a 24-hr period: bait is presented with a choice of a challenge (placebo) diet, and mortality in the test animals must be ≥90% to permit the use the single-feed claim. Is the message communicating what

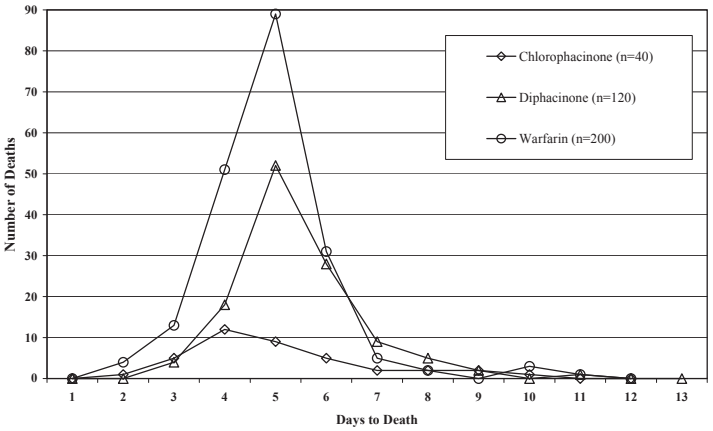

Figure 1. Days to death in house mice – first generation anticoagulants.

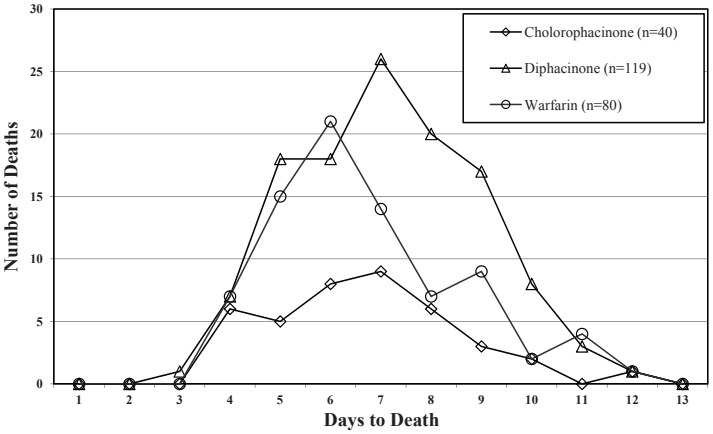

Figure 2. Days to death in laboratory rats – first generation anticoagulants.

takes place in reality? Does this lead to target animal overdosing, resulting in potential secondary hazards? A comprehensive review of the anticoagulants and potential primary and secondary risks was compiled (Erickson & Urban, 2002).

When examining published data on feeding behavior of wild Norway rats, a safe assumption is that a rat eats 20 grams of bait daily for 4 days (Meehan, 1984). The rat then has ingested nearly 50 LD_{50}s of brodifacoum and less than 2 LD_{50}s of warfarin. Warfarin is metabolized and excreted from the rat within 40 hours, while the half-life of brodifacoum exceeds 180 days (Erickson & Urban, 2002). Should a rat consume a sub-lethal dose of brodifacoum in a single feeding subsequent consumption of the bait will result in overdosing and bioaccumulation. Studies with warfarin on various rodent and wildlife species indicate the reduced risk to non-target wildlife when compared to other anticoagulants (Poché & Mach, 2001).

Eason *et al*. (2002) expressed concern over the use of compounds such as brodifacoum stating, "Equally, consideration should be given to banning or restricting the use of second generation anticoagulants where their use is not warranted. Secondary poisoning risk of brodifacoum versus other anticoagulants suggests that switching from brodifacoum to alternative second generation anticoagulants, with similar toxicokinetic profiles would not significantly reduce the risk to non-target species".

Other toxicants, especially bromethalin, are replacing second generation anticoagulants in the US retail market. This compound has not been approved in the European Union because it has no antidote, and is a neurotoxin. The rodent goes into severe convulsions before death. Laboratory and field testing have shown, using standard EPA test methods for Acute Rodenticides, efficacy in house mice ranges from 13–40%, and with rats, less than 40%. The rapid response to the EPA Risk Mitigation measure involving anticoagulants, will result in inferior rodent control products in the US retail market that have the so called 'stop feeding' claim. It is a true statement that because of the extreme discomfort experienced by rodents after eating bromethalin, and subsequent convulsions within minutes, the rodents will stop feeding. Most will survive despite the marketing strategy of 'uses less bait' which helps sway the consumer to buy these products. The rats and mice quickly develop bait shyness which results in poor rodent control and the potential for an increased public health problem.

Time required to eliminate rodents using anticoagulants

Laboratory testing conducted at Genesis Laboratories between 1994 and 2007 utilized the array of testing guidelines developed by the U.S. Environmental Protection Agency (EPA), Office of Pesticide Programs (OPP) guideline series. These studies involved choice tests of anticoagulants to generate efficacy data to support EPA product registrations. Criteria included bait acceptance of 33% (percent test bait consumed divided by the total challenge diet (placebo) and test bait consumption). In addition, a minimum of 90% mortality had to be achieved to consider the data set in the evaluation. Data were compiled to compare time of death from the onset of feeding on baits containing diphacinone, chlorophacinone, warfarin, brodifacoum, difenacoum, bromadiolone, and difethialone.

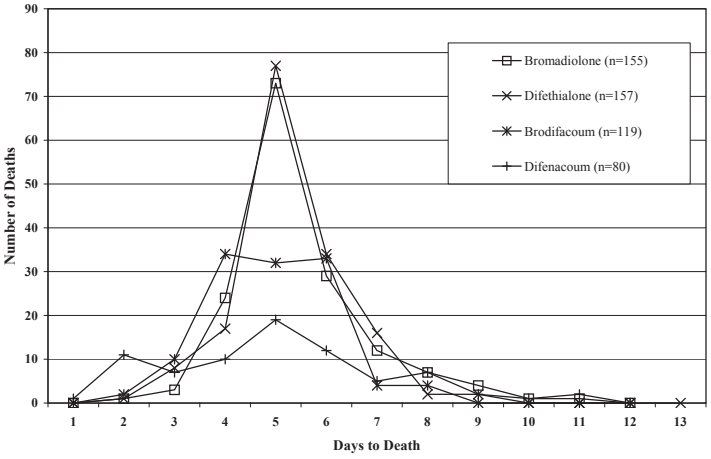

Figure 3. Days to death in house mice – second generation anticoagulants.

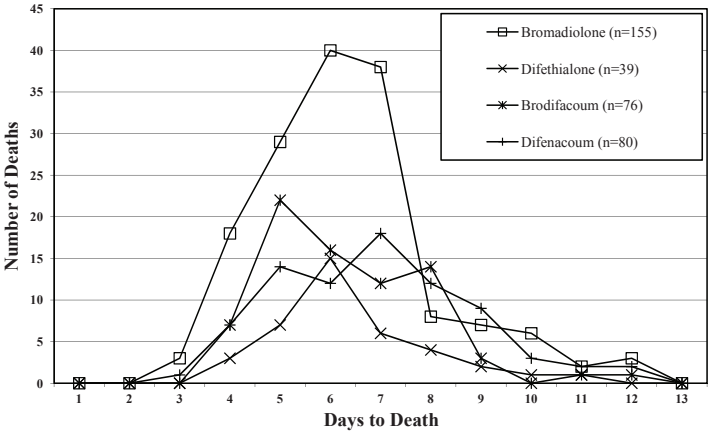

Figure 4. Days to death in laboratory rats – second generation anticoagulants.

The number of rats and mice used varied based on the number of studies conducted. Tests required that a group of 10 males and 10 females be used and that a replication group be presented test material along with a control group. Standard EPA rodent exposure periods for first and second generation anticoagulants were 15 and 3 days respectively. Concentrations of the baits were based on standard active ingredient amounts approved by the EPA and marketed as commercial products: diphacinone 0.005%, chlorophacinone 0.005%, warfarin 0.025%, bromadiolone 0.005%, difenacoum 0.005%, and difethialone 0.0025%.

Data combined from studies with first- and second-generation rodenticides have similar trends in time-to-death for Norway rats and house mice. Figures 1 and 2 present mortality data on house mice and Norway rats in which the first generation compounds were presented to rodents. Figures 3 and 4 display the results from lab tests using second generation rodenticides. With house mice, the mean time until death for brodifacoum and warfarin are similar. In initially compiling these data we had the preconceived notion, as generally thought, that first-generation anticoagulants require more

time to kill rodents. The prevailing thinking within our industry is along the lines that "it takes up to 21 days to kill rodents with warfarin in the field". We suspect part of the reason is that earlier forms of warfarin were not highly purified as they are today. Impurities in warfarin manufactured 30 years ago, were quite distasteful and rendered baits less palatable.

More bait intake results in quicker kill, so the thinking goes, but as these data demonstrate, the acute toxicity of these anticoagulants has no bearing on time-to-death. If one examines the LD_{50} of brodifacoum in rats (0.15 mg/kg) versus warfarin (15 mg/kg), the time until death is almost identical.

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Richard M. Poché is the founder of Genesis Laboratories, Inc. based in Wellington, Colorado USA. He has authored over 100 manuscripts on vertebrate pest management and vector control. He has worked in over 50 countries, including having lived in Niger for four years and Bangladesh for two years. His research interests over the past 35 years have involved product development in the area of rodent and vector (such as mosquitoes and sand flies) control formulations.

David M Poché is a field biologist who has worked with Genesis Laboratories in Wellington, Colorado, USA for over 10 years. He graduated from the University of Northern Colorado in Greeley and studied abroad, for one year, at the University of Wollongong in Wollongong, Australia. He has been a part of many field research efforts, including two years spent in India, and managed a sand fly (vector of visceral leishmaniasis) product development Grant. Domestically, he has been involved in directing studies such as: rodent and wildlife LD_{50}, secondary toxicity, non-target exposure, and choice tests on various native and invasive species. He has been author and co-author on manuscripts pertaining to his work in India.

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