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ABSTRACT: Rodents cause substantial amounts of damage and losses of foodstuffs around the world. While various methods are used to reduce damage and losses to rodents, rodenticides remain the most important tool in the toolbox. However, like all tools, rodenticides have advantages and disadvantages. Several considerations are shaping the future of rodenticide use. These include manufacturing and registration costs, concern about toxicity levels and non-target animal hazards, potential hazards to children, reduced effectiveness of some formulations, and humaneness to the targeted rodents. While there have been very few new developments in rodenticides in the last several decades, new formulations and active ingredients need to be investigated so that these concerns can be addressed. We are conducting studies on some new materials: sodium nitrite, lower concentrations of zinc phosphide, and two-active ingredient formulations (cholecalciferol plus diphacinone). Preliminary results are promising with a number of rodent species. Some materials (sodium nitrite and zinc phosphide) have been encapsulated to avoid low palatability and bait shyness issues. Preliminary cage study results are presented as well as proposed future studies.

Key Words: damage, management, pesticide regulation, risk mitigation, rodent, rodenticide

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INTRODUCTION

Comprising over 1,400 species worldwide, rodents are the largest taxonomic group of mammals (Nowak 1999). Rodent use of habitats is extensive and varied. Most rodent species are relatively small, secretive, prolific, adaptable, and have continuously growing incisors which require constant eroding by gnawing. All rodent species have ecological, scientific, social, and/or economic values. They recycle nutrients, aerate soils, distribute seeds and spores, and affect plant succession. Some provide meat and furs for people. Several species are used in large numbers in medical research. Additionally, they provide an important prey base for many species of predatory animals.

Relatively few (perhaps 5%) rodent species around the world are serious pests. Examples of genera and species of rodents considered to be serious pests around the world were provided by Prakash (1988) and Witmer and Singleton (2010). In the United States (US), native species causing significant damage in various regions include pocket gophers (*Thomomys* spp., *Geomys* spp.), ground squirrels (*Spermophilus* spp.), voles (*Microtus* spp.), deer mice (*Peromyscus* spp.), beaver (*Castor canadensis*), marmots (*Marmota monax*), mountain beaver (*Aplodontia rufa*), and porcupines

(*Erethizon dorsaatum*). Some non-native species are widespread in the US and cause damage as well: commensal rats (*Rattus* spp.), house mice (*Mus musculus*), and nutria (*Myocastor coypus*; Marsh 1988).

Numerous economic and health problems can result from rodent interactions with humans. Damage can occur to agricultural crops (both in the field and to stored foods), forests and orchards, rangelands, property (structures, cables), natural resources (both faunal and floral), and disease hazards may be posed (Marsh 1988, Witmer and Singleton 2010). Singleton et al. (2003) estimated that in Asia alone, the amount of grain eaten by rodents would provide enough food to feed 200 million Asians for a year. When a damage situation occurs, it is very important to determine the species causing the damage, the extent of the damage, and the abiotic-biotic-cultural factors involved before rodent population and damage management strategies are implemented (Singleton et al. 1999, Witmer and Singleton 2010).

RODENT POPULATION AND DAMAGE MANAGEMENT METHODS

Worldwide, a wide variety of methods are used to manage rodent populations directly or to reduce the damage caused by rodents. These methods include physical (e.g., traps, barriers), chemical (e.g., toxic baits, fumigants, repellents), biological/cultural (e.g., resistant plants, crop type, sanitation, habitat manipulation), and others (e.g., bounties, compensation; Witmer and Singleton 2010). Other methods are still in the developmental stages (e.g., fertility control; Nash et al. 2007). Each method has advantages and disadvantages and a site-specific assessment should be made before implementing a rodent damage management program.

Most often, an integrated pest management (IPM) strategy is developed and implemented that uses a variety of methods (Witmer and Singleton 2010). This is important, in part, because a particular method of control (e.g., anticoagulant baits) may become ineffective over time. Other considerations in the resolution of rodent damage situations are rodent population monitoring and the establishment of thresholds for acceptable levels of damage, and for when to implement rodent population control. Some rodent management practitioners suggest less reliance on rodenticides and a more "ecologically-based" approach to rodent damage management (Singleton et al. 1999). Nonetheless, traps and rodenticides remain very important tools in the IPM toolbox for rodent damage management.

RODENTICIDE USE AND ISSUES IN THE UNITED STATES

Rodenticides are widely used in the US for the control of rodent populations in various settings (e.g., agricultural lands, forests, conservation lands, urban-suburban lands; Jacobs 1994). We previously presented numerous aspects of their use in the US (Witmer and Eisemann 2007). Rodenticide use in the US is regulated by the US Environmental Protection Agency (EPA) under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA; Jacobs 1994). A considerable variety of rodenticides are registered for use in the US, and these can be divided into several categories depending on their mode of action and toxicity (Witmer and Eisemann 2007). Generally, these are subdivided into acute rodenticides (e.g., zinc phosphide, cholecalciferol, bromethalin, and fumigants), first generation anticoagulants (e.g., chlorophacinone, diphacinone), and second generation anticoagulants (e.g., brodifacoum, bromadiolone). The characteristics of each of these materials were reviewed by Timm (1994). Many of these are available in one or more formulations: blocks, pellets, on grains or vegetables, powders, liquid formulations, and toxic gas-producing fumigants. Some chemicals used as rodenticides in various parts of the world are either not used in the US (e.g., compound 1080 [monosodium fluoroacetate]) or have very limited use (e.g., strychnine---below ground uses only). Additionally, these materials may be applied in various ways, depending on the situation and regulations: in burrows, near burrow openings or along runways, broadcast over broad areas by

hand or mechanical device, or placed in bait stations. More recently, rodenticides are aerially broadcast from helicopters to eradicate invasive rodents from islands (Witmer et al. 2007). Some rodenticides are available to the general consumer for use in and around homes and other buildings and some limited field applications, while others are restricted use materials available only to trained and certified pesticide applicators. Rodenticides are a multi-million dollar a year industry in the US; nonetheless, these materials are considered minor-use compared to other pesticides such as insecticides and herbicides (Fagerstone 2002). It is also important to remember that while rodenticides are very labor and cost effective, they do not provide a permanent solution to rodent problems. Where abundant food and cover is available to rodents, long-term use of rodenticides is required to keep populations in check. Hence, efforts should be made to reduce the area's carrying capacity for rodents. Long-term use may lead to some negative outcomes: rodenticide resistance in the rodent population and residue accumulation of certain rodenticides (e.g., second generation anticoagulants) leading to hazards to predators and scavengers.

What are some of the issues surfacing regarding the use of rodenticides that make it important for identification and testing of new potential rodenticide formulations and active ingredients? Some of the issues include:

- Manufacturers are removing some products from the commercial market for a variety of reasons
- The US EPA rodenticide hazards mitigation measures have been implemented and resulted in fewer products available and many restrictions on uses
- Some current rodenticide formulations have become much less effective
- Non-target losses and concerns have increased
- Humaneness concerns have increased

A number of recent papers have shown that rodenticides can have impacts on non-target animals in some situations. These include both secondary hazards to predatory and scavenging birds and mammals (Ebbert and Burek-Huntington 2010, Ruder et al. 2011, Thomas et al. 2011, Gabriel et al. 2012) as well as primary hazards to foraging birds (Ebbert and Burek-Huntington 2010, Ruder et al. 2011). Most of these impacts are attributable to anticoagulant poisoning, but in some cases there been have non-target losses due to direct consumption of zinc phosphide rodenticides (e.g., Poppenga et al. 2005). Finally, articles are being published that express concern about the humaneness of methods used for rodent control (e.g., Mason and Littin 2003).

The rodenticides used in the US have undergone a review by the EPA before renewing registrations (Silberhorn et al. 2000). A number of concerns about the safety of rodenticides have been raised, and the review resulted in many changes in what is available and how these products can be used (Jacobs 2002). Recently, the EPA recommended several mitigation measures to reduce the potential hazards of a group of nine rodenticides (brodifacoum, bromadiolone,difethiolone, chlorophacinone, diphacinone, warfarin, bromethalin, zinc phosphide and cholecalciferol) to children, pets, and wildlife (EPA 2007). These measures may have a variety of effects on the production and availability of rodenticides in the US (Schmit 2007, Kaukeinen and Colvin 2008, Hornbaker and Baldwin 2010). Sizable costs are associated with the registration or re-registration of a rodenticide product in the US, and the market and investors can be volatile (Fagerstone et al. 1990, Jacobs 1992). There is somewhat of a trend towards fewer registrations and declining use of rodenticides in the US (Fagerstone et al. 1990, Jacobs 1992).

CHARACTERISTICS OF AN "IDEAL' RODENTICIDE

Assuming new, effective and acceptable rodenticides need to be developed, what are the characteristics that should be looked for in new products? Researchers in Australia (O'Brien 1986, Cowled et al. 2008)

have discussed these ideal characteristics as have others. We compiled a list of desirable characteristics from various sources:

- High toxicity
- Species specificity
- Palatable
- Low human hazard
- No resistance
- Fast-acting
- Painless/humane
- Non-bio-cumulative
- Stable in baits
- Antidote available
- Registerable
- Economical

While it may be difficult to achieve all these characteristics in a single rodenticide product, progress can be made towards a more "ideal" rodenticide. Numerous researchers are investigating potential new rodenticides both in terms of active ingredients and new formulations of existing active ingredients (e.g., Eason 1992, Eason et al. 2010). This is the basis for our research trials summarized below.

RECENT RODENTICIDE TRIALS

Two active ingredients. There has been a growing interest in incorporating two active ingredients into rodenticide baits. There are none currently registered in the US. This approach would involve combining an acute toxicant with an anticoagulant. Connovation, Ltd., New Zealand, has been experimenting with a cholecalciferol plus coumatetralyl bait and more recently with a cholecalciferol plus diphacinone bait. Bell Labs, Wisconsin, has been experimenting with a cholecalciferol plus brodifacoum bait. Some of the advantages of a two active ingredient rodenticide are increased efficacy and reduced concentrations of active ingredients over those currently being used in single active ingredient rodenticides. It has also been suggested that the acute toxicant, because of its rapid "knock down" time, might result in sickened animals retreating to burrows or other refugia before the anticoagulant takes effect and causes their death. This could potentially reduce the risk of predators and scavengers having access to poisoned carcasses.

We tested the efficacy of a cholecalciferol plus diphacinone bait (C+D bait) with California voles (*M. californicus*). These voles cause much damage to artichoke plants, and the traditional baits (chlorophacinone-coated bracts or zinc phosphide-coated bracts) were no longer very effective in reducing vole populations. Our cage trials found both C+D pellets and C+D-coated bracts were very efficacious (70-100% mortality in the various trials) with California voles. A field efficacy trial in California was completed recently, but the data (which is still being evaluated) suggests a lower efficacy level. The field trial will probably be repeated because rodent numbers were rather low at the time of the first trial.

Sodium nitrite. This new active ingredient is being studied as a potential new toxicant for feral pigs in Australia (Cowled et al. 2008, Lapidge et al. 2009) and in the US (Campbell et al. 2011). Much is known about sodium nitrite because it is used as a meat preservative and for various industrial uses. It can be toxic, however, if enough is consumed in a short period of time. This results from the alteration of hemoglobin into methemoglobin which cannot transport oxygen. Enzymes reverse the effect over time so that if the animal does not die, it soon resumes normal activities. Some of the advantages of sodium nitrite are that it is inexpensive, acts quickly, results in very low risk of secondary hazard because it is quickly metabolized, and it has an antidote (methylene blue).

We determined that the LD_{50} for 6 species of wild-caught rodents averaged 246 mg/kg which is similar to the LD_{50} for feral pigs. We also conducted preliminary food bait and liquid bait trials. The results of those trials showed that rodents can eat (up to 60% mortality) or drink (up to 50% mortality) enough sodium nitrite in a short enough period of time to consume a lethal dose. Additional research will be needed to identify a highly palatable food bait and an

appropriate sodium nitrite concentration that results in high mortality levels in rodents.

More effective rodenticides for house mice. Invasive house mice have been problematic to control well or to eradicate from islands with current rodenticides in many situations. Our earlier trials found only 5 of 12 commercial rodenticide products to be effective against house mice (Witmer 2007). We investigated seven new rodenticide formulations to identify more effective alternative rodenticides (different formulation and/or different active ingredients). Five of the 7 new formulations of rodenticides or new active ingredients were found to be efficacious ($\geq$ 70% mortality) and warrant further investigation as potential control methods for invasive house mice. Additionally, a two active ingredient rodenticide (cholecalciferol plus brodifacoum), which is not currently registered in the US, showed promise as a new house mice control tool (100% mortality). These may have some advantages over currently-registered invasive house mice rodenticides. Field trials with these formulations are recommended as a next step in the research and pesticide registration process.

Improvement of existing zinc phosphide and anticoagulant rodenticides. Zinc phosphide rodenticides are widely used around the world. It most cases they have been highly effective in controlling rodent populations. However, in some situations, like the California vole situation described above, they are no longer considered efficacious. This could be for a number of reasons (e.g., bait shyness, low palatability), but the ultimate cause is not known. To make it an effective rodenticide again, we have been conducting trials to 1) determine the effectiveness of reduced concentrations of zinc phosphide in rodenticides, and 2) determine if encapsulated zinc phosphide would be more acceptable/palatable to rodents. In trials with wild-caught voles, we found that zinc phosphide concentrations as low as 0.5% were still highly efficacious (80% mortality). The concentration in existing commercial products is 2%. We also found that the voles consumed more encapsulated zinc phosphide-coated oats at a 0.5% concentration than at concentrations of 1% and 2%.

We have also conducted preliminary trials to determine if an enzyme inhibitor could reduce the rate of metabolism of the anticoagulant rodenticides chlorophacinone and diphacinone in voles. These inhibitors are found in some fruit juices which is why people taking blood thinners (i.e., anticoagulants) are told not to consume grapefruit during treatment. Using wild-caught voles, we found that pomegranate juice was a good inhibitor of anticoagulant metabolism. The level of enzyme inhibition was concentration dependent. Additionally, it was more effective in this role than was grapefruit juice.

CONCLUSIONS

We can assume that rodents will continue to pose challenges to land and resource managers, commodity producers, and homeowners. While many tools and methods are available to reduce rodent populations and associated damage, we need to continue to identify effective, safe rodenticides especially for situations where existing products are not considered effective. It is probably safe to assume that much of the public will continue to be leery of toxicant use, and concerns about non-target hazards and humaneness will increase. Hence, products need to not only be effective, but must also address these other concerns. Continued technology development and transfer are essential to improve the effectiveness and safety of rodenticides. We have summarized our recent research studies which we believe are a step in that direction.

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