Retaining or Retrieving Older and Trying to Identify Novel Rodenticides

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Abstract: Anticoagulant compounds are likely to play an important role in the control of commensal rodents for crop protection and conservation for the foreseeable future. However, there are concerns regarding their persistence and the development of more widespread resistance. We are seeking to retrieve and retain older alternatives as well as developing novel rodenticides. Our three-pronged approach is, firstly, to improve the performance of older non-anticoagulant rodenticides, such as sodium fluoroacetate (1080) and zinc phosphide; secondly to optimise the performance of 1st-generation anticoagulants; and thirdly, to identify alternatives to anticoagulant rodenticides with the same mode of action as *para*-aminopropiophenone (PAPP), which was registered in New Zealand as a predacide in April 2011. Zinc phosphide was also registered in New Zealand for the first time in 2011, and combinations of ultra-low-dose cholecalciferol with first generation anticoagulants are being advanced to provide the performance characteristics of a 2nd-generation anticoagulant with a lower risk of bioaccumulation and secondary poisoning.

Key Words: 1080, cyanide, New Zealand, PAPP, *para*-aminopropiophenone, rodenticides, vertebrate pesticides

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INTRODUCTION

The most prolific period of rodenticide development occurred between the 1940s and the 1980s. First-generation anticoagulant rodenticides and zinc phosphide were developed in the 1940s, 1950s, and 1960s. Then came cholecalciferol, bromethalin, and 2nd-generation anticoagulant rodenticides in the 1970s and 1980s, partly to overcome resistance to the less potent anticoagulants (Buckle and Smith 1994). During this period it was recognised that it was important to have 2 classes of rodenticides, both anticoagulants and alternatives to anticoagulants. In recent times, the need for effective toxicants for field use that are less persistent than 2nd-generation anticoagulants, and therefore likely to be less hazardous to non-target birds and other non-target species, has been highlighted. Ironically, registration requirements in the U.S., Europe, and around the world have reduced the number of options available for rodent management. We believe it is important to retain and refine the use of rodent control tools for conservation, disease control, and agricultural protection, and develop new alternatives to anticoagulants. Ideally, alternatives to existing anti-coagulants would combine limited persistence and humaneness; however, this is a significant challenge.

Considerable effort has been put into the retention of sodium fluoroacetate (1080) to support conservation goals and an effective tuberculosis vector eradication strategy (Eason et al. 2011). In addition, a microencapsulated form of zinc phosphide has been developed, and a low dose of cholecalciferol combined with diphacinone or coumatetralyl is being re-evaluated (Eason et al. 2010a) to provide 3 low residue alternatives.

In April 2011, *para*-aminopropiophenone (PAPP), a methaemoglobinaemia inducer, was registered for the control of predators in New Zealand. PAPP is humane in its mode of action and does not bioaccumulate. It has an antidote and is highly toxic to species like stoats (*Mustela erminea*) (Eason et al. 2010b) but unfortunately not toxic to rodents. Approximately 50 compounds with the same mode of action, including analogues of PAPP, have recently been screened to assess their potency as rodenticides.

METHODS

To test an active ingredient not previously registered

in New Zealand, groups of caged rats were presented with a microencapsulated form of zinc phosphide containing 1.5% a.i. in a palatable paste bait. Coumatetralyl (0.03%) combined with cholecalciferol (0.015%), and diphacinone (0.05%) also combined with cholecalciferol (0.015% and 0.03%), were tested on caged rats in the same bait matrix. Analogues of PAPP were screened for their potency as rodenticides. *In vitro* work was carried out using a methaemoglobin assay involving hepatic microsomes and rat erythrocytes. The toxicity of the most promising candidates from the *in vitro* screening were recently assessed *in vivo* in laboratory rats by oral gavage.

RESULTS

A micro encapsulated form of zinc phosphide containing 1.5% a.i. has been shown to be 100% effective in caged rats. In addition, further toxins are being researched. A combination of coumatetralyl (0.03%) and cholecalciferol (0.015%) has also been confirmed as having high potency in rats, similar to that achieved by diphacinone (0.05%) and cholecalciferol (0.15%). Diphacinone (0.05%) was partially effective as a single-dose rodenticide when combined with cholecalciferol (0.015%), and was more effective when combined with a higher dose of cholecalciferol (0.03%). Both PAPP and sodium nitrite have been developed as vertebrate pesticides in New Zealand and Australia (Eason et al. 2010b). In laboratory rats, neither compound is sufficiently potent to be an effective rodenticide. Approximately 50 compounds with the same mode of action, including analogues of PAPP, have been screened for their potency as rodenticides. This screening has identified a compound with an LD_{50} of approximately 40-50 mg/kg. Further derivatives of this more potent analogue are being synthesized and screened.

CONCLUSIONS

It has been suggested that product innovation needs to be stimulated to encourage alternatives to the current suite of rodenticides, as a number of these are associated with secondary poisoning, bioaccumulation, or are viewed as inhumane (Mason and Littin 2003). We have advanced an improved formulation of zinc phosphide and are confirming the synergistic effects of cholecalciferol when co-administered with 1st-generation anticoagulants. Zinc phosphide was registered for possum (*Trichosurus vulpecula*) control in 2011 and this registration will be extended to cover rodents in 2012.

These developments may provide partial solutions and help provide products that break the cycle of rodenticide resistance (which can develop with overuse of anticoagulants); however, they are not an advance in term of reducing welfare impacts. To produce completely new rodenticides, a new approach is needed. Our current approach is to attempt to build on the platform created by PAPP. We are part-way through a programme of research, development, and registration activity, and further *in vitro* and *in vivo* testing is scheduled over the next 3 years on novel candidates, as well as progression to field trials for those showing promise. Any new tools which emerge would most likely need to be integrated with anticoagulant rodenticides, which are likely to play an important role in the control of rodents for the foreseeable future. Importantly, 1080 has been retained in New Zealand for possum control and is also used as a rodenticide in some settings, such as multispecies possum and rodent control programmes.

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