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# Technology Advances for Vertebrate Pest Eradication

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**ABSTRACT:** Internationally, over the last 20 years the number of tools available for the control of small mammals has declined. Through the efforts of research we have bucked this trend and retained and developed new tools. Three new toxins have been extensively researched and registered, namely para-aminopropiophenone (PAPP) in 2011 for stoats and feral cats; zinc phosphide for possums in 2012; and encapsulated sodium nitrite (ESN) in 2013, for possums and feral pigs. The development of PAPP and ESN, coined red blood cell toxins, developed for humaneness, represent the first new vertebrate pesticides registered for field control of mammalian pests anywhere in the world for >30 years. Research on rodenticides including diphacinone with the additive cholecalciferol (D+C) and a palatable form of norbormide continues. A New Zealand EPA application for D+C was filed in June 2015. More effective killing systems are being researched, and the first successful field trials of resetting toxin delivery devices for possum and stoat control were completed in 2013 and 2014. Improved deployment strategies, integration of humane and selective toxins, lures of greater potency, and improved killing devices aided by species' recognition will transform ground control for endangered species protection. Sodium fluoroacetate (1080) and other important tools have been retained as new tools are emerging from a research and development pipeline. It is important for the future of New Zealand's biodiversity that this focused research continues and we continue to learn and advance new technologies. Our goals are shifting to enable reduction in density of rat, stoat, and possum populations to zero over large scales (i.e., elimination at landscape scale), and to hold these at zero through detection and response, including the use of new technologies for perimeter control as part of barrier systems for conservation.

**KEY WORDS:** 1080, New Zealand, norbormide, PAPP, *para*-aminopropiophenone, resetting devices, sodium nitrite, toxicants

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## INTRODUCTION

Vertebrate pesticides are used to mitigate problems caused by the impact of rodents and other introduced species (Clout 1999, Innes and Barker 1999). They have been used successfully to conserve endangered species (Innes and Barker 1999) and eradicate rodents and other introduced mammals to protect populations of endangered indigenous birds and other animals. We have successfully eradicated invasive mammals from many islands (Bellingham et al. 2010, Russell and Broome 2015); however, we have a long way to go before we can reverse the decline in native species across increasingly large areas of mainland New Zealand. To address this challenge we must retain our existing toolbox and develop new tools and

strategies for longer-term suppression of pest numbers over larger areas, or for eradication.

This paper specifically focuses on research aimed at retaining the registration of important vertebrate pesticides; new initiatives to develop more humane and species-targeted toxins; and also, briefly, reviewing alternative control agents in the field control of vertebrate pests. There are aspirations to move away from the use of pesticides for all pest management issues to control systems based on good biological understanding (Thresher et al. 2014, Goldson et al. 2015). However, in the field of vertebrate pest control, failure to retain and improve pesticides in parallel to researching long-term alternatives will have serious consequences.

## REGISTRATION PROCESSES AND TRENDS

Fundamental and applied research in animals or *in-vitro* test systems and in the field on new toxins and new products has been conducted before their approval and registration. In addition, they have been conducted on older compounds, such as 1080 (sodium fluoroacetate), in anticipation of a re-assessment process (Eason et al. 2010, Eason et al. 2011). In New Zealand, the requirements of the Hazardous Substances and New Organism Act 1996 (HSNO) and the Agricultural Chemistry and Veterinary Medicines Act 1997 (ACVM) must be met, meaning that approvals are required from both the Environmental Protection Authority (EPA) and the Ministry of Primary Industries (MPI). Probably in excess of NZD\$20 million was spent by a consortium of stakeholders over a 15- to 20-year period on research, consultation with community groups and updating 1080 research-based registration dossiers for a re-assessment process that was completed in 2007 (ERMA 2007). This was appropriate in the context of New Zealand being the largest user of 1080 baits. Likewise, a similar re-registration review has been undertaken in Australia by the Australian Pesticide and Veterinary Medicine Authority (APVMA 2008), and in the United States the National Wildlife Research Center (NWRC) completed about 250 studies costing USD\$3 million by resubmission of existing suitable data on 1080, zinc phosphide, and cyanide. Cholecalciferol registrations have recently been discontinued in the European Union due to lack of investment, despite the advantages of cholecalciferol's low secondary poisoning risk versus other toxicants (Eason et al. 2000). The data requirements of the EU Biocide Directive were deemed excessive, and extremely costly to generate relative to their scientific merit and sales volume by the registrants (Eason et al. 2010, Adams 2005, Buckle et al. 2005).

The field of vertebrate pesticide product development can sometimes be challenging, and sustained research effort and investment is required. For example, after approximately a decade of research PAPP was approved for use to control stoats (*Mustela erminea*) and feral cats in 2011. Four years later, the registrant aided by the Department of Conservation completed negotiations with EPA to lift label restrictions that prevent it being used effectively. An approval was granted in March 2011 that imposed requirements to notify all landowners and occupiers within a 3-km radius before beginning a control operation for stoats. This requirement was intended to protect domestic cats. Upon further analysis, it was found that this control made it impractical to use PAPP for the control of stoats. The NZ EPA Committee decided in July 2015 to lift this requirement to enable stoat control operations to go ahead (NZ EPA 2015).

A prolific period of international research and development occurred between 1940 and 1990. Sodium fluoroacetate (1080) was developed in the 1940s, first-generation anticoagulant rodenticides in the 1940s, '50s, and '60s, and cholecalciferol and second-generation anticoagulant rodenticides in the 1970s and 1980s, partly to overcome resistance to first-generation anticoagulants that has occurred overseas following prolonged use in agricultural or urban settings. Prior to 1950, all vertebrate

pesticides were non-anticoagulants, most of them acute or quick-acting, but after the introduction of warfarin and the other anticoagulants the importance of these non-anticoagulants was reduced, at least for rodent control. Following the emergence of resistance in some populations of rodents and residues of the second-generation anticoagulants in wildlife (Young and De Lai 1997, Stone et al. 1999, US EPA 2004, US EPA 2008) interest in non-anticoagulants or at least less persistent 'low residue' vertebrate pesticides has been revived and more new acute substances have been investigated (Eason et al. 2013, Eason et al. 2014, Shapiro et al. 2015a, Shapiro et al. 2015b). This interest has been coupled with the questionable humaneness of second-generation anticoagulants in larger vertebrate pests (Littin et al. 2002). The principal acute vertebrate pesticides used in New Zealand are 1080, cyanide, and cholecalciferol. Zinc phosphide is registered in Australia and the United States, and cholecalciferol is registered in the United States but not Australia. Bromethalin is only registered in the United States and only for commensal rodents. Strychnine is only registered in the United States for underground use to control several species of pocket gophers, but its use has been discontinued in New Zealand. None of the acute acting agents used in New Zealand are currently registered in Europe except for zinc phosphide, which has limited use versus anticoagulants. The extensive field use of acute toxins in New Zealand is a response to the unique challenges we face with multiple species of introduced mammals.

## LOOKING AHEAD: A PIPELINE AND A 3-PRONGED APPROACH

Within a 3-pronged approach, there is need to continue to improve the use of existing tools, complete the development and deployment of emerging technologies, and reach out and explore completely new control approaches.

Prong 1: Retaining and improving toxins and traps already in use and improving how they are used.

Prong 2: New toxins, more effective lures, resetting systems and remote sensing.

Prong 3: Novel non-lethal approaches for pest control including biocontrol, Trojan females, and genetic manipulations.

Failure to retain and improve the use of toxins, including 1080, and complete the development of new toxins and deployment methods will have serious consequences while lethal chemical agents are the mainstay of large-scale mammalian pest control. In addition, there has been a more immediate and compelling reason for past and current research and monitoring. For the last two decades, a focus has been on the retention of product registrations for existing older pesticides and bait products (Eason et al. 1999, Eason et al. 2011; Adams 2005, APVMA 2008). We have retained the use and registration of cyanide and 1080. Both have played an important role in mammalian pest control in New Zealand for several decades. As mentioned previously, 1080 was subjected to a re-registration process in 2006 and 2007. The EPA assessed

1080-related research and monitoring covering bait quality and reduced sowing rates; potential sub-lethal effects, animal welfare issues, secondary poisoning, and understanding risk to non-target species; ecotoxicology; and fate in water, soil, plants, and animals. Reasons for the reassessment included: the fact that 1080 was registered a long time ago when less toxicology and risk assessment was required, the level of public concern about the use of 1080, and the increased use of 1080 in recent years mainly for possum (*Trichosurus vulpecula*) control.

Aspects of the research which underpinned the EPA approval in August 2007 were quality assurance of baits and reduced sowing rates of 1080, improved understanding of 1080 toxicology, and regulatory toxicology to underpin re-registration. Without research of this type and improving baits and baiting practices, accompanied by continued research and monitoring to meet EPA requirements and community expectations, the future use of 1080 will be compromised. EPA allowed the continued use of 1080 but with additional controls on aerial application.

A number of different approaches have been taken by researchers working on new toxins and rodenticides, including retrieval of older compounds and the development of new compounds. Zinc phosphide is an example of retrieval of an older compound not previously used in New Zealand and recently approved for use as a possum control agent by the EPA in August 2011 (Eason et al. 2013). Norbormide is a second example which is still the focus of research and a platform for genome screening for pest-specific toxin receptor targets (Brian Hopkins, Landcare Research, Lincoln, NZ, pers. comm.). PAPP and sodium nitrite are examples of the development of new compounds. PAPP was registered for the control of stoats and feral cats in April 2011 (Eason et al. 2014) and sodium nitrite was registered in 2014 for control of possums and feral pigs (Shapiro et al. 2015b). Desirable features of these new toxins are: (i) they are lethal to the target species, (ii) they are relatively humane, (iii) they are orally active and rapidly absorbed, (iv) they have relatively short half-lives in blood/organs vs. other rodenticides (many have long half-lives), (v) they are not persistent in the environment, (vi) they do not lead to secondary poisoning, (vii) they have an antidote, (viii) they have a reasonable shelf life, and (ix) they have a reasonable cost. The development of these 'red blood cell toxins' is noteworthy because they exhibit all of these features and are the first new vertebrate toxins registered for field control of mammalian pests anywhere in the world for >30 years, and the first designed with humaneness front of mind. However, field experience and research on strategies to make the most of these new toxins and zinc phosphide is still lacking.

Also worth reconsidering are first-generation anticoagulants with a low dose of cholecalciferol as an additive. Diphacinone with cholecalciferol (D+C) as an additive is the best option as an alternative to brodifacoum where bioaccumulation of residues and non-target effects are a concern (Crowell et al. 2013). Cholecalciferol has been used in the past as an additive with first-generation anticoagulants to give them potency similar to that achieved

by second-generation anticoagulants, removing the need to use compounds which are persistent in the environment (Pospichil and Schnorbach 1994). We were pursuing a combination of coumatetralyl and cholecalciferol; however, this has been discontinued in favour of diphacinone and cholecalciferol, as diphacinone is less persistent and more palatable. Bait containing 0.06% cholecalciferol and 0.003% diphacinone has been developed, and dossiers have been filed with the EPA late in 2015 to support the registration of solid bait effective at killing possums and rodents with similar potency to brodifacoum. Time to death in possum is less protracted than achieved by brodifacoum, which is important from an animal welfare perspective (Littin et al. 2002). Separately, we are planning a lower dose of cholecalciferol with diphacinone which will be suitable when just rodents are the target.

New resetting delivery systems that are still under development allow for multiple pest animals (c. 200) to be killed with a single device whilst incorporating responsible toxin delivery techniques (i.e., low risk to non-targets), and these are showing promise in field trials. The resetting systems, termed Spitfires, could in the future be combined with species identification technology to increase their specificity (Blackie et al. 2013, Blackie et al. 2016) and build on earlier prototypes (King et al. 2001, King et al. 2007).

New research on lures is underway and critically important. This is because lures for vertebrates are commonly foods like peanut butter or food-based pastes, but these are perishable and require frequent replenishment, factors that increase control operation costs and decrease control operation efficacy (Jackson et al. 2015). Semiochemical-based lures might address these limitations, and when combined with effective delivery technologies will provide controlled odour release and long-life, factors that will help expand the utility of resetting toxin-delivery systems and traps. Research into semiochemical lures for rats is currently ongoing at Victoria University of Wellington and showing early promise (Jackson et al. 2016). A number of compounds have been identified as attractive to rats, with five compounds outperforming peanut butter in field trials. Research is currently trialing dyad, triad, and tetrad blends to identify possible synergistic effects between compounds that could increase the attractiveness of lures. Furthermore, their integrated chemical image and response-guided approach that statistically associate compounds to a species-specific behavioural response could be used to identify semiochemical lures for other vertebrate pest species.

Recent work on mammalian predators by Garvey et al. (2016) has revealed that dominant predator odour triggers 'eavesdropping behaviour' by stoats, which has implications for improved lures. Ultra-potent lures should expand the range and cost-effectiveness of both resetting toxin-delivery systems and traps. A recent international review paper concluded that these developments offer 'transformational change' in pest control (Campbell et al. 2014). Pen and small-scale field trials have been completed. In the field, the Spitfire is designed to attract and control pests over long periods of time with minimal input and maintenance. Preliminary field trials of resetting

toxin delivery started in earnest in 2013, after several years' experience with prototypes. A tunnel version for stoat control, which delivers repeated doses of PAPP, and an upright version that attaches to trees for possum control and delivers repeated doses of zinc phosphide, have been field tested. Following the completion of further field trials in 2015, the possum Spitfire registration dossiers were filed with the EPA. The possum units are species-specific, lightweight, environmentally robust, and have the ability to kill multiple possums before requiring servicing. Spitfires dispense a measured dose (0.8 g) of a palatable gel containing 12.5% zinc phosphide onto a possum's abdomen. The Spitfire delivery system contains the toxin in a sealed cylindrical container. Handlers therefore have no contact with the gel and there is no spillage or scattering of crumbs as can occur with baits in a bait station. Similarly, the PAPP Spitfire for killing stoats offers similar specificity, and PAPP will not bioaccumulate or cause secondary poisoning. Based on one successful field trial to date, registration dossiers for the PAPP stoat Spitfire were filed in 2015. Rat and multispecies Spitfires are also being advanced in parallel.

Crucial future steps include commercialisation of prototypes; completing registration of toxins and resetting devices for rodents, mustelids, feral cats, and possums; and more extensive and vigorous field testing of efficacy in different control and eradication scenarios. Research into optimum spatial deployment strategies, aiming at minimising device spacing and numbers of servicing visits, still needs to be conducted, as will a continued focus on the performance of new liquid baits used in the devices. Looking to the future, there are aspirations to combine resetting toxin-delivery systems with species recognition to improve specificity for New Zealand and overseas markets. Analysis of footprint, gait, and stride length will allow for mammalian species discrimination by print characteristics as they cross a waterproof, low-cost sensing surface (Irie et al. 2014). Specifications are being extended to detect the prints of animals much less than 1 gram in weight to 1 kg to build on the aspirations of earlier research (King et al. 2007).

In the last 10 years, automatic resetting traps have also been advanced and improved. Early resetting traps that had engineering, welfare or effectiveness flaws have been discontinued. Goodnature Ltd, working with the Department of Conservation, has designed new devices to humanely kill animal pests and then reset themselves (Gillies et al. 2012). Targeted species include stoats, rats, and possums. Field experience continues to be gained with some good results. In conclusion to this section on resetting technology, research is still needed for these tools to get them working effectively, coupled with innovation in terms of how they are used to maximise their cost effectiveness and realise their potential. More effective lures could have a huge impact on their utility.

New persistent, non-lethal, and non-GMO (genetically modified organism) control of vertebrate and invertebrate pests (i.e., the Trojan Female Technique or TFT) is being explored by researchers at Landcare Research, Monash University, and Otago University. The science basis for the research is that naturally occurring mutations that cause

male infertility have now been identified in the maternally inherited mitochondrial DNA (mtDNA). These mutations have been identified in fruit flies and mice and are likely to be widespread in nature. Research aims to harness these mutations, through the release of Trojan females carrying the mutations. The Sterile Male Technique (SMT), commonly applied to invertebrates, has eradicated the parasitic screwworm fly in a number of locations. However, the SMT requires large quantities of sterile males to be produced and released. The TFT could provide similar control for possums, rabbits, stoats, and rats. Genetic options for the control of invasive fishes, which could be applicable to mammals, were recently reviewed, and the Trojan Y and several recombinant options that heritably distort pest population sex ratios are deemed technologically feasible, close to proof-of-concept stage, and are potentially more effective than sterile male release programmes. All genetic options will require prolonged stocking programmes to be effective. Modelling also suggests that these genetic techniques could enhance conventional control (Thresher et al. 2014). Researchers believe the TFT would be highly complementary to and most effective when combined with conventional control (e.g., population reduction obtained with conventional control, and then maintained by the release of Trojan females into the residual population).

New ideas requiring fundamental research enter the pipeline, as proven technologies emerge for uptake in control and eradication programmes or further field experience and research to optimise their utility. New ideas and technologies are advancing; some are new ideas at an early stage, some emerging technologies are close to proof of concept, and some emerging tools are through to registration and close to uptake by pest control professional and community groups.

## CONCLUSIONS

Research has enabled the retention of essential tools such as 1080, cyanide, and brodifacoum, and traps for broad-scale control and eradication programmes, has optimised their use, and is providing new tools for the control of mammalian pest species. In 1994, the recommendation of the Royal Society Science Workshop on 1080 was as follows: "It is important that the potential adverse effects of existing toxicants and products are continually updated...so that appropriate code of practice and safety standards are regularly reviewed, alongside new findings to minimise risk...and alternative safer products are produced." In terms of existing tools, the last 21 years have seen improvement in understanding the risks and the benefits of the use of 1080, brodifacoum, cyanide, and traps in both control and eradication settings. In terms of new tools, the last six years have seen a record period for new vertebrate control product registrations. Registration dossiers were filed with EPA and MPI for microencapsulated zinc phosphide (MZP) for possums, Feratox<sup>®</sup> for wallabies, PAPP for stoats and feral cats, and sodium nitrite for possums and feral pigs. The advances in resetting traps, toxin-delivery systems, and barrier approaches are also indicators of greater flexibility leading to greater choice. Some recent innovations include improving the design of

standard kill traps coupled with wireless technology to make monitoring and control along barriers simple and effective. However, many of these examples are still emerging technologies, and additional research is needed for them to reach their full potential.

A 3-pronged strategy has evolved, accelerating the provision of improved control tools delivered in a research and development pipeline alongside methodologies and strategies for mammalian pest control. This has included seeking toxins with better safety profiles and targeted delivery systems, as well as research on biocontrol, improved traps, lures, monitoring, and species recognition technology. In the field of toxins for mammalian pest control, two types are needed alongside traps for integrated pest management, namely acute or fast-acting poisons, and slower-acting toxins. Comparatively fast-acting compounds include sodium fluoroacetate (1080), which remains controversial and, as a result, has been extensively researched in New Zealand to enable its re-registration and has received recent favourable reviews by the New Zealand Parliamentary Commissioner for the Environment. Brodifacoum is the most widely used slow-acting rodenticide worldwide and is highly effective for controlling rodents and possums. Its tendency to bioaccumulate and cause secondary poisoning has advantages in some situations, but not when repeated control is required or where there are concerns regarding residues and food safety.

Continued fundamental and applied research is essential to achieve endangered species protection, through optimum use of existing tools and the development and uptake of promising emerging and new technologies for the control of rats, stoats, feral cats, and possums at this time. Anything less will cause significant delay in the application of new control and wildlife monitoring technologies and their adoption.

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