.

Trends in vertebrate pesticide use and development: alternatives to 1080 - what and when?

Charles Eason and Shaun Ogilvie

Faculty of Agriculture and Life Sciences, Department of Ecology, Lincoln University, PO Box 84, Lincoln, Canterbury, New Zealand.

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SUMMARY

Effective alternatives to sodium fluoroacetate (1080) for the control of possums, rodents and rabbits and other pests have been or are being developed and registered. This report on what these alternatives are and when new tools will be introduced has been prepared for Regional Council Biosecurity Managers to aid with future planning. Challenging research on biocontrol of vertebrate pests has been a major focus for more than 20 years in both New Zealand and Australia. This focus has left a gap between conventional poisons and the demands and expectations of modern biocontrol that needs to be filled. A new range of effective and acceptable tools is required now, to reduce over reliance on 1080 and provide greater flexibility, which ultimately could result in its replacement. Responding to these needs, renewed efforts are being made to ensure delivery of alternatives within 1-10 years. Experience gained in the introduction of cholecalciferol (Feracol®) and Feratox® which was first registered in 1997, underpins these initiatives. A new consortium, linked with Lincoln University, is working to a timeline, aiming to deliver a suite of improved ecofriendly toxin products available by 2012, and additional products with novel active ingredients targeting possums and other major pests delivered by 2015. Feratox® provides a humane kill of possums without secondary poisoning risk and is now being advanced for Dama and Bennett's wallabies. Registration of Feratox® for wallabies is anticipated in 2009, subject to New Zealand Food Safety Authority (NZFSA) approval. In addition, registration dossiers have been approved by NZFSA and are currently being assessed by the Environmental Risk Management Authority (ERMA) for zinc phosphide. Further registration documents are now being prepared for a combination of cholecalciferol and coumatetralyl to provide an additional alternative to brodifacoum for effective possum, rodent and rabbit control. Anticipated timelines for product availability are 2010 (zinc phosphide) and 2011-13 (cholecalciferol and coumatetralyl) subject to ERMA and NZFSA approvals. In parallel we are pursuing the registration of *para*-aminopropiophenone (PAPP) – a novel poison for humane control of stoats and cats. PAPP research and development has been completed for stoat control, registration dossiers have been vetted by NZFSA and were submitted to ERMA in May 2009. PAPP products should be available in 2010 subject to ERMA approvals. On the platform of proof of concept with PAPP, alternative red blood cell toxicants, including sodium nitrite, are being advanced for feral pigs, possums and rodents. All these developments are facilitated by a sharp focus on research and development that leads to tangible progress along the "registration pipeline" with both NZFSA and ERMA, and uptake of new tools by professional pest control operators. Every effort is being made to conduct high quality research and product development to enable registration to occur as quickly as possible. This momentum should deliver a new generation of improved safer toxins and associated delivery methods designed to minimise the impact of invasive animals. These new red blood cell (RBC) user-safe toxins will be unique, exhibiting humane performance, availability of an antidote, improved efficacy, cultural acceptability and species selectivity.

INTRODUCTION

Pests such as mice, rats, stoats, ferrets, possums and larger mammals continue to cause major harm to biodiversity and some are vectors of Tb. Culling these pests using sodium fluoroacetate (1080) can be very effective, but 1080 use faces rapidly increasing environmental, welfare and social pressures (Eason 2002). Ironically, the

1080 debate has become more polarised since the ERMA reassessment in 2007 (Keating 2007; Philp 2009), and expenditure to retain 1080 and meet increased compliance and consultation requirements continues to escalate.

Opposition to 1080 now compromises large scale conservation efforts and Tb vector control and signals the need for a new generation of control tools that can meet today's challenging social and ecological environments (Eason et al 2008). Some 1080 users have switched to brodifacoum, a second-generation anticoagulant, for possum and rodent control on mainland New Zealand and for pest eradication on Islands. Many Regional Councils have favoured the use of brodifacoum because of its ready availability, lack of regulation and ease of use. However, there is increasing awareness in NZ and overseas that whilst it is an effective control tool, repeat use of brodifacoum alone can result in transfer of residues through the food chain to non-target species (Dowding et al 1999; Eason & Spurr 1995; Eason et al 1999; Stone et al 1999, USEPA 2002). To reduce wildlife exposures and ecological risks, the USEPA is phasing in additional restrictions for second generation anticoagulants products. Except for use around livestock facilities, baits will only be applied by professional operators and applications must be made no further than 50 feet away from any building (USEPA 2008). In NZ bait station use and care must be exercised when ground baiting with brodifacoum. And, there is a need for baits that are effective for controlling mice, rats, possums, mustelids, rabbits, feral cats and feral pigs that contain cost effective alternatives to 1080, which are not persistent, are more widely accepted and unlike 1080 do not cause secondary poisoning.

Research on biocontrol of vertebrate pests has been as seen as the key to providing alternatives to 1080 and has been an important and major focus for investment for more than 20 years in both New Zealand and Australia. Despite considerable commitment, effort and initiatives to bring together various strands of research, establishing the utility of many interesting approaches remains a challenge (Hellstrom 2008; Tyndale-Biscoe & Hinds 2007). Whilst some lines of research are still showing promise there is a gap between conventional poisons and the requirements of modern biocontrol that needs to be filled. Responding to the continuing difficulties with 1080 and emerging difficulties with repeat use of brodifacoum, a Lincoln University consortium has been formed which is focusing on providing alternative technologies within 1-10 years to address this gap. The consortium is working to a timeline, aiming to deliver a suite of improved "ecofriendly" toxin products available by 2012 and products with new active ingredients targeting possums and other major pests delivered by 2015.

As a result there is now progress beyond laboratory and field testing and tangible alternatives to 1080 and brodifacoum for the control of possums, rodents and rabbits and other pests have been or are being developed and registered. This report provides advice on what these alternatives are and when they will be introduced to aid planning. It starts by reviewing very briefly the current suite of tools available. There is then a section that outlines the registration process for new toxins and products in NZ, and finally the pipeline of new products is presented.[1] This report provides detailed information for Regional Council Biosecurity Managers and a shortened version has also been prepared to provide information that can be presented to a wider

[1] This report covers new product developments being advanced by the Lincoln University grouping and not by other providers.

audience including Councillors, senior local government managers, stakeholder and community groups and industry sectors.

CURRENT VERTEBRATE PESTICIDES

Vertebrate pesticides, or Vertebrate Toxic Agents (VTAs) fall into two classes: anticoagulant and non-anticoagulant agents. Anticoagulants include pindone, diphacinone, coumatetralyl, and brodifacoum. Non-anticoagulant toxicants include any substance which does not fall into the former category, such as cyanide, sodium fluoroacetate (1080), and cholecalciferol.

When considering the history of toxin development and use in NZ it is apparent that there has been considerable reliance on 1080 for several decades, which has been coupled with efforts to make its use safer and more effective (Eason et al. 2006). Cyanide and phosphorus have in the past provided alternatives to 1080 for ground control of possums as pindone has for rabbits (Rammell and Fleming 1978). In the 1990s brodifacoum and cholecalciferol were introduced and the use of diphacinone and coumateralyl has increased more recently as less persistent alternatives to brodifacoum for rodent control.

Acute acting compounds

Sodium fluoroacetate (1080) is effective for controlling pests in a variety of bait formulations and is the only poison commonly used for aerial control of pests in NZ. Carcasses of animals poisoned with 1080 are very hazardous to dogs for many months (Meenken and Booth 1997), and there is some debate about the humaneness of 1080 (Sherley 2007). NZ is the only country in the world that uses relatively large amounts of 1080, and its use remains under scrutiny (Keating 2007; Philp 2009).

Cyanide pastes were predominately used until Feratox® was developed to increase the effectiveness of cyanide for possum control and reduce the risk of exposure of operators. Cyanide is potent, it does not cause secondary poisoning of dogs, it is favoured by some who oppose the use of 1080 and it is humane (Gregory et al. 1998).

Phosphorus is used by only a few operators. It is only available to licensed operators and is usually added to paste bait for possum control. It is generally considered inhumane (O'Connor et al 2007), and its use has been associated with the secondary poisoning of dogs (Gumbrell and Bentley 1995).

Cholecalciferol (vitamin D_3) was developed in NZ for controlling possums (Eason 1991) and is now registered in Feracol® paste bait, Pestoff DECAL Possum Bait® and No possum gel®, with Feracol® paste bait also now registered rodent control. There is low risk of secondary poisoning of dogs and birds are much less susceptible to cholecalciferol than to 1080 (Eason et al 2000).

Slower acting anticoagulant compounds

First-generation anticoagulant rodenticides (e.g. pindone, diphacinone, coumatetralyl), and second-generation anticoagulants (e.g. brodifacoum) all interfere with the synthesis of clotting factors, which results in hemorrhaging and death. First-

generation anticoagulant rodenticides were developed in the 1950s and 60s, and second-generation anticoagulants in the 1970s and 80s partly to overcome resistance in rodents. Possums are only partly susceptible to first-generation anticoagulants. The second-generation anticoagulants such as brodifacoum are more toxic to possums (Eason et al. 1994).

Pindone has proved most effective for rabbit control, and is also registered for possum control but is not so effective in this species. Diphacinone is more toxic than pindone and is registered primarily for field control of rodents. The persistence of diphacinone is similar to pindone and both are rapidly eliminated and do not bioaccumulate like the second-generation anticoagulants. Coumatetralyl is registered in NZ for rodent control and is considerably more persistent than diphacinone and pindone (Eason et al 2008).

Brodifacoum is the most well known second-generation anticoagulant and has been used successfully in recent rodent eradication programmes on offshore islands to protect populations of endangered indigenous birds. Repeated field use has resulted in wildlife contamination and problems associated with persistence have been compounded by its inhumaneness when used to control larger vertebrate pests such as possums (Littin et al 2002). NZ field use of brodifacoum is unique. No other country uses persistent pesticides in the field and in 2008 the US EPA initiated moves to restrict the sale of compounds like brodifacoum to the consumer market. As mentioned in the introduction, wildlife contamination extends to native birds as well as game species and residue will occur in livestock unless it is used carefully around farms. Because of this the Department of Conservation strictly limits the repeat use of brodifacoum on department owned land.

Table 1. Advantages and disadvantages of traditional and newer tools registered 1950-2005.

Toxin	Pros	Cons	Comment
1080	Cost-effective Not persistent (except in carcasses)	Secondary poisoning of dogs No antidote Controversial Very limited use outside NZ/Australia	Continued use of 1080 is under intense pressure. Having a range of tools takes the pressure off 1080 use.
Cyanide	Cost-effective Not persistent No secondary poisoning Humane	Only registered for possums	Feratox® has improved the utility of cyanide. Registrations are now being extended to new pest species
Phosphorus	Cost-effective	Inhumane No antidote Causes secondary	Limited use

		poisoning of dogs	
Cholecalciferol	Effective Low secondary poisoning risk Low toxicity to birds	Expensive compared with 1080	New formulations are being developed that will be less expensive (see below)
Pindone	Effective on rabbits Less persistent than brodifacoum Antidote	May causes primary or secondary poisoning of birds when used at high aerial sowing rate for control of rabbits. Not effective on possums Antidote	Although registered for possums not effective unless they are present at very low density
Diphacinone	Effective on rodents Can be used repeatedly Less persistent than brodifacoum and coumatetralyl Antidote	Not as effective as brodifacoum on possums and not registered for possum control Low but not no risk of primary or secondary poisoning risk Antidote	Registered in US for aerial rodent control for island conservation
Coumatetralyl	Effective on rabbits Less persistent than brodifacoum	Effective on rodents More persistent than diphacinone Some risk of primary or secondary poisoning risk Antidote	Similar potency to diphacinone for rodents but more persistent
Brodifacoum	Effective on rodents and possums Easy to use-effective for maintenance control Antidote	Persistent and bioaccummulates on repeat use through the food-chain. Primary & secondary poisoning in non-targets can occur Not humane in possums Antidote	Current use patterns and of ease of access are likely to lead to increased incidence of non-target contamination.

REGISTRATION PROCESSES AND TRENDS

Processes

In NZ the requirements of the Hazardous Substances and New Organism (HSNO) Act (1996) legislation must be met, along with the requirements of the Agricultural Chemistry and Veterinary Medicines (ACVM) Act, 1997. The registration process is challenging as approvals are required from both the Environmental Risk Management Authority (ERMA) and the New Zealand Food Safety Authority (NZFSA); consultation with Maori is a prerequisite, and welfare considerations are a key component of the registration assessment process for vertebrate pesticides as well as the need for demonstrating effective control of pests with minimum non-target impact in field trials. The steps in the two agency process are as follows:

1. Pre-screen NZFSA
2a. Full assessment NZFSA
2b. Pre-screen ERMA
3. Full assessment ERMA-which will include public notification and receipt of submissions and public hearings
4. ERMA approval
5. Finalisation of NZFSA registration

Registration[2] has become a means not only for regulating the use patterns of pesticide products, but also for ensuring that human safety and environmental health are considered. To assist in this process toxicology studies in animal or in-vitro test systems are usually conducted before the registration of new products. Alternatively, they may be conducted on older compounds, such as with 1080, in anticipation of a re-assessment process (Eason and Turck 2002; Eason et al 2009c). The principles that have underpinned the development of regulatory testing of pesticides to assess the risk to humans are listed below:

- Adverse reactions in humans can be predicted from the toxic effects observed in laboratory animals treated with chemicals.
- Administration of high doses improves the predictability of animal experiments.
- Comparison of the dose causing toxicity in animals and prediction of human exposure forms the basis for risk assessment.

Similarly the principles that underpin the development of testing of pesticides to assess the risk to the environment are listed as follows:

[2] NB The registration of new active ingredients or new products is not a "rubber stamp". Some compounds or products may never be registered and others may be delayed if ERMA or NZFSA request additional data as a result of their initial or in-depth assessments. Risk of failure can be reduced by interaction with these agencies, and consultation with Maori during the research and development process and it is important that the research providers and companies involved focus their research such that data and reports are provided that address key safety and efficacy requirements. In addition to the formal NZFSA/ERMA processes other agencies will have codes of practice and processes for vetting the use of VTAs. For example the Department of Conservation (DoC) has an internal risk assessment process overseen by a Pesticide Advisory Group which analyses risks and benefits associated with new product use before allowing the field use of a new product on DoC land.

- Adverse reactions in non-target terrestrial and aquatic species can be predicted from the toxic effects observed in surrogate species exposed to chemicals in laboratory conditions, when coupled with field observations.
- Administration of high doses improves predictability.
- Ecotoxicology, when combined with residue and fate data, forms the basis for risk assessment and environmental protection.

These studies allow for the characterisation of a chemical in terms of its potential to cause genetic mutations, foetal abnormalities, target-organ toxicity in humans and toxicity to non-target species.

A typical registration package for a vertebrate pesticide may include, in addition to laboratory and field trials on the effectiveness of the product, relevant toxicology and environmental studies, such as: acute toxicity (oral, dermal, inhalation), mutagenicity, and data from longer-term studies in laboratory animals and in-vitro testing. Metabolism, ecotoxicology in terrestrial and aquatic invertebrates, vertebrates and plants, and environmental fate and residues studies may also be important. For vertebrate pesticides it has been recognised that understanding the likely exposure risk of non-target species determined by well designed field trials forms a key component of the risks versus benefit assessment for new products.

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Trends

For the last two decades, a focus of many organizations involved in vertebrate pest control has been on the retention of product registrations for 1080 bait products for field use. In excess of $15M has been spent in the last 15 years on research, consultation with community groups and updating 1080 registration dossiers for a re-assessment of 1080 that was completed in 2007 (ERMA 2007; Eason et al. 2008). This was appropriate in the context of NZ being the largest user of 1080 and that 1080 baits are delivered aerially for possum and rat control with over-arching objectives to reduce damage to native forest and eradicate bovine tuberculosis. Likewise, a similar re-registration review has concurrently occurred in Australia by the Australian Pesticide and Veterinary Medicine Authority (APVMA 2008).

This requirement to build up registration dossiers on existing compounds has often driven research priorities sometimes at the expense of research on alternatives including new lower risk initiatives. Nevertheless, end-users including Regional Councils, DoC and the Animal Health Board (AHB) in NZ and environmental protection agencies around the world encourage the replacement of persistent or unpopular vertebrate pesticides or delivery techniques with more humane or less persistent alternative toxicants (EPA 2008, ERMA 2007). New product innovation is being stimulated to encourage alternatives to the current suite of vertebrate pesticides, as a number of these compounds, as indicated in Table 1, are associated with secondary poisoning or bioaccumulation or they are viewed as inhumane or too expensive.

There are significant challenges but product innovation and delivery is simply about inventors, researchers, manufacturers, and pest control professionals with practical skills working in close collaboration with stakeholders. The closer this collaboration and the more uncomplicated the lines of collaboration are, the greater the chances of

success. These collaborative ingredients are key to the advances outlined below, and collaboration between New Zealand, Australian and US researchers and stakeholders are making these aspirations a reality.

THE PIPELINE

New NZ registration of established vertebrate pesticides

Past research has improved the effectiveness and safety of all pest control products, including refining and reducing the amount of 1080 used in aerial applications (Eason et al 2006). Nevertheless, secondary poisoning, persistence and bioaccumulation of many toxins remains a concern. To counter this, we are developing single and multi-species bait types for sustained field use incorporating "low-residue" toxicants, namely zinc phosphide, cholecalciferol, and a combination of coumatetralyl and cholecalciferol, in new bait formulations. In addition the registration of Feratox® is being extended and new formulations of cyanide are being developed for a variety of pest species (Eason et al 2008).

Part 1: Products that contain vertebrate pesticides already in use in NZ.

We have been extending the registration of existing products and active ingredients that are already approved by ERMA and the NZFSA and viewed as "ecofriendly" (see Table 2a). For example, since its registration in 1997 Feratox® has become the accepted method for cyanide baiting with more than six million pellets sold annually for possum control. As its use has strong community support and it is used by hunters and trappers as well as professionals, extending this registration to include Dama and Bennett's wallabies is a logical step (Lee et al 2009).

Cholecalciferol has the advantage of low secondary poisoning risk and low toxicity to birds. All the currently available commercial baits contain cholecalciferol at a concentration of 0.8%, regardless of the formulation type. The active ingredient cholecalciferol is expensive and if efficacy and humaneness can be achieved with a lower concentration of toxin in existing products the price of bait could be reduced. The acute LD_{50} is reported to be 16.8 mg/kg for possums (Jolly et al 1995). Research funded by the Animal Health Board suggests that possums are more susceptible to cholecalciferol than previously supposed. The LD_{50} is 9 mg/kg for cholecalciferol in rabbits when dosed by oral gavage (Eason et al 1993) and 4.4 mg/ when given in bait (Henderson and Eason 2000). Recent work has established that baits containing half the current dosage of cholecalciferol are just as effective as the 0.8% baits against possums, when similar amounts are eaten (Hix et al 2009a), and field trials are planned in both paste and solid baits in 2009 to support product registrations.

Table 2a. New products containing vertebrate pesticides already in use in NZ, introduction dates product advantages and comments.

Toxin and product	Projected Registration Dates	Advantage	Comment	Chances of success
Cyanide/Feratox® for wallaby control-	3rd Qtr 2009	Enabling humane possum and dama	Cage and field trial data and	VERY

extending the existing registration for possum		wallaby control without 1080	registration dossiers submitted to NZFSA in 2009. Aided by DoC & RC support and collaboration with Tasmanian agencies.	HIGH
Cyanide/Feratox® for ferret and feral pig control	2011	Disease monitoring and humane kills	Technical challenges still need to be overcome - subject of current research focus supported by AHB	MOD
Low dose (0.4 %) cholecalciferol *paste* Feracol®- half the current concentration of 0.8% targeting possums and rodents.	2010	Less expensive than current cholecalciferol baits with lower risk to non-targets	Cage trial completed. Field trials scheduled for mid 2009 aided by support from AHB and multispecies bait development by FRST.	VERY HIGH
Low dose (0.4 %) cholecalciferol in multispecies *solid bait* half the current concentration of 0.8%-targetting possums and rodents	2010	Less expensive than current cholecalciferol baits with lower risk to non-targets	Cage trial and field trials scheduled for 2009 multispecies bait development aided by support from FRST.	VERY HIGH

Part 2: Products that contain vertebrate pesticides NOT already in use in NZ.

Zinc phosphide was first used as a rodenticide in 1911 in Italy. Zinc phosphide is an effective acute field rodenticide that has been in use for over 50 years with very few non-target hazards. It is still used as a rodenticide in the USA, as well as in Australia, China and the Asia-Pacific region. In the USA it has been used to control rats, mice, voles, ground squirrels, prairie dogs, muskrats, hares and gophers. In Australia it is used for rodent control. It found favour because of the comparatively low risk of secondary poisoning following its field use when compared with strychnine or 1080 (Hood 1972; USEPA 1998). Zinc phosphide is a quick-acting compound with clinical signs first appearing from 15 minutes to 4 hours, and death after a lethal dose occurs generally in 3-12 hours. The oral toxicity of zinc phosphide is accounted for by the toxicity of the phosphine it produces when hydrolysed by the acid of the stomach; death is mediated by a combination of cardiac failure and respiratory failure (Osweiler 1985). It is surprising, given that it lacks secondary poisoning, it is registered internationally and it is inexpensive, that it has not been registered in NZ before now. This may have because of taste aversion which has been overcome with an

encapsulated formulation for NZ use. A concerted effort by many NZ researchers, including PestTech, Lincoln University and Connovation are now coming to fruition (see Table 2b). In parallel in the USA considerable research investment has been expended over the last decade to sustain the field use registrations for zinc phosphide and meet new EPA requirements (pers comm. Dr Kathy Fagerstone, USDA National Wildlife Research Center, Fort Collins, Colorado USA). The National Wildlife Research Center has provided valuable toxicology dossiers prepared for the EPA to Connovation/PestTech to support the NZ registration of zinc phosphide with ERMA in exchange for NZ data and reports.

Cholecalciferol + coumatetralyl (C+C) also has a track record overseas. In Europe, cholecalciferol has been added to baits containing coumatetralyl (Racumin® plus) to overcome anticoagulant resistance in rats and mice. AHB has funded the development of 'C+C' for controlling possums, and it is currently being developed in multispecies baits for controlling rats and mice as part of the Lincoln University FRST programme (Eason et al. 2008)[3]. Bait containing 0.015% cholecalciferol and 0.03% coumatetralyl (C+C) has been developed, and dossiers are being prepared for submission for registration in 2009. C+C is effective at killing possums, rodents and rabbits even though the amount of cholecalciferol is a fraction of that used in current cholecalciferol baits (Ray Henderson, PestTech NZ pers comm.). Whilst zinc phosphide is more akin to 1080, in that it is kills more quickly than anticoagulants, C+C by contrast is slower acting and offers the advantages of brodifacoum without persistent residues. Death occurs in 12 days in possums and 5 days in rats and mice; it has effectiveness similar to brodifacoum, is less persistent than brodifacoum, and animals poisoned with C + C will die more quickly than those poisoned with brodifacoum (Ray Henderson PestTech NZ pers comm.).

For both zinc phosphide and C+C there is a common development strategy which is to first register a product for control of possums and then extend this registration to include rodents and then rabbits (see Table 2b & c). Zinc phosphide is initially being registered in a paste bait, as there are technical challenges linked to the stability of zinc phosphide in solid bait matrices which are currently being addressed. Ultimately it is intended that there will be solid bait and paste formulations of both zinc phosphide and C+C (Ray Henderson PestTech NZ pers comm.).

Table 2b. New products containing zinc phosphide, likely introduction dates[4] , product advantages and comments.

Toxin and product	Projected Registration Dates	Advantage	Comment	Chances of success
Zinc phosphide 1.5% *paste* for	Mid 2010	Cost -effective Quick acting like	Cage and field trial data and registration	MOD to HIGH-aided by

[3] FRST's "Smart Pest Control" March 2007 – Sept 09 has facilitating much of the "behind the scenes" research and development, this ends soon.

[4] The projected registration dates in Table 2b are dependant on continued AHB support for research as well as financial and in-kind commitment from Connovation and PestTech to enable completion of chemistry, manufacturing and registration dossiers. In absence of FRST support for ZP and C+ C other help from other investors including Regional Councils will be requested to meet these dates.

possum control		1080 Low secondary poisoning risk vs. 1080. Not persistent. Widely used by international trading partners e.g. US/AUS	dossier submitted to NZFSA in 2009 and to ERMA. Aided by AHB support and FRST Sensible to register in NZ - as an inexpensive back up to 1080.	collaboration with US agencies in preparation of registration dossiers
Zinc phosphide 1.5% *paste* for multispecies control of possum, rats, mice and rabbits.	Late 2010 or early 2011	As above and provides cost-effective alternative to 1080 and for targeting rodents and possums in one hit.	Cage trials completed in rats and mice in 2008 with 100% kill Field trials are planned in 2009. Aided by FRST funding support.	VERY HIGH once registration has been achieved for possum control.
Zinc phosphide 1.5% *solid bait* for possum control	Late 2011 or early 2012	As above and will provide greater flexibility in how zinc phosphide can be used	Aided by AHB support and FRST funding. Sensible to register an "acute" toxin in a solid bait - as an inexpensive back up to 1080	MOD-HIGH
Zinc phosphide 1.5% *solid bait* for multispecies control of possum, rats, mice and rabbits.	2012	As above and will provide greater flexibility in how zinc phosphide can be used	Aided by FRST funding.	HIGH Once registration has been achieved for possum control

Table 2c. New products containing C+C, likely introduction dates[5], product advantages and comments.

[5] The projected registrations in Table 2c are also dependant on continued co investors inluding AHB support for research as well as financial and in-kind commitment from Connovation and PestTech to enable completion of chemistry, manufacturing and registration dossiers. Help from other investors including Regional Councils will be requested to meet these dates.

Toxin and product	Projected Registration Dates	Advantage	Comment	Chances of success
C+C *solid bait* for possum control	2011/12	Alternative to brodifacoum – slow acting Low secondary poisoning risk vs. 1080. Not persistent.	Research complete registration dossier in prep for submission late in 2009 or early 2010	MOD – will improve once interaction with NZFSA & ERMA start to advance
C+C *solid bait* for multispecies control of possum, rats, mice and rabbits.	2012	As above and provides cost-effective alternative to target rodents and possums in one hit.	Cage trials completed in rats and mice in 2008 with 100% kill Field trials are planned in 2009. Aided by FRST funding support.	HIGH once registration has been achieved for possum.
C+C *paste bait* for possum control	Late 2012 early 2013	As above and will provide greater flexibility	Research will not start on this until C+C is registered in solid bait.	MOD-HIGH
C+C *paste bait* for multispecies control of possum, rats, mice and rabbits.	2013	As above and provides cost-effective alternative to target rodents and possums in one hit.		HIGH once registration has been achieved for possums.

NZ registrations of a new generation of vertebrate pesticides.

As indicated above there have been no registrations of new active ingredients, (the chemicals in the baits) in this field since the development of brodifacoum and cholecalciferol in the 1970/80s. There is an exciting opportunity, and a challenge, to develop new vertebrate pesticides/rodenticides which are a quantum leap ahead in terms of humaneness and improved target specificity. Looking to the future, we seek to increasingly combine "low-residue" characteristics (see Appendix Table 1) with humaneness (Eason et al 2008). In the medium to longer term we aim to replace conventional poisons with innovative biologically-sound alternatives, enabling better more acceptable vertebrate pest management (see Table 3).

A new class of compounds is now emerging targeting red blood cells in mammalian pests. At the core of the research is the important discovery that targeting red blood

cells (RBCs) with toxins induces a humane death. PAPP (*para*-aminopropiophenone) represents the first compound in this class and is a potent and selective toxin for mustelid and feral cat control. Sodium nitrite, which has the same mode of action as PAPP, represents the second compound in this class. It contrasts with PAPP in that it is less selective, it is a broad spectrum toxin but with modest toxicity compared to most vertebrate pesticides (Lapidge and Eason 2009).

Recent progress, following the completion of successful field trials in 2008, has been rapid with the registration of PAPP for advancing the control of stoats and feral cats, and dossiers for chemistry and manufacturing, toxicology, efficacy, ecotoxicology and non-target impacts, and welfare filed with the NZFSA in 2008 and ERMA in 2009. Amongst this class of compounds PAPP represents a partially selective toxin, whereas sodium nitrite at high doses is an example of a broad spectrum toxin.

PAPP was originally studied as a treatment for cyanide poisoning in the 1940s (Rose et al. 1947) and subsequently in humans as a treatment for radiation poisoning in the 1970s in the UK (Bright and Marrs 1983). It is toxic to carnivores, with birds and humans being less sensitive (Murphy et al 2007; Eason et al 2009a). The LD_{50} for PAPP in stoats and cats is < 10 mg/kg. This selectivity is primarily due to the different metabolic pathways that occur in carnivores as opposed to other animals (Wood et al. 1991). The toxin is being developed for humane control of stoats and feral cats in NZ, and foxes, feral cats and wild dogs in Australia. The toxic effects of PAPP are related to its ability to reduce the oxygen carrying capacity of the red blood cell through the formation of methaemoglobin. The onset of symptoms is rapid and stoats, cats and foxes are usually unconscious within 30-45 minutes (Murphy et al. 2008). This leads rapidly to a lack of oxygen to the brain and other vital organs and death due to respiratory failure. Methylene blue is an effective antidote to PAPP toxicity and is available from veterinarians. It will reverse the methaemoglobinaemia induced by PAPP.

In the same way as the completion of zinc phosphide registration dossiers has been made possible by the exchange of data and reports with the USDA National Wildlife Research Center, the registration of PAPP is facilitated by close collaboration between NZ agencies and the Invasive Animal Cooperative Research Centre in Australia and contacts with UK toxicologists. Data sharing and exchange is a pivotal component of the registration strategies for both NZ and Australia. For example Australian reports optimizing antidote treatments have been provided to us (Dall and Spencer 2007) and critical confidential toxicology reports (Lackenby 1987 a & b) generated when PAPP was being investigated as a drug have been obtained from the UK contacts. PAPP has low toxicity to most bird species, no secondary poisoning risk and has a simple highly effective antidote. It represents the first new active ingredient to be field tested as a vertebrate pesticide for >30 years and the only one with humaneness as the primary consideration.

Sodium nitrite is a common salt that is currently at an early stage of research and investigation as a feral pig and possum toxin. In pigs recent research has shown it causes lethargy, reduced consciousness and coordination and death in approximately two hours (Eason et al 2009d). The toxicology of sodium nitrite is well understood because of its use as a preservative agent in meat. Sodium nitrite like PAPP is an inexpensive methaemoglobin forming compound and has limited secondary poisoning

risks. The toxic effects of sodium nitrite, like PAPP, are related to its ability to reduce the oxygen carrying capacity of the red blood cell and methylene blue is the recommended antidote. Current investigations into its potential use for pig control are underway with Lincoln University and Connovation researchers collaborating with Regional Councils. Again international data sharing will be key to the success of the development of sodium nitrite as a VTA as illustrated by joint work by Australian and NZ researchers on species susceptibility to sodium nitrite (Lapidge and Eason 2009) and the provision of reports by Australian veterinarians which establish the humaneness of this compound in pigs (Porter and Kuchel 2009).

The LD_{50} for sodium nitrite is > 100 mg/kg for most species, and as methaemoglobinaemia needs to be induced rapidly to cause death it has most potential for pest species such as pigs and possums that tend to devour their food quickly. Species such as rodents which nibble at baits or cache will experience a transient sub-lethal effect given the relatively low toxicity of sodium nitrite. Hence sodium nitrite is unlikely to be an effective rodenticide even thought that it appears to be an effective toxicant for pigs.

In parallel to initiating testing of sodium nitrite and completing and submitting registration dossiers for PAPP for stoats and feral cat control in 2008/09, research has been initiated screening PAPP analogues and compounds with a similar mode of action in rodents and larger pests like possums and feral pigs alongside work on the susceptibility of non-target species (Eason 2007 a, b; Eason and Lapidge 2008; Eason et al 2009 b, d). Amongst this class of compounds PAPP represents a selective toxin, whereas sodium nitrite at high doses is and example of a broad spectrum toxin. Insights into the toxicity of these and related compounds are being generated in rodents, in other mammals and new test systems at the University of Auckland and Lincoln University. Systematically investigating the effect of substituents on the aromatic ring of PAPP which would increase potency or allow other species to be targeted could lead to exciting developments based on chemicals in the PAPP family. Other means of targeting red blood cells are also being considered as rational ways forward for new VTAs.

PAPP and sodium nitrite should be perceived as the prototypes, and we believe that we can improve on these compounds to produce more potent broad spectrum and selective species specific toxins, with low toxicity to birds, based on the PAPP platform which will facilitate more effective predator and multispecies control, delivered by 2015[6]. We hope to be able to develop and register other compounds (e.g. sodium nitrite and analogues of PAPP) with the same mode of action to target the RBCs of other pests.

Further specificity could be achieved by combining novel toxins with novel delivery systems which will facilitate control of pests with more infrequent servicing and extend the range and effectiveness of ground control. For example a tunnel system designed with compressed CO_2 gas will propel a measured amount of PAPP paste onto the abdomen of pests as they pass over a trigger. A dose is subsequently delivered orally when the animal licks and grooms its abdomen. Cage trials have

[6] Links to a new FRST's programme entitled "Pest Control for the 21st Century" involving Lincoln and Auckland University focused on novel vertebrate pesticides and delivery systems.

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achieved proof of concept stage for this method of killing stoats, indicating that a device capable of safely delivering multiple lethal doses of toxin without regular resetting can be produced (Hix et al 2009 b & c).

Most of the current endeavours described above are focused on advancing new products along the registration pipeline and ensuring that we fully exploit the potential of the red blood cell toxins. Other initiatives include the exploration of methylxanthines, components of chocolate, for their toxicity to possums, and research supported by Nag Pae o te Maramatanga to identify useful natural plant toxins. Whilst these avenues of research may appear as long shots the work on methylxanthines is linked with our colleagues at the USDA National Wildlife Research Center (Johnston 2005) and a component of the toxic plant karaka has already been proven to be toxic to possums (Gregory et al 2000).

Table 3. New products based on a new generation of vertebrate pesticides, likely introduction dates[7] , product advantages and comments.

Toxin and product	Registration Dates	Advantage	Comment	Chances of success
PAPP paste for stoat control	2010	Selective and humane targeting of stoats and feral cats. Low toxicity to most bird species. Low risk of secondary poisoning Simple highly effective antidote.	Cage and field trial data and registration dossiers submitted to NZFSA and to ERMA Jan-May 2009. Aided by DOC support and extension work supported by FRST	MOD to HIGH – aided by collaboration with Australian agencies in preparation of registration dossiers
PAPP paste for stoat and feral cat control	mid 2010	As above and provides cost-effective alternative to 1080 predator control.	Cage trials completed in cats in 2008 with 100% kill. Field trials will be completed by July in 2009. Aided by DoC funding support.	VERY HIGH once registration has been achieved for stoat control.
PAPP delivered in repeat dose tunnels	Late 2010/early 2011 for stoats and 2012 for feral cats 2013 multispecies	As above and sustained control without rebaiting	Technically challenging but cage trials promising	MOD-HIGH given that registration will piggy back on PAPP paste

[7] Subject to continued investment by Connovation and support from FRST and other agencies.

	tunnel			registration
Sodium nitrite for nuisance feral pigs	2011	Humane. Low risk of secondary poisoning Simple highly effective antidote.	Pen trials completed in 2008. Field trials will be completed in 2009/10. Aided by RC funding support	MOD-HIGH given that registration will aided by co-investment by Aus agencies
Sodium nitrite for possums	2012	As above.	Preliminary pen trials completed in 2009. Aided by AHB funding support. Effective in no-choice studies – taste masking still required	MOD-HIGH given that registration will aided by co-investment by Aus agencies
More potent (than sodium nitrite) broad spectrum RBC toxin	2013	As above	At concept stage	MOD – will improve as research advances
PAPP like rodenticide and/or combined rodenticide and mustelid toxin	2013/14	As above	At concept stage	MOD – will improve as research advances
PAPP like possum selective toxin	2014	As above	At concept stage	MOD – will improve as research advances
Natural toxins and methylxanthines	2011-2014	At concept stage	At concept stage with pen trials on methylxanthines in possums in 2009 aided by AHB support	MOD – methylxanthines research aided by US collaboration.

CONCLUSIONS

Over the last 3 decades considerable effort has been put into improving the effectiveness and safety and refining the use of 1080. Nevertheless, safer rodenticides are required now in NZ, in advanced more cost-effective delivery systems to enable improvements in conservation of endangered species, including the expansion of areas where native species are protected and also to sustain Tb vector control and eradication.

Whilst this will be a new and significant challenge for the 21st century, new target research is bearing fruit. Effective alternatives to sodium fluoroacetate (1080) and brodifacoum for the control of possums, rodents and rabbits and other pests have been or are being developed and registered. In the last 6 months (Dec 2008 – June 2009)

we had a record period for new product registration advancement. Extensive registration dossiers were filed for microencapsulated zinc phosphide (MZP) for possums, Feratox® for wallabies, and *para*-aminopropiophenone (PAPP) for stoats with ERMA & NZFSA.

There are no "silver bullet" replacements for 1080 or brodifacoum. A suite of more effective and acceptable tools is being developed now, to reduce over reliance on 1080 and to provide greater flexibility and which ultimately could result in its replacement. There is now an intense focus on delivery of alternatives within 1-10 years. Experience gained in the introduction of cholecalciferol (Feracol®) and Feratox® which was first registered in 1997 underpins these initiatives. Our new consortium, linked with Lincoln University, is working to a timeline, to deliver a suite of improved ecofriendly toxin products available by 2012, and additional products with novel red blood cell toxins targeting rodents, possums and other major pests delivered by 2015.

In 2009 Feratox® is being advanced for Dama and Bennett's wallabies. Registration of Feratox® for Dama wallabies is anticipated soon, subject to New Zealand Food Safety Authority (NZFSA) approval. In addition, registration has been approved by NZFSA and an application is currently being assessed by Environmental Risk Management Authority (ERMA) for zinc phosphide. Registration dossiers are also now being prepared for a combination of cholecalciferol and coumatetralyl to provide additional alternative toxins for effective possum, rodent and rabbit control. Anticipated timelines for product availability are 2010 (zinc phosphide) and 2011-13 (cholecalciferol and coumatetralyl) subject to ERMA and NZFSA approvals. In parallel we have pursued the registration of *para*-aminopropiophenone (PAPP) – a novel poison for humane control of stoats and cats. PAPP research and development has been completed for stoat control, registration dossiers have been vetted by NZFSA and were submitted to ERMA in May 2009. PAPP products should be available in 2010 subject to NZFSA and ERMA approvals.

On the platform of proof of concept with PAPP, alternative red blood cell toxicants, including sodium nitrite, are being advanced for feral pigs, possums and rodents. All these developments are facilitated by a sharp focus on research and development that leads to tangible progress along the "registration pipeline" with both NZFSA and ERMA, and uptake of new tools by professional pest control operators. Every effort is being made to conduct focused high quality research and product development to enable registration to occur as quickly as possible. This momentum should deliver a new generation of toxins and associated delivery methods designed to minimise the impact of invasive animals.

Table 4. A summary of the new registration pipeline[8]

Type	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15
Products that contain vertebrate pesticides already in use in NZ.	Feratox® for wallaby control. Less expensive cholecalciferol paste and solid bait	Cyanide for pigs/ferrets				
Products that contain vertebrate pesticides NOT already in use in NZ.	Zinc phosphide 1.5% *paste* for possum	Zinc phosphide 1.5% *paste* for possums rodents	Zinc phosphide solid baits for possums and rodents C+C *solid bait* for multispecies control	C+C *paste bait* for multispecies control of possum, rats, mice and rabbits.		
NZ registrations of a new generation of vertebrate pesticides	PAPP paste for stoat and feral cat control	PAPP delivered in repeat dose tunnels	Sodium nitrite for nuisance feral pigs	Sodium nitrite for possums	More potent PAPP like rodenticide and/or combined rodenticide and mustelid toxin	PAPP like possum selective toxin + other RBC toxins Natural toxins and methylxanthines

These new red blood cell (RBC) user-safe toxins will be unique, exhibiting humane performance, availability of an antidote, improved efficacy, cultural acceptability and species selectivity and fill a gap between conventional poisons and the demands and expectations of modern biocontrol that needs to be filled.

Our short-medium term focus is on registering new compounds for ground control. This is a significant milestone in itself. If and when these registrations are achieved and practical experience has been gained over at least 2-3 years, the next logical step is to consider which compounds are suitable for aerial control of pests. Diphacinone is an alternative that has already been identified with potential for aerial control of rodents, particularly where repeat use is likely (Eason and Ogilvie 2009) and cholecalciferol baits could be considered if new formulations are as hoped substantially less expensive than current bait. A key advantage of diphacinone and cholecalciferol is that they are already registered for field use and could be registered for aerial application in the short to medium term. C+C and zinc phosphide are also future candidates. Availability and registration status could influence which might be the best to develop as an alternative to 1080 for aerial control. Research and development needs to be consolidated over the period 2010-15 if any of these new options are to become available for aerial control in the future. In the medium to

[8] These timelines are not only subject to regulatory approval but continued stakeholder support both in kind and also with contracted research.

longer term, the preferred alternative to 1080 for aerial application would be a novel, humane red blood cell toxin, related to PAPP. In parallel work to improve the cost-effective use of ground control over larger areas with advanced delivery systems that can sustain control for months or years (Hix et al. 2009 b,c), should enable larger areas of land to be treated by new ground control strategies reducing the need for aerial baiting.

It is hoped that this report on what these alternatives are and when they will be introduced has prepared the Regional Council Biosecurity Managers to aid with future planning. A 3 page summary of this report is being prepared for wider circulation.

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APPENDIX

Appendix Table 1 Summary of classification of vertebrate pesticides based on comparative pharmacokinetics and expectation for persistence of residues in sub-lethally exposed target or non-target species.

Group	Compound	Half-life values in papers summarized above	Likely persistence of residues after sub-lethal residue exposure
1	cyanide	+	12 to 24 hours
	sodium nitrite	+	12 to 24 hours
	zinc phosphide	+	12 to 24 hours
	para-aminopropiophenone	+	4 days
	1080	< 11 hours	7 days
2	pindone	2.1 days	4 weeks
	diphacinone	3-8 days*	6 weeks
3	cholecalciferol	10-68 days	3 months
	coumatetralyl	50-70days	4 months
4	brodifacoum	130-350 days	24 months or longer
	bromadiolone	170-318 days	24 months or longer
	flocoumafen	220 days	24 months or longer

+ no published value but likely to be < 12 hours * These value is based on data from rats and pigs and results from cattle are not included at this stage as the data in this species from Bullock et al 1979 and Eason et al 2009 is inconsistent and requires clarification.