A re-evaluation of potential rodenticides for aerial control of rodents

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A re-evaluation of potential rodenticides for aerial control of rodents

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ABSTRACT

Rodent control is carried out extensively in New Zealand to protect the native fauna and flora. This review outlines the advantages and disadvantages of different rodenticides as alternatives to sodium fluoroacetate (1080), and their suitability for aerial application. It includes existing rodenticides and those in the registration 'pipeline', as well as those that are not currently available in New Zealand. In the short to medium term, the focus for aerial baits should be on those compounds already registered in New Zealand or other countries. Aerial brodifacoum baiting is appropriate in isolated situations, but is not suitable for repeated use on the mainland, as brodifacoum is highly persistent and will bioaccumulate. Diphacinone has been registered for field use in New Zealand and the US Environmental Protection Agency has recently registered it for aerial control of rodents for conservation purposes; therefore, this is a logical first choice for control in New Zealand. Cholecalciferol is the next best option, as there is no secondary poisoning and thus there would be lower risk to non-target bird species; this is currently registered for field use as a rodenticide in bait stations. The third option is cholecalciferol in combination with coumatetralyl, which should be more effective than cholecalciferol alone, and the fourth is zinc phosphide. In the longer term, the preferred alternative to 1080 would be a novel, humane red blood cell toxin, related to para-aminopropiophenone (PAPP). PAPP is an attractive new pesticide that is being developed for stoat (*Mustela erminea*) and feral cat (*Felis catus*) control; however, the rodenticidal potential of this class of compounds still remains to be determined. Availability and registration status could influence this priority list in the future. A strategy to manage mice (*Mus musculus*) and sustain rat (*Rattus* spp.) control needs to be flexible and integrate non-anticoagulant and anticoagulant use.

Keywords: rodents, rodenticides, aerial control, anticoagulants, non-anticoagulants

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1. Introduction

Three rodent species were introduced to New Zealand from Europe. The Norway rat (*Rattus norvegicus*) arrived in the late 1700s and, away from human habitation, is mainly associated with wetland habitats. The ship rat (*Rattus rattus*) arrived towards the end of the 19th century and is the most widespread species in New Zealand, particularly suited to forested areas. The house mouse (*Mus musculus*) is widely distributed throughout the country in forests, sand dunes, pastures and tussock grasslands. Both ship and Norway rats have a direct impact on native wildlife by eating birds, eggs, lizards and invertebrates. The ship rat is generally a greater threat because of its climbing ability. Mice are predators of native invertebrates and, on occasion, small reptiles and birds (Innes 2005).

Sodium fluoroacetate (1080) is the vertebrate pesticide widely used for aerial control of possums (*Trichosurus vulpecula*) and rodents in New Zealand (Eason 2002). However, its use is controversial, and it remains under scrutiny by the Environmental Risk Management Authority (ERMA) and the broader community (Philp 2009). Although 1080 can be very effective at culling animal pests (a solution developed in the 1940s), its use faces increasing and often fiercely articulated environmental, welfare and social pressures. Ironically, the 1080 debate has become more polarised since the ERMA reassessment in 2007 (Philp 2009). Therefore, New Zealand needs new, publicly acceptable rodent and possum toxins that can be aerially applied. It would also be advantageous to use toxins that act on different physiological processes, to prevent the development of bait shyness, aversion and resistance (Eason et al. 2008). This review evaluates the merits of a range of rodenticides as alternatives to sodium fluoroacetate (1080), particularly with regard to their suitability for aerial application for rodent control.

Rodenticides are classified into two categories: non-anticoagulant acute poisons and anticoagulants (Table 1). The anticoagulants are themselves separated into first-generation and second-generation chemicals: the second-generation anticoagulants were developed later and are more toxic. A new candidate vertebrate pesticide, para-aminopropiophenone (PAPP), is also currently being developed for predator control, and this compound, analogues, or compounds with a similar mode of action may have potential as a safer rodenticide (Eason et al. 2008, 2009).

TABLE 1. COMMON AND CANDIDATE RODENTICIDES AND VERTEBRATE PESTICIDES.
Adapted from information in Hone & Mulligan (1982) and Prakash (1988).

EXISTING AND OLDER NON-ANTICOAGULANTS	NOVEL ANTICOAGULANT COMPOUND	ANTICOAGULANTS*		COMBINATIONS
		INDANDIONES	COUMARINS	
Zinc phosphide Strychnine Cholecalciferol Bromethalin Norbormide	Para-aminopropiophenone (PAPP)	Pindone (1) Diphacinone (1)	Warfarin (1) Coumatetralyl (1) Brodifacoum (2)	Cholecalciferol + coumatetralyl

* (1) = first-generation anticoagulant; (2) = second-generation anticoagulant. See section 4 for further explanation about indandiones and coumarins.

In the following sections, the history, mode of action and appropriateness of different rodenticides for aerial control of rodents are reviewed. The key features of the existing or former non-anticoagulant rodenticides are first covered, followed by the key features of the existing anticoagulant rodenticides. The potential of the new candidate vertebrate pesticide PAPP is then explored. An analysis of the relative merits of the compounds described and current research and development activities in this field are considered in the closing discussion sections. The review has been assisted by a new Lincoln University Foundation for Research, Science and Technology (FRST) programme entitled 'Smart Pest Control' (March 2007 to June 2009), which is focusing on new multispecies baits, including solid baits containing 1080, zinc phosphide and cholecalciferol, for ground and aerial control of rodents and possums.

2. Non-anticoagulant rodenticides

This section outlines the advantages and disadvantages of a range of non-anticoagulant poisons. Each of these compounds has a different mode of action and different properties.

2.1 ZINC PHOSPHIDE

General information and history of use

Zinc phosphide was first used as a rodenticide in 1911 in Italy (Marsh 1987; US EPA 1998). It is an effective acute field rodenticide and was the most widely used rodenticide worldwide until the introduction of anticoagulant compounds in the 1940s and 1950s (US EPA 1998). It is still used as a rodenticide in the USA, Europe, Australia, the Asia-Pacific region and China (Marsh 1987). In the USA and Australia, it is used for field control of rodents, having found favour because of the comparatively low risk of secondary poisoning following its field use when compared with strychnine or 1080 (Marsh 1987; Eason et al. 2008).

Zinc phosphide has been developed in a paste bait in New Zealand, firstly as a back-up alternative to 1080 for possum control. An extensive database has been amassed to support the registration of a paste containing 1.5% zinc phosphide for possum control. This was filed with the New Zealand Food Safety Authority (NZFSA) in July–August 2008 and with ERMA in December 2008. The Animal Health Board (AHB) has funded the development of zinc phosphide for possum control, and its use in multispecies baits for controlling rats and mice is currently being developed as part of the Lincoln University FRST programme. As an extension to this programme, solid bait that would be suitable for aerial application will be developed, if this research continues beyond 2009.

Mode of action

Zinc phosphide is a fast-acting compound, with clinical signs of poisoning first appearing from 15 minutes to 4 hours after intake and, following a lethal dose, death generally occurring in 3–12 hours (Marsh 1987). The oral toxicity of zinc phosphide is accounted for by the toxicity of the phosphine it produces when hydrolysed by stomach acid. The emetic action of the zinc portion reduces the toxicity of zinc phosphide to some non-target species; however, rats lack a vomiting reflex (Marsh 1987; US EPA 1998). Death is mediated by a combination of cardiac failure and respiratory failure (Osweiler et al. 1985). The poison is considered moderately humane (similar to 1080) (Fisher et al. 2004).

Toxicity

Zinc phosphide is a broad-spectrum toxin, but there are some marked differences in susceptibility between species (Table 2). The LD_{50} for Norway rats is around 40 mg/kg. Some bird species are more susceptible to zinc phosphide (e.g. LD_{50} for the white-throated goose (*Anser albifrons*) is 7–5 mg/kg) (Hone & Mulligan 1982).

TABLE 2. ACUTE ORAL TOXICITY (LD_{50} mg/kg) FOR ZINC PHOSPHIDE.
Prepared from information contained within Hone & Mulligan (1982).

SPECIES	LD_{50} mg/kg
Pig (*Sus scrofa*)	20–40
Dog (*Canis familiaris*)	20–40
Cat (*Felis catus*)	40
Norway rat (*Rattus norvegicus*)	40
Kiore (Pacific rat) (*Rattus exulans*)	23
Goose (Anatidae)	7.5
Northern bobwhite (*Colinus virginianus*)	13
Duck (*Anas platyrhyncha)*	36

Summary of key features

Advantages:

- Highly toxic to rodents
- Inexpensive
- Used in the field in USA/Australia
- Non-persistent
- Comparatively low secondary poisoning risk

Disadvantages:

- Lacks specificity and more toxic to birds than mammals
- No antidote
- Not yet registered in New Zealand—pending 2009/10

Recommendations

Zinc phosphide is not recommended for aerial control of rodents at this time because of the potential hazard to non-target species. Once registrations are achieved firstly for possum control and subsequently for multispecies baits targeting rodents and possums, aerial application of solid baits containing zinc phosphide could be progressed if field experience with ground baiting is favourable. However, special attention would need to be taken with regard to non-target impacts on birds.

2.2 STRYCHNINE

General information and history of use

Strychnine is found in the seeds of the tree *Strychnos nux-vomica.* The alkaloid has been used for rodent and vertebrate pest control since the mid-1800s (Schwartze 1922). The first recorded use of strychnine in Australia was in the 1880s, and it is still used there to control mouse plagues (Mutze 1989). In 1986, the US Environmental Protection Agency (EPA) suspended all above-ground registrations of strychnine, allowing only underground uses (US EPA 1996). It is not currently registered for use in New Zealand.

Mode of action

Strychnine is a fast-acting poison that is readily absorbed into the circulatory system from the intestinal tract. Highest concentrations of strychnine are found in the blood, liver and kidneys. It is a neurotoxin. Poisoned animals often die in less than 1 hour as a result of respiratory failure (asphyxia), but death may take 24 hours or longer. Strychnine is considered inhumane, with the typical signs of strychnine poisoning being restlessness and muscular twitching, which progress to convulsive seizures and violent muscular spasms before death (Osweiler et al. 1985).

Toxicity

The LD_{50} for Norway rats is 5–6 mg/kg (Prakash 1988). The oral LD_{90} for mice is approximately 5 mg/kg. It is highly toxic to all mammals, but slightly less so to birds (Mutze 1989) (Table 3).

TABLE 3. ACUTE ORAL TOXICITY (LD_{50} mg/kg) OF STRYCHNINE.
Prepared from information provided in Hone & Mulligan (1982) and Osweiler et al. (1985).

SPECIES	LD_{50} mg/kg
Rat (*Rattus rattus*)	5–6
Mouse (*Mus musculus*)	5
Cat (*Felis catus)*	0.75
Norway rat (*Rattus norvegicus*)	6.8
Duck (*Anas platyrhyncha*)	2.9
Pigeon (*Columba livia*)	2.1

Summary of key features

Advantages:

- Highly toxic to rodents
- Inexpensive

Disadvantages:

- Causes secondary poisoning
- Inhumane
- Not registered for use in New Zealand

Recommendations

Strychnine is not recommended for aerial control of rodents. It is inhumane, hazardous, would cause secondary poisoning and is not registered in New Zealand.

2.3 CHOLECALCIFEROL

General information and history of use

Cholecalciferol (vitamin D_3) was developed as a rodenticide in the 1980s (Marshall 1984). It was first registered in New Zealand in 1999, in paste bait containing 0.8% cholecalciferol (Feracol®). This was based on work carried out in the early 1990s, which demonstrated the susceptibility of possums to cholecalciferol (Eason 1991; Eason et al. 1996). It is registered as an alternative to 1080 for possum control because of the relative low risk of secondary poisoning of dogs (*Canis familiaris*) and low toxicity to birds (Eason et al. 2000). In 2008, the registration status of the bait Feracol® containing 0.8% cholecalciferol was extended to cover rodents as well as possums, based on data from pen and field efficacy trials (Baigent et al. 2007; Hix et al. 2007) and currently, in 2009, a paste and solid bait formulation containing 0.4% cholecalciferol is being developed (Hix et al. 2009).

Mode of action

Death usually occurs 3–7 days after a lethal dose (Marshall 1984; Eason et al. 1994). To become biologically and toxicologically active, cholecalciferol must undergo metabolic conversion to 25-hydroxycholecalciferol (25OHD). This metabolite is then transferred to the kidney and converted to 24-, 25- or 1,25-dihydroxycholecaliferol. The latter metabolite is the most biologically active form of vitamin D_3 (Keiver et al. 1988). At toxic doses, this active metabolite mobilises calcium stores from the bones into the bloodstream, while also decreasing calcium excretion by the kidneys. The net result is calcification in the cardiovascular system, kidneys, stomach, lungs and muscles. In possums and rodents, death probably occurs as a result of heart failure. In other species, including cats (*Felis catus*) and dogs, renal failure (caused by vessel blockage and nephrocalcinosis—calcium deposition in the kidneys) and gastrointestinal haemorrhage appear to be more prominent (Dorman & Beasley 1989; Jolly et al. 1993).

Sub-lethal poisoning of target species can cause prolonged anorexia and wasting, which creates ethical and animal welfare concerns. Therefore, current baits are designed with the appropriate concentration of cholecalciferol to ensure maximum potency and limited suffering (Eason et al. 1996). Cholecalciferol is likely to cause some discomfort prior to death, but is considered more humane than anticoagulants (O'Connor et al. 2003a).

Toxicity

There is variation between species in the response to cholecalciferol, and importantly birds are less susceptible than mammals (Eason et al. 2000). The LD_{50} for cholecalciferol in Norway rats and house mice is very similar. Possums and rabbits (*Oryctolagus cuniculus*) appear to be particularly sensitive to cholecalciferol (Jolly et al. 1995). In the USA, the use of cholecalciferol has also been explored for controlling rock squirrels (*Spermophilus* spp.), gophers (*Thomomys* spp.) and ground squirrels (*Spermophilus* spp.) (Tobin et al. 1993). Cats appear to be less susceptible than possums, but toxicity is less consistent, with some cats surviving doses of up to 200 mg/kg, and others dying at 50 mg/kg. The LD_{50} in ducks (*Anas platyrhyncha*) is > 2000 mg/kg (Eason et al. 2000) (Table 4).

Cholecalciferol baits prove fatal to rats and mice if eaten in sufficient amounts over 1 night. A lethal dose may also accumulate after 2 or 3 nights of feeding. As a general rule, field results are best if sufficient bait is eaten on the first and second nights. Cholecalciferol is considered especially useful for controlling house mice, because mice have sometimes proven more difficult to control with anticoagulant rodenticides.

TABLE 4. ACUTE ORAL TOXICITY (LD_{50} mg/kg) OF CHOLECALCIFEROL. Prepared from information provided in Eason (1993), Eason et al. (1994) and Jolly et al. (1995).

SPECIES	LD_{50} mg/kg
Rabbit (*Oryctolagus cuniculus*)	9.0
Possum (*Trichosurus vulpecula*)	16.8*
Norway rat (*Rattus norvegicus*)	42.5
Mouse (*Mus musculus*)	43.6
Dog (*Canis familiaris*)	80.0
Duck (*Anas platyrhyncha*)	2000.0

* Reduced to 9.8 mg/kg when administered with calcium.

Summary of key features

Advantages:

- Effective rodenticide
- Low risk of secondary poisoning
- Less toxic to birds than 1080
- A useful single-dose alternative to 1080
- No long-term residue risks in sub-lethally exposed animals
- Currently registered for use in New Zealand

Disadvantages:

- Expensive compared to 1080
- Although treatment for accidental poisoning of pets is available, this is complex

Recommendations

Cholecalciferol is worth considering as a toxin for aerial control of rodents. However, lethal and sub-lethal poisoning of non-target species, e.g. pigs (*Sus scrofa*) and deer (Cervidae), would need to be avoided, as this could cause prolonged sickness and loss of appetite. In aerial bait, cholecalciferol would have lower risk to non-target bird species than zinc phosphide or 1080. The new low-dose cholecalciferol at 0.4% would have less risk to non-targets and is likely to be less expensive than the current 0.8% formulation.

2.4 BROMETHALIN

General information and history of use

Bromethalin was developed in the 1970s. It is a single-feeding rodenticide that is registered for use in the USA; however, its use is restricted to bait stations in and around buildings for the control of commensal rodents (Dreikorn 1978). In the 1970s, bromethalin was evaluated for use in Europe; however, because of concerns regarding humaneness, the dossier was not submitted and bromethalin is not registered in Europe (Alan Buckle, formally with Zeneca, UK, pers. comm.).

Mode of action

Bromethalin-poisoned animals do not feel ill immediately, allowing for adequate ingestion of the toxin. Appetite is suppressed after ingestion of a lethal dose and death does not occur until 2 days after ingestion. Poisoned animals exhibit tremors, convulsions and prostration prior to death, which usually occurs within 18 hours of the onset of symptoms. Bromethalin is a neurotoxicant and rodents that are resistant to anticoagulants show no resistance to bromethalin. Possums are not susceptible to poisoning with bromethalin, so it could only be used to target rodents.

Bromethalin uncouples oxidative phosphorylation in the mitochondria of the central nervous system. This leads to diminished activity of the enzyme that transports sodium and potassium across the cell membrane (Na+/K+ ATPase), which results in a fluid build-up manifested as fluid-filled vacuoles between the myelin sheaths (the cover surrounding nerve cells) (Dreikorn 1978). This vacuole formation in turn leads to an increased cerebrospinal fluid pressure and increased pressure on nerve axons, resulting in reduced nerve impulse conduction, paralysis and death.

Toxicity

Bromethalin is toxic to most species at ranges of 2–13 mg/kg (Table 5). In the USA, non-target impacts are limited by the restriction of the use of this poison to small-scale rodent infestations. Secondary poisoning studies in dogs have demonstrated that they are at low risk (Jackson et al. 1982). However, based on poisoning incidents, it seems that cats are more susceptible than dogs.

TABLE 5. ACUTE ORAL TOXICITY (LD_{50} mg/kg) FOR BROMETHALIN.
Prepared from information in Hone & Mulligan (1982).

SPECIES	LD_{50} mg/kg
Rat (*Rattus rattus*)	2.0–10
Cat (*Felis catus*)	1.8
Rabbit (*Oryctolagus cuniculus*)	13
Chicken (*Gallus domesticus*)	8.3
Northern bobwhite (*Colinus virginianus*)	4.6 and 11.0

Summary of key features

Advantages:

- Highly toxic to rodents
- Alternative to 1080
- Comparatively low secondary poisoning risk

Disadvantages:

- Lacks specificity—toxicity to birds and mammals similar
- No antidote
- Not registered for use in New Zealand

Recommendations

The development of bromethalin for aerial control of rodents is not recommended at this time. It has no special advantages over other alternatives to 1080 and, unlike cholecalciferol, is toxic to birds and is not currently registered in New Zealand.

2.5 NORBORMIDE

General information and history of use

Norbormide is a selective rat toxicant, being specifically toxic to Norway rats. It was developed in the 1960s, but its use was discontinued in the 1970s as anticoagulant toxins became more popular. Taste aversion limited its effectiveness and field efficacy results were poor (Telle 1967). Landcare Research has been investigating ways of overcoming taste aversion to norbormide and the development of analogues (Bova et al. 2001; Cavalli et al. 2004; Ricchelli et al. 2005).

Mode of action

After a lethal dose, very minor symptoms can occur within the first few minutes; more pronounced symptoms occur after 30 minutes and most deaths occur within 8–24 hours. Norbormide causes vasoconstriction (narrowing) of small arteries and vasodilation (widening) of large arteries in rats (Roszkowski et al. 1964; Roszkowski 1965; Bova et al. 1996), which causes a rapid fall in blood pressure. Death probably results from circulatory disorders and heart failure due to irreversible coronary constriction. The constriction of small blood vessels is rapid and unique to rats (Bova et al. 1996, 2001; Cavalli et al. 2004; Ricchelli et al. 2005). As it is comparatively fast acting, it is likely to be more humane than most other rodenticides.

Toxicity

Norbormide is toxic to Norway rats. Ship rats are less susceptible, and mice and all other species are resistant to this toxin (Table 6). The lack of toxicity of this compound to most animals makes it unique.

TABLE 6. ACUTE TOXICITY (MEAN LD_{50} mg/kg) OF NORBORMIDE IN RATS, MAMMALS AND BIRDS.
Prepared from information in Roszkowski et al. (1964), Roszkowski (1965) and Russell (1965).

SPECIES	ROUTE OF ADMINISTRATION	LD_{50} mg/kg (RANGE)
Brown rat (wild Norway rat) (*Rattus norvegicus*)	Oral	12 (10–13)
Black rat (ship rat) (*Rattus rattus*)	Oral	52.0 (47.0–57.0)
Wild Hawaiian rat (*Rattus exulans*)	Oral	c. 10
Cotton rat (*Sigmodon hispidus*)	Oral	300–1000
Mouse (*Mus musculus*)	Intraperitoneal	390 (291–523)
	Oral	2250 (1760–2880)
White-footed deer mouse (*Peromyscus leucopus*)	Oral	>1000
Cat (*Felis catus*)	Oral	>1000
Dog (*Canis familiaris*)	Oral	>1000
Rabbit (*Oryctolagus cuniculus*)	Oral	>1000
Duck (*Anas platyrhyncha*)	Oral	>1000
Goose (Anatidae)	Oral	>1000
Chicken (*Gallus domesticus*)	Oral	>1000
Pigeon (*Columba livia*)	Oral	>1000
Turkey (*Melleagris gallopavo*)	Oral	>1000

Summary of key features

Advantages:

- Potentially an effective rodenticide
- Low risk of secondary poisoning
- Less toxic to birds than 1080
- A useful single-dose alternative to 1080
- No long-term residue risks in sub-lethally exposed animals

Disadvantages:

- Not toxic to mice
- Not registered in any country
- Not produced in commercial quantities and expensive

Recommendations

The development of norbormide for aerial control of rodents in New Zealand is not recommended due to its lack of toxicity to mice and lower toxicity to most other rodents: whilst it is toxic to Norway rats, it is far less toxic to ship rats, which are the rodent of most concern in New Zealand. It is not currently registered in any other country and the lack of registrations dossiers for this compound would considerably delay it use.

3. Anticoagulant rodenticides

Anticoagulant rodenticides can be separated into two groups: first-generation anticoagulant rodenticides, which were developed between the 1940s and 1960s, and second-generation anticoagulant rodenticides, which were developed in the 1970s and 1980s. All anticoagulant rodenticides have the same mode of action: they interfere with the normal synthesis of vitamin K-dependent clotting factors, which results in bleeding and death. However, the second-generation anticoagulants, which were developed partly to overcome resistance, are more toxic than the first-generation anticoagulants (Hadler & Shadbolt 1975).

In the liver cells, the biologically inactive vitamin K1-2,3 epoxide is reduced by a microsomal enzyme into biologically active vitamin K, which is essential for the synthesis of prothrombin and other clotting factors (VII, IX and X). Anticoagulant rodenticides' antagonism of the enzyme vitamin K1-epoxide reductase causes a gradual depletion of the active form of the vitamin, and consequently of vitamin K-dependent clotting factors, which results in an increase in blood-clotting time until the point where no clotting occurs. The greater potency of second-generation anticoagulants and their greater potential to affect wildlife is related to their greater affinity for the enzyme that reduces vitamin K (vitamin K-epoxide reductase), resulting in a greater accumulation and persistence of vitamin K in the liver and kidneys after absorption (Parmar et al. 1987; Huckle et al. 1988). This in turn results in bioaccumulation through the food web, increasing non-target deaths after repeated field use for rodent control (Eason et al. 2002). There are two classes of anticoagulants: the indandiones and coumarins. The indandiones are less persistent in the liver of sub-lethally poisoned animals (Fisher et al. 2003), and therefore less likely to bioaccumulate in the food web. The first-generation anticoagulants contain representatives from each class, whereas all second-generation anticoagulants are coumarins.

For all anticoagulants, death is likely to occur within 5–7 days of the initial ingestion of a lethal dose (Buckle & Smith 1994; Littin et al. 2000). All anticoagulants are considered relatively inhumane (O'Connor et al. 2003a), but are more acceptable in rodents (Littin et al. 2000) than in possums (Littin et al. 2002), as time to death is shorter (Litten et al. 2000).

The principal use of anticoagulants worldwide has been for the control of commensal rodents, primarily Norway rats, ship rats and house mice. For example, brodifacoum, a second-generation anticoagulant, is aerially sown for rodent control on islands in New Zealand and around the world, and has been very successful (Eason et al. 2001). However, any field use of persistent anticoagulants has been controversial, and in the USA concerns about wildlife contamination have resulted in the EPA Rodenticide Mitigation Decision May 28th 2008, which stated that all second-generation anticoagulant rodenticides (SGARs) such as brodifacoum were to be removed from the consumer market and could only be sold for use by farmers and only around farm buildings; an exception to this is for 'one-off' conservation use, e.g. for islands. Only two rodenticides, brodifacoum and diphacinone, have been registered in the USA for aerial control of rodents (US EPA 2008).

In the sections below, several first-generation anticoagulants are reviewed. However, only one second-generation anticoagulant is discussed (brodifacoum). This is because it has already been established that brodifacoum is effective for aerial control of rodents, albeit with side effects that make it unsuitable for repeated use, and that the other second-generation anticoagulants have similar toxicological properties with no advantages over brodifacoum (Eason et al. 2001, 2002). Brodifacoum, like other second-generation anticoagulants, is not readily metabolised and the major route of excretion of unbound compound is through the faeces. This means that there is a far greater risk of secondary poisoning to non-target species than for the first-generation anticoagulants. Where there is repeated field use, widespread wildlife contamination extends to native birds as well as game species (Young & de Lai 1997; Eason et al. 2002). Hence, the important question to be addressed is which of the first-generation anticoagulant rodenticides is most appropriate as an alternative to brodifacoum when repeat rodent control is needed.

3.1 FIRST-GENERATION ANTICOAGULANTS

3.1.1 Pindone

General information and history of use

Pindone belongs to the indandione class of anticoagulants. Pindone was synthesised in 1937 (Beauregard et al. 1955) and was developed as a pesticide in the early 1940s. It has been used worldwide to control rodents, though its use for the control of rats and mice has decreased following the introduction of more potent anticoagulants, such as diphacinone. Pindone has proved most effective for rabbit control (Eason & Jolly 1993). To control rodents, it is used in baits containing 250 mg/kg (250 ppm) active ingredient (Prakash 1988).

Mode of action

Like the other anticoagulant toxicants, pindone interferes with the normal synthesis of vitamin K-dependent clotting factors in the liver. Clinical signs of toxicosis in animals will usually reflect some manifestation of haemorrhage (Osweiler et al. 1985), which causes pain or discomfort depending on the site of the haemorrhage in the body (Littin et al. 2000, 2002).

Toxicity

There are limited acute toxicity data available for pindone, but these data show variation between species (Table 7). For first-generation anticoagulants such as pindone, either very large single doses or repeated smaller doses are generally needed to induce death. However, rabbits appear to be particularly susceptible to pindone: a single dose of approximately 18 mg/kg is sufficient to kill rabbits, and the repeat dose (7 days) LD_{50} is only 0.52 mg kg^{-1} day^{-1}. In contrast, pindone doses of up to 12 mg kg^{-1} day^{-1} do not cause clinical or post-mortem haemorrhage in sheep (*Ovis aries*), and possums appear to be even more resistant to pindone, with an LD_{50} of 51 mg kg^{-1} day^{-1} for 5 days (Jolly et al. 1994).

Non-target research conducted in Australia provides information on the susceptibility of horses (*Equus caballus*), cattle (*Bos taurus*), goats (*Capra*

hircus), chickens (*Gallus domesticus*), dogs and cats to pindone. All these species were less susceptible than rabbits (Martin et al. 1991). Pindone is rapidly eliminated following sub-lethal exposure (Fisher et al. 2003).

TABLE 7. ACUTE ORAL TOXICITY (LD_{50} mg/kg) OF PINDONE.
Prepared from information in Beauregard et al. (1955), Oliver & Wheeler (1978), Hone & Mulligan (1982) and Eason & Jolly (1993).

SPECIES	LD_{50} mg/kg
Rabbit (*Oryctolagus cuniculus*)	6–18
Dog (*Canis familiaris*)	50
Norway rat (*Rattus norvegicus*)	75–100
Sheep (*Ovis aries*)	c. 100
Possum (*Trichosurus vulpecula*)	>100

Summary of key features

Advantages:

- Effective for rodent control
- Highly effective for rabbit control
- Antidote available
- Less persistent than brodifacoum
- Registered for use in New Zealand

Disadvantages:

- Not potent
- Inhumane in larger animals

Recommendations

Pindone is a possible option for aerial control of rodents and it is already registered in New Zealand. However, diphacinone (section 3.1.3) would be more effective, as it is more potent as a rodenticide (Buckle & Smith 1994).

3.1.2 Warfarin

General information and history of use

Warfarin belongs to the coumarin class of anticoagulants. Like pindone, it is one of the earliest first-generation anticoagulant rodenticides. It has been used in a range of rodent baits since it was first introduced in 1947 (Prakash 1988).

Mode of action

Like the other anticoagulants, warfarin inhibits the synthesis of vitamin K-dependent clotting factors. In addition, warfarin is reported to induce capillary damage. In general, the symptoms of poisoning appear relatively slowly. In rats, death is likely to occur within 5–7 days of the initial ingestion of a lethal dose, which is similar to other anticoagulants (Buckle & Smith 1994; Littin et al. 2000).

Toxicity

The toxicity of warfarin varies according to species and whether the individual was exposed to a single dose or multiple doses (Table 8). For example, in rats the single dose LD_{50} is 50–100 mg/kg, whereas the multiple dose LD_{50} is 1 mg/kg for 5 days (Osweiler et al. 1985).

TABLE 8. ACUTE ORAL TOXICITY (LD_{50} mg/kg) OF WARFARIN.
Prepared from information in Osweiler et al. (1985).

SPECIES	SINGLE DOSE (mg/kg)	REPEATED DOSE (mg/kg)
Pig (*Sus scrofa*)	3	0.5
Dog (*Canis familiaris*)	50	5
Rat (unspecified)	50–100	1
Cat (*Felis catus*)	50–100	1

Summary of key features

Advantages:

- Effective for rodent control
- Antidote available
- Less persistent than brodifacoum

Disadvantages:

- Not potent
- Inhumane
- Not registered for use in New Zealand

Recommendations

Warfarin is not recommended for aerial control of rodents, as it is not currently registered for use in New Zealand and has no advantages over diphacinone (see section 3.1.3).

3.1.3 Diphacinone

General information and history of use

Diphacinone belongs to the indandione class of anticoagulants. It is more toxic than warfarin or pindone to most rodents. In New Zealand, it is registered primarily for rodent control, although it has also been incorporated into fish-based bait for ferret (*Mustela putorius*) control. It has been identified as a non-persistent anticoagulant (Fisher et al. 2003). As mentioned above, diphacinone has been developed for field use in the USA and has recently been registered by the US EPA for aerial control of rodents for conservation purposes, providing an alternative to brodifacoum (US EPA 2008).

Mode of action

Like other anticoagulants, diphacinone inhibits the formation of vitamin K-dependent clotting factors. Clinical and post-mortem signs of toxicosis and humaneness are as for other anticoagulants (Osweiler et al. 1985; Buckle & Smith 1994; Littin et al. 2000).

Toxicity

There is some variation between species in susceptibility to the toxic effects of diphacinone (Table 9). Diphacinone is more toxic than pindone or warfarin to most rats and mice. A diphacinone dose of 3 mg/kg will kill rodents in 5–8 days. Rats can withstand relatively high single doses of this toxicant, but are unable to survive doses of < 1 mg/kg when ingested over 5 successive days (Hone & Mulligan 1982). The acute toxicity of diphacinone in mice has not been properly defined; however, mice on Buck Island have been killed after consuming an average dose of 46.9 mg/kg of diphacinone (Gary Witmer, National Wildlife Research Centre, USA, pers. comm.). This is much lower than the published LD_{50} range of 141–340 mg/kg for mice (Hone & Mulligan 1982). The LD_{50} for 5 days also suggests that house mice are susceptible to diphacinone.

As for pindone, diphacinone is rapidly eliminated from the liver (Fisher et al. 2003). Consequently, diphacinone will have a lower tendency to cause secondary poisoning when compared with brodifacoum or similar second-generation anticoagulants.

TABLE 9. ACUTE ORAL TOXICITY (LD_{50} mg/kg) OF DIPHACINONE.
Prepared from information in Hone & Mulligan (1982).

SPECIES	LD_{50} mg/kg
Rat (unspecified)	3.0; < 1 over 5 days
Dog (*Canis familiaris*)	3.0–7.5
Cat (*Felis catus*)	14.7
Rabbit (*Oryctolagus cuniculus*)	35.0
Pig (*Sus scrofa*)	150.0
Mouse (*Mus musculus)*	7.05 over 5 days
Mallard duck (*Anas platyrhynchos*)	3158.0

Summary of key features

Advantages:

- No license required
- Effective for rodent control
- Antidote available
- Less persistent than brodifacoum
- Registered for use in New Zealand
- Approved by US EPA for aerial control of rodents

Disadvantages:

- Less potent than brodifacoum

Recommendations

Diphacinone represents a safer alternative to brodifacoum for the repeat aerial control of rodents, and it is already being used in this manner for the eradication of rodents from islands (US EPA 2008). Diphacinone is reported to have similar potency to coumatetralyl, but is less persistent (Buckle & Smith 1994; Fisher et al. 2003), making it a preferred option. Its international registration status provides a platform of data and dossiers, which could be extended to support its use for aerial control of rodents in New Zealand.

3.1.4 Coumatetralyl

General information and history of use

Coumatetralyl belongs to the coumarin class of anticoagulants. It was developed in 1957, and is marketed worldwide as Racumin®. It is used as a tracking powder, or as a cereal bait, wax block or paste for rodent control. It is registered in New Zealand for rodent control (Eason & Wickstrom 2001).

Mode of action

Like other anticoagulant rodenticides, coumatetralyl inhibits the formation of vitamin K-dependent clotting factors and rodents die within 5–7 days after ingesting a lethal dose of the toxin. Coumatetralyl is less persistent (in sub-lethally poisoned animals) than brodifacoum, but considerably more persistent than diphacinone (Parmar et al. 1987; Fisher et al. 2003), and will have similar humaneness to other anticoagulant rodenticides.

Toxicity

There are comparatively few acute toxicity data for coumatetralyl (Table 10). Aside from reports of pets gaining access to bait, there are also few references to non-target deaths. In recent studies, coumatetralyl-poisoned rat carcasses were fed to weka (*Gallirallus australis*) and ferrets: 1 out of 10 ferrets died, but no weka were killed (O'Connor et al. 2003b).

TABLE 10. ACUTE ORAL TOXICITY (LD_{50} mg/kg) OF COUMATETRALYL.
Prepared from information in Hone & Mulligan (1982).

SPECIES	LD_{50} mg/kg	
Rat (*Rattus rattus*)	16.5	(single dose)
	0.3	(5 days)
Pig (*Sus scrofa*)	1.0–2.0	(1–7 days)
Hen (*Gallus domesticus*)	50.0	(8 days)

Summary of key features

Advantages:

- Effective for rodent control
- Antidote available
- Less persistent than brodifacoum
- Registered for use in New Zealand

Disadvantages:

- Not as potent as brodifacoum
- More persistent than diphacinone

Recommendations

Coumatetralyl is already registered in New Zealand and has the potential to be used for aerial control of rodents, as a safer alternative to brodifacoum. However, diphacinone would be a better option, as it is reported to have similar potency to coumatetralyl but is less persistent.

3.1.5 Cholecalciferol + coumatetralyl (C+C)

General information and history of use

In Europe, cholecalciferol has been added to baits containing coumatetralyl (Racumin® plus) to overcome anticoagulant resistance in rats and mice (Pospischil & Schnorbach 1994). AHB has funded the development of cholecalciferol + coumatetralyl (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). Bait containing 0.015% cholecalciferol and 0.03% coumatetralyl has been developed, and dossiers are being prepared for submission for registration in 2009/10. C+C is effective at killing possums and rodents, even though the amount of cholecalciferol is a fraction of that used in current cholecalciferol baits (Pospischil & Schnorbach 1994; Ray Henderson, Pest Tech Ltd, NZ, pers. comm.).

Mode of action

Death occurs in 12 days in possums and 5 days in rats and mice (Ray Henderson, Pest Tech Ltd, NZ, pers. comm.). The primary toxic effects of C+C result from hypercalcaemia (i.e. cholecalciferol poisoning). Coumatetralyl acts as a synergist, enhancing cholecalciferol toxicity by blocking vitamin K_2-dependent proteins that are involved in calcium regulation. These factors substantially enhance cholecalciferol-induced arterial and tissue mineralisation (Pospischil & Schnorbach 1994; Ray Henderson, Pest Tech Ltd, NZ, pers. comm.). C+C has a similar effectiveness to brodifacoum, but is less persistent and more humane, since animals poisoned with C+C will die more quickly than those poisoned with brodifacoum (Ray Henderson, Pest Tech Ltd, NZ, pers. comm.).

Toxicity

At this stage, there is limited available data on this combination. Information is being generated in confidence to support a new product registration (Ray Henderson, Pest Tech Ltd, NZ, pers. comm.). Ruminants and birds are less susceptible to C+C than small mammalian pests (Table 11).

TABLE 11. SUSCEPTIBILITY OF VARIOUS SPECIES TO CHOLECALCIFEROL + COUMATETRALYL (C+C).
Data supplied by Ray Henderson (Pest Tech Ltd, NZ, pers. comm.).

SPECIES	SUSCEPTIBILITY (% KILLED)	
	PRIMARY POISONING (BAIT)	SECONDARY POISONING (EATING POISONED POSSUMS)
Mouse (*Mus musculus*)	100% (n = 20)	
Rat (*Rattus rattus*)	100% (n = 20)	
Chicken (*Gallus domesticus*)	0% (n = 12)	0% (n = 12)
Sheep (*Ovis aries*)	0% (n = 12)	
Cat (*Felis catus*)		0.17% (n = 12)*

* Death occurred over a 10-day period after eating 1–4 possums.

Summary of key features

Advantages:

- Effective rodenticide
- Low risk of secondary poisoning
- Less toxic to birds than 1080
- A useful single-dose alternative to 1080
- No long-term residue risks in sub-lethally exposed animals

Disadvantages:

- Not yet registered for use in New Zealand—pending 2009/10
- Although treatment for accidental poisoning of pets is available, this is complex

Recommendations

C+C is worth considering as a toxin for aerial control of rodents, since it will be as potent as brodifacoum (see below) without the concerns of prolonged contamination of the food web that dog the use of brodifacoum (Eason et al. 2002). Registration dossiers are being prepared initially for C+C for possum control, which could be extended to rodents and aerial control of rodents. It would have a lower risk to non-target bird species than zinc phosphide or 1080.

3.2 SECOND-GENERATION ANTICOAGULANTS

3.2.1 Brodifacoum

General information and history of use

Brodifacoum is the most well known and commonly used rodenticide worldwide. The rodenticidal properties of brodifacoum were first described in the early 1970s (Hadler & Shadbolt 1975). It is a very potent anticoagulant that is active against rats and mice, including strains that are resistant to warfarin and other anticoagulants. A single ingestion of 1 mg/kg is usually sufficient to kill (Hone & Mulligan 1982). Brodifacoum has been used successfully in recent rodent eradication programmes on offshore islands (Eason et al. 2001) to protect populations of endangered indigenous birds. It is also used to control possums in New Zealand (Eason et al. 2002).

Mode of action

The onset of symptoms and death usually occur within 1 week in rodents (Littin et al. 2000). Like other anticoagulant toxicants, brodifacoum acts by interfering with the normal synthesis of vitamin K-dependent clotting factors in the liver. The resultant haemorrhaging will cause pain or discomfort and lameness, depending on the site of the haemorrhage in the body (Littin et al. 2000, 2002).

Toxicity

As for all second-generation anticoagulants, only a single dose of brodifacoum is needed to induce death if sufficient toxicant is ingested. Brodifacoum is extremely toxic in a number of animal species, but the toxicity does vary between species (Table 12). In most mammals, LD_{50} values are 1 mg/kg or less. Some higher values have been reported in sheep and dogs, but there is considerable variability in these reports (LD_{50} in sheep = 5–25 mg/kg; and in dogs = 0.25–3.56 mg/kg).

TABLE 12. ACUTE ORAL TOXICITY (LD_{50} mg/kg) OF BRODIFACOUM FOR MAMMAL SPECIES.
Prepared from information in Godfrey (1985) and Eason & Spurr (1995).

SPECIES	LD_{50} mg/kg
Pig (*Sus scrofa*)	0.1
Possum (*Trichosurus vulpecula*)	0.17
Rabbit (*Oryctolagus cuniculus*)	0.2
Cat (*Felis catus*)	0.25–25
Dog (*Canis familiaris*)	0.25–3.56
Rat (*Rattus rattus*)	0.27
Mouse (*Mus musculus*)	0.4
Bennett's wallaby (*Wallabia rufogrisea frutica*)	1.3
Sheep (*Ovis aries*)	5–25
Canada goose (*Branta canadensis*)	<0.75
Pukeko (*Porphyrio porphyrio melanotus*)	0.95
Blackbird (*Turdus merula*)	>3.0
Hedge sparrow (*Prunella modularis*)	>3.0
Mallard duck (*Anas platyrhynchos*)	4.6
Black-billed gull (*Larus bulleri*)	<5.0
Silvereye (*Zosterops lateralis*)	>6.0
Australasian harrier (*Circus approximans*)	10.0

Summary of key features

Advantages:

- Generally available
- Effective for rodent control
- Antidote available
- Registered for use in New Zealand

Disadvantages:

- High risk of secondary poisoning
- Persistent (> 9 months) in liver
- Expensive compared to 1080

Recommendations

Brodifacoum has been proven as an effective alternative to 1080 for aerial control of rodents, but it is not recommended for repeated aerial control of rodents. One-off use for eradication can result in benefits that significantly outweigh non-target effects (Eason et al. 2001, 2002) and this use pattern is recommended.

4. New non-anticoagulant candidate compounds

In this section, we examine the potential of a new candidate vertebrate pesticide, para-aminopriophenone (PAPP), for aerial control of rodents. This is currently being developed for the control of stoats and cats in New Zealand.

4.1 PARA-AMINOPROPIOPHENONE (PAPP) AND RELATED COMPOUNDS

General information and history of use

Para-aminopropiophenone, or PAPP, was originally studied as a protection from the effects of radiation and then for the treatment of cyanide poisoning. It is toxic to carnivores, with birds and humans being less sensitive (Fisher & O'Connor 2007; Murphy et al. 2007). The toxin is being developed for the humane control of stoats and feral cats in New Zealand, and foxes (*Vulpes vulpes*), feral cats and wild dogs in Australia. The effectiveness of PAPP or related compounds as rodenticides is a current field of research (Eason et al. 2009).

Mode of action

The toxic effects of PAPP are related to its ability to reduce the oxygen carrying capacity of the red blood cells, resulting in haemoglobin rapidly being converted into methaemoglobin. This sharply reduces the oxygen carrying capacity of the blood, which leads rapidly to unconsciousness and death due to respiratory failure; for example, cats and foxes are usually unconscious within 30–45 minutes. Methaeglobinaemia inducing agents like PAPP are humane, as they induce lethargy and death follows rapidly (Murphy et al. 2007). Methylene blue, which is available from veterinarians, will reverse the effects of PAPP and thus can be administered as an antidote (Murphy et al. 2007).

Toxicity

Cats and stoats are generally more susceptible to PAPP than most other species (Table 13). However, related compounds that are more toxic to rodents are being explored (Eason et al. 2009).

TABLE 13. ACUTE ORAL TOXICITY (LD_{50} mg/kg) FOR PARA-AMINOPROPIOPHENONE (PAPP).

Prepared from information in Savarie et al. (1983) and O'Connor (2002).

SPECIES	LD_{50} mg/kg
Cat (*Felis catus*)	5.6
Fox (*Vulpes vulpes*)	14.1
Stoat (*Mustela erminea*)	9.3
Ferret (*Mustela putorius*)	29
Possum (*Trichosurus vulpecula*)	>500
Wallaby (*Wallabia rufogrisea frutica*)	89
Mouse (*Mus musculus*)	223
Rat (*Rattus rattus*)	221

Summary of key features

Advantages:

- Simple antidote
- Humane (very rapid action)
- Low secondary-poisoning risk

Disadvantages:

- Not yet registered for use in New Zealand—pending 2009
- Effectiveness in baits for rodents unknown
- Some toxicity to birds

Recommendations

PAPP or related compounds could be considered as an option for aerial control of rodents as well as cats and stoats if current research shows they have effective rodenticidal properties in mice and rats. Bait specifications similar to those for aerial 1080 would need to be developed to limit non-target impacts.

5. Discussion

Brodifacoum is the most potent alternative to 1080 currently available. The LD_{50} for rats is 0.27 mg/kg and for mice is 0.4 mg/kg, and it has been used aerially to eradicate rats from several islands off the coast of New Zealand (Taylor 1984; Taylor & Thomas 1989, 1993; Towns 1991). However, brodifacoum is also extremely toxic to a number of other species, which, coupled with its tendency to bioaccumulate, makes it unsuitable for routine aerial broadcast on mainland New Zealand.

From the first-generation anticoagulant class of compounds, diphacinone represents the best alternative option to 1080 for the aerial control of rodents at present, as it is more potent than pindone or warfarin, and equipotent but less persistent than coumatetralyl (Fisher et al. 2003). This is supported by the recent registration of diphacinone by the US EPA for aerial broadcast for conservation purposes (US EPA 2008). Another alternative to 1080 worthy of consideration is cholecalciferol, particularly at the 0.4% loading concentration, as this compound lacks toxicity to birds and will not bioaccummulate (Eason et al. 2000). Zinc phosphide, and a cholecalciferol and coumatetralyl combination are options to consider further when they have been registered and have an established safety record in New Zealand (Eason et al. 2008). Norbormide would not be as suitable, as it is too species-specific, is not effective on mice, and is no longer registered anywhere in world. Bromethalin has few advantages over other options except that it is already registered in the USA, although not for field use; at least $500,000 would be needed to research and develop this compound for field use in New Zealand.

New toxins that act on different physiological processes could usefully prevent the development of bait shyness, aversion or resistance. Para-aminopropiophenone (PAPP) is being developed for stoat and feral cat control in New Zealand, and the rodenticidal potential of this class of compounds will be determined in 2009/10. If a suitable new rodenticide is identified from this new class of red blood cell toxicants, then aerial bait containing a new toxin with a different and humane mode of action from conventional rodenticides may become an option in the future.

As an alternative option, at some stage in the future toxins extracted directly from New Zealand plants may be more acceptable to the New Zealand public than some of the synthetic toxins we use at present. For some plant species (e.g. tutu *Coriaria arborea*, karaka *Corynocarpus laevigatus* and kowhai *Sophora microphylla*), the toxicity to rodents (including LD_{50} information), toxin extraction methods and the chemistry of the toxicant have already been described. Researchers at Lincoln University are currently exploring the potential of natural New Zealand toxins.

The Department of Conservation, FRST, AHB and others are already undertaking research to advance the use of alternatives to 1080 for the control of rodents and possums, and it will be important to extend this research to develop the necessary information to support their use and registration for aerial control of rodents.

In the short to medium term, the focus should be on those compounds that are already registered in New Zealand or other countries. Thus, the preferred alternatives to 1080 are, in order:

1. Brodifacoum for island eradication or exceptional 'one-off' use on the mainland
2. Diphacinone
3. Cholecalciferol
4. C+C
5. Zinc phosphide

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. However, C+C and zinc phosphide are also well advanced towards registration.

In the longer term, the preferred alternative to 1080 would be a novel, humane red blood cell toxin, if it can be successfully developed.

Availability and registration status could influence this priority list in the future. Research and development needs to be consolidated if any of these new options are to become available for aerial control of rodents.

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