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Reflections on Improvements in the Use of Vertebrate Pesticides in New Zealand: 1996 - 2006

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ABSTRACT: Vertebrate pesticides for wild animal control in New Zealand came under scrutiny in the 1980s and 1990s, which engendered considerable research to update the toxicology databases of older compounds, such as 1080 or diphacinone, to meet current international registration standards. In parallel there was a focus on identifying "use patterns" and formulations that are effective at killing pests and less hazardous to other wildlife. Improved bait quality and reduced sowing rates for 1080 bait for possum control in New Zealand, down from 10-15 kg of bait per hectare to 1-3 kg, has been accompanied by increased effectiveness and reduced non-target risk. This has been coupled with an improved understanding of 1080 toxicology and risk communication amongst pest control professionals and with the community. In addition, in vivo metabolism and persistence studies coupled with field surveys have improved understanding of the toxicokinetics and non-target effects of different anticoagulants. This enabled improved choice of tools for island versus mainland use in New Zealand. The risks associated with "one-off" applications of baits containing second-generation anticoagulants for rodent eradication on islands are considered to be very substantially outweighed by the potential benefits to their ecosystems. On the mainland, contamination of wildlife and game species and risk of secondary poisoning have been substantially reduced by switching from second- to first-generation anticoagulants. Finally, these developments were coupled with the identification of improved baits for ground control of possums and rodents, such as encapsulated cyanide and gel baits containing cholecalciferol, which in turn reduced an over-reliance on 1080 and anticoagulants alone. Nevertheless, safer use patterns, improved formulations and target specificity, and new vertebrate pesticides are still required, and this will be a major challenge for the 21st Century.

KEY WORDS: 1080, anticoagulants, New Zealand, non-targets, regulatory toxicology, toxicokinetics, vertebrate pesticides

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INTRODUCTION

The chemicals used for controlling vertebrate pests are classified as 1) anticoagulants, which include warfarin, pindone, diphacinone, coumatetralyl, difenacoum, bromadiolone, brodifacoum, flocoumafen, and difethalione, or 2) non-anticoagulants, which include any substance that does not fall in the former category, such as strychnine, cyanide, zinc phosphide, sodium monofluoroacetate (1080), cholecalciferol, and calciferol.

Vertebrate pest control in New Zealand principally targets rodents, possums, mustelids, and rabbits and is undertaken using baits, usually cereal pellets containing a poison. The poisons most widely used include 1080, and anticoagulants and cyanide, with increasing use of cholecalciferol. It is likely we will need these tools for the foreseeable future for control of disease and conservation purposes.

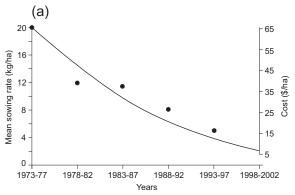
The risk to non-target wildlife, livestock, pets, or humans from baits containing vertebrate pesticides will be determined in part by the animal's intrinsic susceptibility, the properties of the poisons used (such as their toxicokinetics), bait design and their deployment methods, and the site-specific complexities of the food webs in areas in which they are used, which may limit or exacerbate the exposure of non-target species. Whilst the poisons used for vertebrate pest control in New Zealand

have remained largely unchanged (Eason et al. 2000), the way they are used has improved considerably.

In the 1990s, concerns were frequently expressed by the community with regards to the use of 1080 and other toxins, and there were different concerns amongst pest control operators about the continued availability of tools for conservation and Tb control (Seawright and Eason 1994). It is timely to reflect on the improved use of vertebrate pesticides and improvement in community support for endangered species protection and disease control in New Zealand.

Achievement 1: Quality Assurance to Enable Reduced Aerial Sowing Rates

Aerial control using 1080 (sodium monofluoroacetate) baits has been widely used in New Zealand since the late 1960s for the control of introduced brushtail possums (*Trichosurus vulpecula*). As recently as the early 1990s, high application rates of up to 15 kg/ha of 1080 baits were being used. Considering that only 1 or 2 baits were required to kill a possum, these sowing rates were excessive. This was primarily a consequence of 1) bait being of highly variable size, toxicity, and palatability, and 2) baiting coverage being as much as 48% incomplete (Morgan 2004). Since possums lose appetite 30-60 minutes after eating a 1080 bait, it was essential that



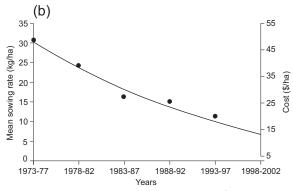


Figure 1. Mean bait sowing rates for a) pellet and b) carrot baits from 1973 to 2002. CPI-adjusted cost (NZ\$/ha) for these control operations was highly linearly related to application rate, so the corresponding cost for each application rate is indicated by the right-hand axis. Points on the graphs refer to sowing rate (from Morgan 2004).

aerial distribution of small, sublethal baits should be avoided, not only to achieve high mortality but also to avoid the creation of bait-shy surviving populations (Morgan *et al.* 1996) and to reduce the risk to invertebrates and birds that may feed on small fragments of bait (Harrison 1978, Notman 1989). Bait specifications were therefore developed that converted scientific understanding of key parameters (e.g., susceptibility to 1080) into practical manufacturing advice.

Once bait of higher quality became available, it was possible to further reduce sowing rates. Field studies were undertaken to assess the coverage achieved in normal aerial baiting operations. Large gaps, up to 400 m in width, were often found between baiting swaths, and these were potentially refuges in which possums could survive. Sowing baits at 3 kg/ha was as effective as at 10 kg/ha, indicating the potential for substantially reducing operational costs by using machinery capable of distributing baits uniformly at low rates (Morgan 1994). Navigational guidance systems were evaluated and found to improve the accuracy of bait distribution such that complete coverage could be achieved. These findings encouraged the reduction in bait sowing rates that had begun to occur as a result of growing experience among pest managers (Figure 1), and by 1997 average kills had increased from 70% (during the 1970s) to over 90% at a reduced cost of around NZ\$9 million annually (Morgan et al. 1997) and with reduced non-target mortalities (Spurr 2000).

Achievement 2: Improved Understanding of 1080 Toxicology

Fate in Animals

Absorption, metabolism, and excretion studies in laboratory animals since the 1950s have shown that sublethal amounts of 1080 are excreted both unchanged and as a range of non-toxic metabolites. In laboratory rodents dosed with sublethal doses, 1080 is rapidly absorbed and distributed through the soft tissues and organs. This contrasts with the action of commonly used anticoagulant rodenticides, such as brodifacoum, which are extremely persistent. Sodium monofluoroacetate is excreted as unchanged fluoroacetate and a range of metabolites including fluorocitrate. Defluorination (i.e.,

detoxification or breakdown) of 1080 and fluorocitrate has been demonstrated in animals and other living organisms (Eason *et al.* 1993*b*).

The earliest reports on rats suggested that some 1080 was retained for 1-4 days. In a more recent study using mice, 1080 concentrations in plasma, muscle, and liver decreased by half after less than 2 hours. Prolonged persistence of 1080 in animals after sublethal exposure is unlikely, and this has been confirmed for larger animals, such as rabbits, goats, possums, and sheep (Eason *et al.*) 1994). The highest concentrations occur in the blood, with moderate levels in the muscle and kidneys, and the lowest concentrations in the liver. All traces of the toxin are therefore likely to be eliminated within 1 week. The significance of comparatively rapid metabolism and excretion is that 1080 is unlikely to bioaccumulate in the food chain and the "withholding period" for livestock that are suspected of having had contact with 1080 baits can be defined (Eason et al. 1994).

However, for some reason in the 1990s rapid elimination of 1080 was confused with safety and lower risk of toxicity. As we all know, 1080 is extremely poisonous, with an LD_{50} of 1 mg/kg or less for many species (Atzert 1971, Eisler 1995).

Toxicology and Pathology

Known affected sites in animals following 1080 exposure include the heart, lungs, liver, kidneys, and foetus. Pathological changes can be produced by single lethal doses or prolonged sublethal exposure.

In the mid-1990s, a study showed that lesions associated with 1080 exposure in sheep included scattered foci of fibrous tissue in the myocardium and mild degeneration in the striatum, hippocampus, and nucleus tractus solitarius in the brain. However, ewes that survived exposure to 1080 (including single and repeated doses for 5 days) did not experience any adverse long-term effects (Wickstrom *et al.* 1997). Although 1080 itself is not cumulative, studies in sheep and laboratory rats demonstrate that cumulative damage to the heart or other organs can occur from repeated exposure to sublethal doses of 1080 (Wickstrom *et al.* 1997, Eason and Turck 2002). Obviously, livestock must not be allowed access to toxic baits, and even partially degraded

baits should be regarded as hazardous. Furthermore, human exposure at any significant level must not occur. We have ensured this is the case in New Zealand by regular monitoring and improved handling practise. Our improved understanding of these risks and potential effects has allowed managers to continue to improve pest control practise to ensure human exposure amongst those involved in pest control does not occur.

Achievement 3: Regulatory Toxicology

Laboratory-based regulatory toxicology studies allow for the characterisation of a chemical in terms of its potential to cause genetic mutations, foetal abnormalities, and target-organ toxicity, as well as defining no-observable-effect levels (NOELs) on which drinking water standards are set. The NOELs are needed for setting rigorous acceptable daily intakes (ADI), which can form the basis for determining a maximum acceptable value (MAV) in drinking water.

A battery of laboratory-based toxicology studies were completed in the USA before 1995. These included 17 studies on product chemistry, 6 studies on wildlife hazards, and 4 studies relevant to human health. The results from these studies were summarised in the proceedings of a science workshop on 1080 (Fagerstone et al. 1994, Seawright and Eason 1994) (see Table 1). The most relevant of these studies to the health of those involved in pest control in New Zealand was on acute dermal toxicity of 1080 in rabbits. In this test, 5 male and 5 female rabbits were treated dermally with each of 4 dose levels of 1080 paste. The estimate LD₅₀ was approximately 300 mg/kg versus 0.4 mg/kg when orally ingested. It had long been known that 1080 can be absorbed through the gastrointestinal tract, but was less readily absorbed through the intact skin. However, the result of this study demonstrated that poor dermal absorption of 1080 does not imply no absorption, and there were obviously implications with regards to enforcing strict codes of practise and appropriate protective clothing for those involved in the manufacture or handling of 1080 baits- which are fully understood and enforced, as mentioned in the previous section.

In addition to toxicity data, it is now necessary to provide answers to the following general questions: Does 1080 alter genetic material (i.e., is it mutagenic?), and

does it cause birth defects (i.e., is it a developmental toxicant?). Results of 3 different, complementary tests indicate that 1080 is not mutagenic. Results of developmental toxicity studies in rats showed that a single dose had no effect. However, when female rats were exposed to relatively high doses (0.33 and 0.75 mg/kg) for about 30% of their gestation, mild skeletal effects were detected. The NOEL for development effects was 0.1 mg/kg/day based on observations of bent ribs at 0.33 mg/kg/day (Eason *et al.* 1999).

The NOEL for rats administered 1080 via oral gavage for 90 days was 0.075 mg/kg/day. Microscopic changes in the testes and heart were seen in males dosed with 1080 at 0.25 mg/kg/day for 90 days. Adverse effects of a single large dose and repeated 1080 doses have been described in many studies in rats confirming that during sublethal exposure to 1080 the most sensitive sites for toxicity are the heart, epididymides, testes, and foetus (Eason and Turck 2002).

In conclusion, at high doses 1080 causes death. At substantial sublethal doses above NOEL, 1080 may affect a number of organs, predominantly those with high metabolic activity, e.g., the heart and testes. The sublethal effect on testes is distinct from those mediated by "classical" endocrine disruptors. Effects on the testes are likely to occur through inhibition of the Krebs Cycle–a different mechanism to the well-recognized "endocrine disruptors" like DDT, which have specific actions mediated by hormone receptors.

Toxicology studies have defined the NOELs for sustained exposure. As mentioned in the previous section, the results are of greatest relevance to workers in the pest control industry (at the plants manufacturing baits), who work with 1080 on a day-to-day basis. Clearly they underpin the use of strict safety procedures at these factories and when 1080 baits are used in the field. They do not indicate risk to the general public under normal and careful use.

Achievement 4: Improved Community Interaction

Increased use of 1080 in the 1980s and 1990s in New Zealand has been met by increased opposition. Several anti-1080 organisations emerged, and subsequently a national network was formed in 1993 called the "1080 Action Network New Zealand (TANNZ)" to coordinate

Table 1.	Toxicology	studies re	quired to	satisfy red	gulatory	requirements.

Study types required for registration of a new pesticide	Status of 1080 database		
Acute toxicity	Extensive databse in the literature (see Rammell and Fleming 1978, Seawright and Eason 1994, Eisler 1995)		
Skin and eye irritation	Completed (see Fagerstone et al. 1994)		
Skin sensitisation	Completed (see Fagerstone et al. 1994)		
Mutagenicity studies	Completed (see Eason et al. 1999)		
Three-month feeding studies	Completed (see Eason and Turck 2002)		
Developmental toxicity (teratogenicity, reproductive toxicity)	Completed (see Eason et al. 1999)		
Metabolism/ pharmacology studies	Extensive published database		
Environmental studies	Extensive published database (see Parfitt et al. 1994, Eason 2002) but		
	Good Laboratory Practise studies to EPA specifications still not		
	completed.		

newsletters and fund protest activity and court cases. TANNZ and most other anti-1080 groups or individuals recognize the threat Tb poses to New Zealand's farming industry and agree that possum numbers need to be reduced to protect forests. They believe that ground hunting methods based around trapping, cyanide, and the use of bait stations are environmentally, culturally, and socially much more acceptable methods than aerially-sown 1080. Those in favor of aerial sowing 1080 baits believe that it is the most cost-effective option for inaccessible terrain.

There were >800 newspaper articles published in New Zealand on 1080 during 1994 (Chong Press Clipping Bureau). Occasionally, misinformation or confrontation resulted in sensational media stories (Eason 1995). In contrast, articles on 1080 in the media are a rarity in 2005 and 2006.

In the late 1980s, a technical response to this opposition had been to declare 1080 as "safe", and even on occasions swallow a bait at a community meeting. Whilst this approach had impact, it was counter-intuitive to many, and early in the mid-1990s we developed a more interactive approach discussing the issues at stake—the pros and cons of different approaches. Special efforts were made to be inclusive, and to clearly indicate what we knew and what we did not. Any discussion started with a declaration that we would not describe poisons as "safe" and "not shield from risks".

This approach has been extended in the last decade and, coupled with the greater success of control operations, community support has improved. Community engagement is paramount and new approaches to the discussion of risk with the community are continuing to evolve (Shaun Ogilvie, Lincoln Univ., Canterbury, N.Z., pers. commun.).

Achievement 5: Understand Toxicokinetics in Risk Assessment

In the 1990s, we identified a need to select suitable toxicants for field use that are effective but less persistent than second-generation anticoagulants and therefore likely to be less hazardous to non-target species (Eason et al. 2002). The tendency for anticoagulants to persist in mammalian liver is influenced by the magnitude of the dose ingested and the relative affinity of the compound for receptors in the liver, which determine the hepatic elimination half-life and the proportion of the dose retained (Parmar et al. 1987). Accordingly, liver tissue has been the focus for most investigations anticoagulant persistence, although there were few data on the comparative hepatic persistence of anticoagulant rodenticides in mammals where either compounds or species have been compared. The hepatic half-life of brodifacoum has been reported as 130 days in rats (Parmar et al. 1987), 252 days in possums (Eason et al. 1996b), and >250 days in sheep (Laas *et al.* 1985). Thijssen (1995) estimated a hepatic half-life of 7-10 days for warfarin in rats, while residues in the liver of pigs that survived a dose of warfarin had declined to near the analytical limit of detection by 30 days (O'Brien et al. 1987). The persistence of pindone in mammalian liver has been described for dogs (Fitzek 1978) and sheep (Nelson and Hickling 1994). Bullard *et al.* (1976) reported that cows dosed with diphacinone had detectable liver residues 90 days after dosing. None of these previous studies allow the accurate definition of persistence of any of the anticoagulants in tissues for comparative purposes and selection of tools for best management practise.

Comparative pharmacokinetics is an important basis for assessment of risk to non-target species. The hepatic persistence of second-generation anticoagulants, such as brodifacoum, in the liver of mammals was well characterized in comparison to first-generation anticoagulants, although estimates of plasma retention for the latter group are available in the literature. Recommendations on preferred anticoagulants for field use in New Zealand were made on estimates of their persistence in the liver of a range of mammal species, based on relatively few published studies. This literature suggests low-singledose-potency anticoagulants such as warfarin and pindone persist in the liver for 0.5-1 months, moderatesingle-dose-potency anticoagulants such as diphacinone and coumatetralyl persist in the liver for approximately 6 months, and high-single-dose-potency anticoagulants such as bromadiolone, brodifacoum, and flocoumafen persist in the liver for more than 12 months (Eason et al. 2002).

The persistence of sublethal (approximate LD₁₅) oral doses of brodifacoum, warfarin, pindone, and diphacinone in the livers of laboratory rats was comprehensively compared more recently to determine whether earlier recommendations were appropriate. At one end of the spectrum, retention of brodifacoum in liver characterized by a relatively long half-life of 113.5 days, compared with half-lives of 26.2 days for warfarin, and 3 and 2 days for diphacinone and pindone, respectively (Fisher et al. 2003). These results suggest that the indandinone anticoagulants diphacinone and pindone present a shorter-term and, therefore, reduced risk of secondary poisoning to predators and scavengers than the coumarin anticoagulants warfarin and brodifacoum (Fisher et al. 2003). This has allowed for more confident recommendations and selection of less persistent anticoagulants for field use.

Achievement 6: Appropriate Use "Patterns" of Anticoagulants

New Zealand has many islands that are actual, or potential, refuges for endangered native biota. Starting in the 1980s and gaining momentum in the 1990s, pest invasion on islands have been actively managed, and islands once occupied by rodents are being reclaimed. Until the mid-1980s, there were very few islands entirely free of animal pests. Large, more easily located mammals such as possums, pigs, and goats were the first to be targeted, and some were eradicated from islands in the early 1900s. These restoration programs involved hard work and diligence, particularly as the last few individuals of any species were always the most difficult to locate and kill.

A series of rodent eradication attempts on islands in the past 25 years, using bait in stations and applied from the air, has been spectacularly successful (Taylor and Thomas 1989, 1993; Towns *et al.* 1993, Empson and Miskelly 1999). To date >45 islands have been cleared of rodents, and brodifacoum use has had an obvious benefit on valuable island ecosystems. The use of brodifacoum to protect populations of indigenous birds, reptiles, and invertebrates endangered by rats and mice is a departure from the normal pattern of use that has gained increasing favor in many countries (Eason *et al.* 2001).

In parallel to its use to eradicate rats from islands, there was an increased use of brodifacoum baits delivered from bait stations for possum and rodent control on mainland New Zealand (Eason and Spurr 1995, Innes and Barker 1999), raising concerns about contamination effects on other fauna. Although second-generation anticoagulants such as brodifacoum are used extensively throughout the world, they are mostly employed for the control of commensal rodents (i.e., those living in close association with man and his domestic animals) (Colvin et al. 1991). While primary exposure of non-target fauna may be reduced by the use of effective bait stations, secondary exposure is more difficult to manage. detected brodifacoum residues in game animals such as pigs and deer and a range of avian species including weka, morepork, harrier, pukeko, grey duck, mallard duck, black-backed gull, robin, saddleback, chaffinch, mynah, magpie, and blackbird (Eason et al. 2001). Of less concern was the detection of brodifacoum in cats and stoats, introduced species regarded as pests and largely responsible for the decline of native birds, such as kiwi. Because of the potential for contamination of wildlife, broadscale field use of brodifacoum in New Zealand was discontinued in the late 1990s. Nevertheless, limited use of brodifacoum baits in bait stations is extremely valuable for controlling localized populations of possums that have developed entrenched bait shyness. This sometimes occurs where acute pesticides (1080, cyanide, or cholecalciferol) have been used ineffectively due to poor bait quality, climatic effects, or repeated usage of the same bait type. The bait shyness is overcome when the pest animal initially samples a small quantity of bait containing an anticoagulant, experiences no ill effects, and continues to consume baits eventually ingesting a lethal quantity (Morgan and Ross 2001).

Switching from brodifacoum to alternative secondgeneration anticoagulants, with similar toxicokinetic profiles, would not reduce the risk of exposure and bioaccumulation in non-target species, although the risk of toxicoses might be less (dependent on the potency of the alternative rodenticide, the amount of active ingredient in bait types, the amount of bait eaten, or the amount ingested by scavengers eating poisoned carcasses). Currently, first-generation anticoagulants (which are less persistent), alone or in combination with cholecalciferol and encapsulated cyanide, and traps are being used in preference to brodifacoum on mainland sites. These toxicokinetic assessments have been improved by an increasing understanding of the properties of different rodenticides.

Achievement 7: Improved Choice for Ground Control

Humane fast-acting poisons such as cyanide have many advantages (Gregory et al. 1998); however, pastes

used in the early 1990s liberated cyanide gas, which deterred possums and was hazardous to operators. Working with a small private company in Auckland, we developed Feratox[®] in 1997, an encapsulated pellet for possum control (Gregory *et al.* 1998). This has greatly enhanced ground control of possums.

Much of the public disapproval of 1080 resulted from the accidental poisoning (primary and secondary) of dogs, an unfortunate consequence of dogs being 25 times more sensitive to 1080 than possums. In the early 1990s, there were intense efforts to identify safer alternatives to 1080 (Eason 1991, Eason et al. 1993a). Determination of the risks presented to dogs through use of cholecalciferol showed that it was much lower to pets and birds (Eason et al. 1996a,b), and this underpinned the development of cholecalciferol baits that can be used preferentially close to habitation where dog risks are higher. Additionally, baits have been developed with extremely long field life. For example, cholecalciferol gel bait remains palatable and toxic to possums for 26 months under field conditions (Morgan 2006), and such baits are expected to substantially reduce the cost of sustained control of vertebrate pests.

CONCLUSIONS

In this paper, we have summarised seven areas where substantial gains have been made in the last decade in mammal pest control in New Zealand:

- 1. Improved quality assurance of baits and reduce sowing rates of 1080 for possum control
- Improved understanding of 1080 toxicology and management practise
- 3. Experimental and regulatory toxicology database to meet registration requirements
- 4. Improved community support for wildlife management
- Improved our understanding of the importance of toxicokinetics
- A rationale for the choice of anticoagulants for different uses
- 7. Improved formulations and choice.

These are just some of the examples that have enabled improved delivery and more effective pest control of the highest standard, delivering disease control and conservation outcomes with minimal side effects. There are opportunities for useful products, based on research in the 1990s on alternatives to 1080 (Eason *et al.* 1993a), and more recent work that has enabled us to be more selective in our choice of anticoagulants (Fisher *et al.* 2003). Further research is also underway to improve target specificity and provide more species-specific baits and poisons.

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