Smarter Pest Control Tools with Low-Residue and Humane Toxins

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Abstract: Considerable effort has been put into retaining older vertebrate pesticides and improving the effectiveness and safety of pest control. Nevertheless, conventional control targeting single species is sometimes still associated with non-target impacts, bioaccumulation of toxins, fluctuating pest numbers, and unexpected ecological consequences. To counter this, we are developing multi-species bait types for sustained field use that are more palatable to vertebrate pest species. We are incorporating "low-residue" toxicants, namely zinc phosphide, cholecalciferol, diphacinone, and a combination of coumatetralyl and cholecalciferol, in new bait formulations. Looking to the future, we seek to increasingly combine "low-residue" characteristics with humaneness. New humane formulations of cyanide are being developed for a variety of pest species, and para-aminopropiophenone is being introduced for predator control in New Zealand as part of the product development and registration pipeline.

Key Words: 1080, anticoagulants, cyanide, multi-species baits, PAPP, persistence, residues, regulatory toxicology, toxicokinetics, vertebrate pesticides, welfare, zinc phosphide

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INTRODUCTION

For the last two decades, the focus worldwide of many private and public sector organisations involved in vertebrate pest control has been on the retention of product registrations of existing pesticides for field use. For example, in New Zealand (NZ), probably in excess of NZ $10M has been spent in the last 15 years on research, consultation, public relations, and the 1080 re-assessment process under the HASNO Act. In some cases, research has helped select more appropriate pesticides for field use; however, the requirement to build up registration dossiers on existing compounds frequently has driven research priorities and restricted new developments. The need to focus resources sometimes means that useful compounds are lost and others with less merit are retained. As an example, cholecalciferol registrations have recently been discontinued in Europe, despite the advantages of low secondary poisoning risk (Eason et al. 1996a,c), due to the imposition of EU Biocide directive requirements (Roger Sharples, Sorex Ltd, per commun.). Whilst the poisons used for vertebrate pest control have remained largely unchanged in NZ (Eason et al. 2006), the way they are used has improved. Past achievements include: i) improved quality assurance of baits and reduced application rates of baits, increasing effectiveness with reduced cost (Morgan 1994) and reduced non-target mortalities (Morgan 2004); ii) improved information on environmental persistence, regulatory and experimental toxicology, underpinning safer use of vertebrate pesticides (Fagerstone et al. 1994, Eason et al. 1999, Eason and Turck 2002); and iii) improved community support for wildlife management. Special efforts have been made to work with communities. Interactive approaches have evolved, as illustrated by the Lincoln University website that provides technical information on 1080 for Maori, the indigenous people of New Zealand (see www.lincoln.ac.nz/1080), which frequently is used in meetings and workshop settings. Community engagement is paramount, and different approaches to the discussion of risk and benefit with different communities are continuing to evolve, alongside the development of new tools, including alternatives to 1080.

In this paper, we suggest that despite the technical and registration challenges involved in new product development, there is a need to re-focus on refinement and replacement of existing products. Our goal is to produce better tools for sustainable field control programmes, including new multi-species baits. Our strategy is to combine the best of the old and the new pesticides. As part of this process, we have gone to some length to discriminate between persistent and less persistent pesticides. In the following three sections of this paper, we start with an analytical review of the comparative pharmacokinetics of rodenticides and vertebrate pesticides and the link between metabolism, excretion, and non-target species risks. This is followed by a section on multi-species bait development. The final section provides an update on new products that will increase the range of species that can be humanely killed in NZ wildlife management programmes.

LOW-RESIDUE VERTEBRATE PESTICIDES

Development of "low residue" alternatives to sodium fluoroacetate (1080) or brodifacoum will avoid the secondary poisoning of dogs associated with 1080

(Meenken and Booth 1997) and bioaccumulation risks and non-target impacts of brodifacoum and similar compounds (Eason et al. 1996b, 2001). To aid our selection of low-residue compounds, we have put emphasis on comparative pharmacokinetics and the tendency of pesticides to bioaccumulate in the food chain, rather than focus on the persistence of residues in carcasses. The published scientific literature in this field spans over 50 years of research in different laboratories, employs a large variety of different animal species, uses different dosing approaches, and is incomplete. Despite these deficiencies, synthesis of the information is possible, and overall patterns of metabolism emerge. Where there are no persistence data in sub-lethally-exposed animals, we have referred to the persistence data that has been generated from lethally-exposed animals to help elucidate and complete the comparative process.

Our analyses revealed a huge variation in the way that the different vertebrate pesticides are absorbed, distributed, metabolised, and excreted. At one end of the spectrum, there are compounds that are very water soluble, rapidly absorbed, well distributed, and equally rapidly excreted, such as 1080 and cyanide. There are others such as cholecalciferol, para-aminopropiophenone (PAPP, a candidate predacide), and diphacinone, which are extensively metabolised to more hydrophilic metabolites, and others which are lipophilic, poorly metabolised, and exhibit unique receptor binding characteristics. To help distinguish between different compounds and add some clarity, we have classified the vertebrate pesticides into 4 groups, based on their persistence in sub-lethally exposed animals.

Group 1 – Sub-lethal doses of these poisons are likely to be substantially excreted within 24 hours (e.g., cyanide, zinc phosphide, PAPP, and 1080). Whilst most of a sub-lethal dose of all these poisons is likely to be substantially excreted within 24 hours, in the case of 1080, complete excretion of all residues may take up to 4-7 days.

Concentrations of cyanide, even in the carcasses of poisoned animals, decline very rapidly in the first 48 hours after ingestion, and residue concentrations are negligible after one week (Morriss et al. 2003). In NZ, hunters skin possums killed with cyanide and sometimes feed them to their dogs with no ill effects. Zinc phosphide breaks down in the stomach; its decomposition products are absorbed both as phosphine and as phosphide. Excretion occurs as exhaled phosphine from the lungs, and other metabolites including phosphoric acid and phosphate are excreted in urine and faeces (WHO 1976, Johnson and Fagerstone 1994). In the stomach of carcasses, zinc phosphide concentrations decline rapidly, and a half-life of 3.4 days has been calculated for residues after poisoning (Brown et al. 2006). In sub-lethally poisoned animals, elimination processes for cyanide and zinc phosphide are likely to be much quicker, with elimination half-life values of less than 12 hours. PAPP is metabolised to hydrophilic compounds, and after sub-lethal exposure, animals will excrete these metabolites in the urine within 24 hours (Wood et al. 1994). Compound 1080 is rapidly absorbed into the blood and distributed through the soft tissues and organs. Highest concentrations of 1080 occur in the blood, and most residues of 1080 or its metabolites will be eliminated 1-4 days after a sub-lethal dose. The elimination half-life in blood is 11 hours or less in sheep, goat, rabbit, mouse, and possums (Eason et al. 1994a,b). Like other compounds in this group, 1080 will not readily bioaccumulate, but in contrast to cyanide, zinc phosphide, and PAPP, it can persist in carcasses at hazardous concentrations that will be lethal to dogs and other scavengers for several months (Meenken and Booth 1997).

Group 2 – Residues resulting from sub-lethal doses of these poisons are likely to be substantially cleared from the body within 2 to 4 weeks (e.g., pindone and diphacinone).

Pindone and diphacinone lack the hepatic persistence that restricts the utility of other anticoagulant rodenticides for repeated field use. The short hepatic half-life of 2.1 days for pindone in rats is similar to the 3-day half-life obtained in rats for diphacinone (Fisher et al. 2003). In sheep, pindone residues were detected in the liver and fat for 8 days, but at 2 weeks none or very little was detected (Nelson and Hickling 1994). In pigs dosed with diphacinone, a half-life in the liver of 5.43 days was determined (Fisher 2006). In contrast to the studies described above, Bullard et al. (1976) reported that cows dosed with diphacinone had liver residues detectable at 90 days after dosing. We are repeating diphacinone persistence studies in cattle and pigs in 2008 to clarify earlier inconsistencies. It is our belief, based on the comparative rat studies in which both pindone and diphacinone had almost identical half-lives, coupled with the general lack of species variation in metabolism and excretion of individual anticoagulant compounds, that the persistence profile for diphacinone in cattle and pigs will be similar to that for pindone in sheep. Hence, we have classified both pindone and diphacinone in Group 2.

Group 3 – Residues resulting from sub-lethal doses of these poisons are likely to be cleared from the body within 2 to 4 months (e.g., cholecalciferol and coumatetralyl).

Coumatetralyl has a hepatic half-life in sub-lethally exposed rats reported both as 55 days (Parmar et al. 1987) and nearly 70 days (Eason et al. 2003), which is substantially greater than for the indandiones pindone and diphacinone. However, when 0.4 mg/kg was given to rats at 12 weekly intervals, coumatetralyl residues in liver did not bioaccumulate after this repeat dosing and declined consistently to near the limit of detection at 12 weeks (Eason et al. 2003). Hence, compounds in this group could still be used without risk of bioaccumulation in non-target wildlife, if they are used at reasonable intervals. Cholecalciferol is metabolised to 25-hydroxycholecalciferol (25OHD). This metabolite is then converted to 24, 25-, or 1,25-dihydroxycholecaliferol. Persistence studies in possums with cholecalciferol indicated that elevated concentrations of 25OHD are likely to persist for several weeks in animals that had received sub-lethal doses. In sub-lethally poisoned animals, 25OHD is more persistent than rapidly-eliminated poisons, like cyanide or PAPP, but is less persistent than second-generation anticoagulants (Eason et al. 1996c). The half-lives of the active metabolite 25OHD are 10.5 - 12 days in vitamin D-deficient hu-

mans, 15-36 days in humans when vitamin D status was normal, and 25-68 days in humans and cattle during vitamin D toxicity. Interestingly, the half-life of 25OHD is shorter in seals than in other mammals, which probably explains the resistance of this species to cholecalciferol toxicity (Keiver et al. 1988). The main advantage of cholecalciferol versus 1080 is the low risk of secondary poisoning, and whilst residue concentrations have not been measured in carcasses, if present they are likely to be at concentrations that are not hazardous (Eason 1991).

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 in Text	Likely Persistence of Residues after Sub-Lethal Residue Exposure
1	cyanide	+	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 days	6 weeks
3	cholecalciferol	10 - 68 days	3 months
	coumatetralyl	50 - 70 days	4 months
4	brodifacoum	130 days	24 months or longer
	bromodiolone	170 days	24 months or longer
	flocoumafen	220 days	24 months or longer

+ no published value, but likely to be <12 hours.

Group 4 – Residues resulting from sub-lethal doses of these poisons may not ever be completely cleared from the body (e.g., bromodiolone, brodifacoum, difenacoum, and flocoumafen).

Brodifacoum, like other second-generation anticoagulants, is not readily metabolized, and the major route of excretion of unbound compound is through the faeces. All of the second-generation anticoagulants are unique with regards to strong affinity to receptors in the pancreas, kidney, and liver. This is reflected in the unusually long hepatic half-lives in liver recorded for these chemicals. For example, brodifacoum was detected in the liver of sheep 128 days after oral administration (Laas et al. 1985). Parmar et al. (1987) found that elimination half-lives of radio-labeled brodifacoum, bromadiolone, and difenacoum from rat liver were 130, 170, and 120 days, respectively. Flocoumafen in rats was eliminated with a half-life of 220 days, and in quail in 155 days (Huckle et al. 1989). In sheep receiving sub-lethal doses of flocoumafen (0.2 mg/kg) and pindone (10 mg/kg), flocoumafen was detectable for 128 days; in contrast, pindone was undetectable in the liver after 16 days (Nelson and Hickling 1994). Not surprisingly, given the unusual persistence of brodifacoum, residues have been measured in game animals such as pigs and deer and a range of avian species, and links between bioaccumulation and non-target mortality have been established wherever there is extensive and continuous field use of brodifacoum (Eason et al. 2001).

Our analysis has led us to be selective in the active ingredients we use in new products for sustained field use, based on the different pharmacokinetic profiles in animals. In conclusion, we have identified new ways of perceiving vertebrate pesticides and have re-classified them into 4 groups based their pharmacokinetics and the link between metabolism, excretion, and non-target species risks (see Table 1). In the following sections, we describe the development of new low-residue tools utilising compounds in Groups 1, 2, and 3. We intend to try to avoid rodenticide resistance and reduce secondary and tertiary poisoning risks associated with brodifacoum (Eason et al. 2002) and other poisons (Meenken and Booth 1997) by developing a suite of less environmentally-persistent toxins such as diphacinone, zinc phosphide, coumatetralyl, and cholecalciferol.

MULTI-SPECIES BAITS

In response to concerns relating to conventional control that just targets single species (Innes et al. 1995, Sweetapple and Nugent 2007) we recently commenced, in 2007, a new Foundation of Research and Technology Programme in NZ. We are producing 'designer' baits to better target rodents, with an emphasis on house mice (*Mus musculus*) and also multi-species baits for control of mice, ship rats (*Rattus rattus*), and brushtail possums (*Trichosurus vulpecula*) to facilitate sustained endangered species programmes. The research programme has three themes:

Multi-Species Bait for Aerial Application

Cage trials are identifying new solid bait matrices that are palatable to mice, rats, and possums, and we are developing encapsulated toxins coupled with taste masks in solid baits to overcome the deterrent effects of 1080, zinc phosphide, cholecalciferol and coumatetralyl in combination, and diphacinone. These deterrent effects are particularly hard to overcome in mice.

In the development of new solid baits, the first stage was to improve palatability of non-toxic bait. This was measured as the percentage of test bait eaten relative to total bait consumption (i.e., test + control), using EPA standard rodent bait as the control for rats and mice, and RS5 (Animal Control Products–ACP, Wanganui, NZ) cereal pellets for possums. Our best test baits were then compared with Detex blox (an international standard), RS5, and No. 7 cereal baits (obtained from ACP, Wanganui) in a randomized block design by presenting test bait (+ control) to 18 individually-caged possums and rats and 18 pairs of mice over a 6-day period. The weight of test and control bait eaten by each animal during an 18-hr period overnight was measured and the percent palatability of bait types compared by repeated measures ANOVA (see Table 2).

Multi-Species Bait for Ground Control

Cage and pen trials are identifying new paste bait matrices that are palatable to mice, rats, and possums also incorporating encapsulated toxins coupled with taste masks in paste baits to overcome the deterrent of zinc phosphide,

Table 2. Solid bait type and palatability in 3 species.

Bait	Type	Manufacture	Respective Palatability (%)*		
			Possums	Rats	Mice
A	NZ new multi-species	cereal	85.4^{cde}	93.5^{be}	79.5^{cde}
B	NZ new multi-species	extruded	79.1^{cde}	79.0^{ade}	79.3^{cde}
C	RS5	cereal	50.0^{abe}	86.2^{de}	54.0^{abe}
D	No.7	cereal	53.6^{abe}	57.1^{abc}	58.5^{be}
E	DB	moulded block	28.1^{abcd}	44.1^{abc}	32.8^{abcd}

* Letters alongside palatability denote treatments that are significantly different (P<0.05).

Table 3. Paste bait type and palatability in 3 species.

Bait	Type	Respective Palatability (%)*		
		Possums	Rats	Mice
A	New multi-species paste 1	63.0^{c}	78.0^{cde}	81.0^{cde}
B	New multi-species paste 2	62.0^{c}	81.0^{cde}	83.0^{cde}
C	ACP peanut-butter based paste	44.0^{abd}	28.0^{abe}	48.0^{abde}
D	ACP apple based paste	63.0^{c}	20.0^{ab}	20.0^{abc}
E	ACP wonder lure paste	46.0	15.0^{abc}	30.8^{abc}

* Letters alongside palatability denote treatments that are significantly different (P<0.05).

Table 4. Comparative welfare assessments and ranking in terms of time to onset of symptoms, duration of symptoms, the severity of symptoms and time to death in possums, based on the evaluation of results from three research publications.

Toxicant	Onset	Duration	Death	Signs	Rating
Feratox® Gregory et al. 1998	3 mins	12 mins	18 mins	Unconscious after 6 mins	High
1080 Littin et al. 2004	1.5 - 2.5 hours	9.5 hours	11.5 hours	Tremors, spasms, retching, vomiting, seizures	Mod
Brodifacoum Litten et al. 2002	14 days	7 days	21 days	External bleeding, lame, crouching	Low

cholecalciferol and coumatetralyl in combination, and diphacinone.

A similar process was followed as for the multispecies aerial bait described above. The first stage of this process has required the palatability of non-toxic paste baits to be improved. Palatability was determined by presenting paired trays containing an 'industry standard' (as a control) and testing baits to individually-caged possums, rats and mice. Palatability was measured as the percentage of test bait eaten in relation to total bait consumption (i.e., test + control). Subsequently, 2 new pastes and 3 types of existing commercial baits were measured in a randomized block design by presenting each bait (+ control) to 21 individually-caged possums over a 7-day period, presenting each delivery system to 21 individually-caged rats over a 7-day period, and presenting each delivery system to 21 pairs of mice over a 7-day period. The baits presented in a randomized block design were: A) New Multi-species Paste 1, B) New Multi-species Paste 2, C) Animal Control Products' Wanganui apple paste, D) Animal Control Products' Wanganui peanut paste, and E) Animal Control Products' Wanganui wonder-lure paste (see Table 3).

Demonstration Field Assessments using Aerial and Ground Control

Communities are eager to take a leadership role in endangered species protection. New baits and traps will be trialled with community groups. A suite of novel control tools that can be used by unlicensed pest control operators will be assessed by communities involved in rodent, possum, and predator (mustelid and feral cat) control.

At this stage of the pro-gramme, we have completed the first phase of palatability trials with new solid and paste baits. We have achieved what was deemed difficult and developed new solid bait and 2 new paste baits that are both significantly more palatable to possums, rats, and mice than our control baits, RS5 and EPA rodent bait, and the other commercial baits we have tested (see Tables 2 and 3).

Beyond these developments of low-residue toxins (with low secondary poisoning risk) and new multi-species bait types, we see a future where only toxins and doses of these that have been proven to be humane are used. This would combine the best of the old and new poisons and is covered further in the next section.

Combining the Best of the Old and the New

This section starts with a comparison of the humaneness of cyanide with two commonly-used alternatives and concludes by reporting progress on the development of PAPP as a predacide. Cyanide and PAPP are classified as Group 1 compounds in the section above on pharmacokinetics. They combine the desirable features of being low-residue compounds and being humane. Feratox®, a cyanide-containing pellet product, was first registered for possum control in 1997. Cyanide

is compared with 1080 and brodifacoum, based on past research on the possum. A simplified set of welfare criteria have been used and the poisons ranked on a scale of high, moderate, or low in terms of their performance from a welfare perspective (see Table 4).

Cyanide was outstanding, 1080 was moderate to low when compared with cyanide, and brodifacoum was poor from a welfare perspective, in possums. Cyanide in the pellet formulation causes average loss of consciousness in 6 minutes and death in 18 minutes (Gregory et al. 1998). The humaneness of a poison is linked to its mode of action. In the case of cyanide, it blocks uptake and utilization of oxygen in the presence of normal oxygenation of the blood. Hypoxia leads to rapid depression of the central nervous system, respiratory depression, and death (Gregory et al. 1998). Since we have demonstrated this poison can be humane, we are now focusing on continuing to extend its utility to humanely kill other introduced mammalian pests in NZ. In 2008, we have scheduled experiments to test cyanide pellets in Dama and Bennett's wallabies and ferrets – exploring the potential of cyanide for humane culling of pest species other than possums.

On the platform of Feratox®, which sets the "gold standard" for humaneness, we are hoping to register a proprietary formulation of PAPP that has been developed in a paste. The toxic effects of PAPP are related to the rapid formation of methaemoglobin. Hypoxia and central nervous system depression precede death. This is quite a different mode of action from cyanide, but the end result, hypoxia of the brain and a humane death, is similar. Carnivore species appear to be much more susceptible than birds (Savarie et al. 1983, Shafer et al. 1983), so PAPP potentially has some degree of target specificity. Hence, PAPP paste has the potential to become the second vertebrate pesticide product in NZ designed with humaneness as a primary consideration. Currently, we are completing field trials with radio-collared feral cats (*Felis catus*) and stoats (*Mustela erminea*).

CONCLUSIONS

Our research is providing improved tools for pest control. Many current tools rely on the use of increasingly unpopular poisons, or poisons that are linked with secondary poisoning or are inhumane. The sustained field control of pests with second-generation anticoagulants, like brodifacoum, has resulted in wildlife contamination and non-target deaths. Hence, the development of safer humane toxins and/or delivery systems is highly desirable.

We are currently incorporating low-residue toxicants, namely zinc phosphide, cholecalciferol, diphacinone, and a combination of coumatetralyl and cholecalciferol, in new bait formulations. Looking to the future, we seek to increasingly combine low-residue characteristics with humaneness. We will continue investigations to identify more humane poisons for controlling other vertebrate pest species.

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