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A review of existing and potential New World and Australasian vertebrate pesticides with a rationale for linking use patterns to registration requirements

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Registration is a necessarily sophisticated evaluation process applied to vertebrate pesticide products. Although conducted to minimise any potential impacts upon public health, the environment and food production, the all-encompassing process of registration can stifle innovation. Vertebrate pesticides are rarely used to control pest animals in food crops. In contrast to agrochemicals, relatively small amounts of vertebrate pesticides are used (<0.1%), usually in solid or paste baits, and generally by discrete application methods rather than by broad-scale spray applications. We present a hierarchy or sliding scale of typical data requirements relative to application techniques, to help clarify an evolving science-based approach which focuses on requiring data to address key scientific questions while allowing waivers where additional data have minor value. Such an approach will facilitate the development and delivery of increasingly humane, species-targeted, low residue pesticides in the New World, along with the phasing out of less desirable chemicals that continue to be used due to a lack of alternatives.

Keywords: toxin; regulation; environmental safety; data requirements; America; Australia; New Zealand

1. Introduction

This paper specifically focuses on mammalian pest control in the New World, in particular the United States of America, New Zealand and Australia (the Australian zoogeographical region and Australasia), due in part to: (i) past collaborative research aimed at retaining the registration of important vertebrate pesticides (Seawright and Eason 1994; Eason and Turck 2002), and (ii) new initiatives in these countries to develop more humane and species-targeted toxins and anti-fertility agents for the field control of vertebrate pests (Lapidge et al. 2007).

The United States Environmental Protection Agency (US EPA) definition of a pesticide is any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest (http://www.epa.gov/pesticides/about/index.htm). The term pesticide applies to insecticides, herbicides, fungicides, and various other substances used to control pests. Similar definitions are used by pesticide regulators in Australia, specifically the Australian Pesticide and Veterinary Medicine Authority (APVMA), and in New Zealand, specifically the Environmental Risk Management Authority (ERMA). Not surprisingly, other commonalities exist between the processes of pesticide regulators in these regions, and calls have been made for greater collaboration and harmonization in the registration of vertebrate pesticides (Lapidge et al. 2007). Such a process is currently occurring in the European Union through the Biocidal Products Directive (98/8/EC), whereby mutual recognition of regulatory product dossiers across the 25 member states of the EU is the aim (Adams 2005; Buckle et al. 2005).

The purpose of all pesticides is to prevent undesirable damage to agriculture, the environment and society. In relation to vertebrate pesticides, damage is reduced through the use of rodenticides, avicides, fumigants, repellents and oral or injectable contraceptives (Hone and Mulligan 1982; Ramey et al. 1994; Eason et al. 2006; Lapidge et al. 2007). Examples of the different chemicals used are presented in Table 1. These compounds fall into two broad categories: lethal and non-lethal. Lethal compounds include anticoagulant and non-anticoagulant agents, acute toxicants, and fumigants. Non-lethal compounds include repellents and contraceptives.

Vertebrate pesticides for mammalian pest control are normally delivered using baits including grain, cereal pellets, pastes or meat, or are aerosolized in fumigants, and most recently are delivered by injection. They are used to control pests around homes and on farms to reduce losses to agricultural production and to prevent transmission of disease from wild animals to livestock or people. In the New World there is also a very considerable emphasis on the use of these compounds in conservation settings to protect

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Table 1. Classes of compounds used to control terrestrial vertebrate pests in the New World and Australasia (including those currently in development).

Target action	Class	Target organism	Active ingredient
Lethal Control Agents	Anticoagulant toxicants	Mammalian	1st Generation
			Pindone
			Warfarin
			Coumatetralyl
			Diphacinone
			Chlorophacinone
			2nd Generation
			Brodifacoum
			Difethiolone
			Flocumafen
			Difenacoum
			Bromadiolone
	Acute toxicants	Mammalian	Zinc Phosphide
			Cholecalciferol
			Bromethalin
			Strychnine
			Sodium cyanide
			Sodium fluoroacetate (Compound 1080)
			Para-aminopropriophenone (PAPP)
			Sodium nitrite
		Avian	3-Chloro-p-toluidine HCL (DRC-1339)
		Reptilian	Acetaminophen
	Fumigants	Mammalian	Aluminum phosphide
			Magnesium phosphide
			Sodium nitrate, carbon (gas cartridge)
		Reptilian	Methyl bromide
Non-lethal control agents	Repellents	Mammalian	Thiram
			Egg-acrylic
			Predator odors
			Dried blood
		Avian	Methyl anthranilate
			Anthraquinone
			4-aminopyridine
			Methiocarb
	Contraceptives	Mammalian	Gonadotropin releasing hormone
			Porcine zona pellucida
		Avian	Nicarbazin

threatened native species. Australian ecosystems have been severely affected by introduced mammals. For example, New Zealand wildlife evolved in the absence of mammalian predators (Parkes and Murphy 2003) and birds have been particularly affected by the introduction of non-native predators, with over 40% of the pre-human land bird species now extinct, and the proportion of birds classed as threatened one of the highest in the world (Clout 1997). Similar impacts have been recorded in Hawaii (Messing and Wright 2006). Vertebrate pesticides are used to mitigate conservation problems caused by the impact of rodents and other introduced species, such as possums in New Zealand and foxes in Australia, on indigenous plants and animals in unique ecosystems and island habitats (Sadleir 1994; Dickman 1996; Eason et al. 1996; Towns and Broome 2003; Parkes and Murphy 2003). They have been used successfully to conserve endangered species (Innes and Barker 1999) and eradicate rodents and other introduced mammals to protect populations of endangered indigenous birds and other animals on islands around the world (Courchamp et al. 2003; Towns and Broome 2003).

Despite the need for effective tools for conservation and protection of agriculture from pest impacts, over the last 50 years the number of vertebrate pesticides registered worldwide has plummeted. The USA has potentially seen the largest drop from 72 federal registrations in 1960 to 30 by 1998 (Ramey et al. 1992; Fagerstone and Schafer 1998). Contrary to this, animal pest-caused economic losses have increased over this period (Conover and Decker 1991), and now exceed US$30 billion per annum (Conover et al. 1995; Pimentel et al. 2000). A principal reason for the drop in registrations has been the substantial increase in data requirements, and associated financial burden, that has caused industry and government agencies to discontinue undertaking often important but minor use registrations (Fagerstone et al. 1990). The low use nature of vertebrate pesticides, and the even lower profit margins on most products, means that sufficient profit cannot be generated to fund the registration studies required, nor the annual registration maintenance fees (Fagerstone et al. 1990). For comparison, the Roundup® herbicide generates annual profits in excess of US$2 billion for Monsanto, allowing the

company to fund future registration data requirements. Conversely, sodium cyanide is an important vertebrate pesticide registration held by the US Animal and Plant Health Inspection Services (for management of coyotes, foxes and feral dogs; Fagerstone et al. 2004), particularly for US grazing enterprises, that generates limited profit and would no longer be registered if not for government support. A similar process of re-registration 'data call-ins' has occurred in New Zealand (Eason et al. 1997; ERMA 2007), and in the EU with the Biocidal Products Directive, which in Europe has also resulted in substantially fewer vertebrate pesticides being available (Adams 2005).

The considerable expense of developing new products (a new predacide in Australia and New Zealand, para-aminopropiophenone (PAPP), will be in excess of AUS$5M; Lapidge et al. 2007), the challenging and onerous registration process for minor use vertebrate pesticides, and the lack of return on investment leading to market failure in the industry has meant that progress within the field of vertebrate pesticide product development can sometimes be stifled. This has no doubt led to the continued use of compounds that are considered undesirable or inhumane (Mason and Littin 2003) due to a lack of financial incentives to develop and register more appropriate actives. Fortunately such anomalies have been recognised by regulators. The US EPA has accepted reduced data requirements for registrations of gas cartridges (sodium nitrate and carbon active), Livestock Protection Collars (1080 active) and M-44 mechanical ejectors (sodium cyanide active) (Fagerstone and Schafer 1998) due to their minor and selective use patterns that minimize unintended exposures. If the US EPA had demanded the 110, 55 and 56 originally requested re-registration studies respectively for these products (of which 24, 40 and 29 were submitted, respectively), then the registrations would likely have been discontinued and less desirable alternatives would likely have been sought.

From a New World and Australian perspective we need to retain and refine the use of important tools for conservation and agricultural protection, and mitigation of disease transmission until such time that we have developed new and improved active substances and alternative control tools. In this context we have reviewed and analysed the registration process for vertebrate pesticides. In this paper we propose a hierarchy or sliding scale of typical data requirements for vertebrate pesticide application techniques to help clarify the evolving science-based approach which is increasingly being accepted for their registration. The registration process focuses on both the active ingredient and the final formulated product for all classes of pesticides. This proposal is supported by providing information in the following sections on: (1) the background on examples of individual vertebrate pesticides registered in the New World and Australia, with a focus on those used for the field control of vertebrate pests, rather than commensal rodents; (2) the traditional basis for pesticide registration; (3) current trends in vertebrate pesticide registrations; and (4) the usage and use patterns for agrochemical products in general versus vertebrate pesticides.

2. History and characteristics of individual vertebrate pesticides

This section includes historical details, toxicology, common usage and mode of action of vertebrate pesticides commonly used in the New World and Australasia for the field control of vertebrate pests. Worldwide some naturally occurring vertebrate pesticides, such as cyanide and strychnine, have been used for hundreds, possibly thousands of years, and zinc phosphide has been used as a rodenticide for nearly 100 years. The most prolific period of vertebrate pesticide development occurred between 1940 and 1990. Sodium fluoroacetate (1080) was developed in the 1940s, first generation anticoagulant rodenticides in the 1940s, 1950s and 1960s, and cholecalciferol and second generation anticoagulant rodenticides in the 1970s and 80s, partly to overcome resistance. To illustrate some of the characteristics of vertebrate pesticides, features of the more commonly used compounds are briefly summarized below. More detailed reviews of the characteristics, international application and toxicology of these compounds can be found elsewhere (Prakash 1988; Hayes and Laws 1991; Buckle and Smith 1994).

2.1. Acute acting compounds

The principal acute vertebrate pesticides used in the USA, Australia and New Zealand are zinc phosphide, sodium fluoroacetate (1080) and cyanide. Cholecalciferal has increasingly important field use applications in New Zealand and is registered in the USA. Bromethalin is only registered in the USA and only for commensal rodents. Strychnine is only registered in the USA for underground use to control some rodent species such as pocket gophers and moles. Prior to 1950 all vertebrate pesticides were non-anticoagulants, most of them acute or quick acting, but after the introduction of warfarin and the other anticoagulants the importance of these non-anticoagulants was reduced, at least for rodent control. After the emergence of resistance in some populations of rodents and residues of the second generation anticoagulants in wildlife (Young and De Lai 1997; Stone et al. 1999; US EPA 2002, 2008) interest in non-anticoagulants or at least less persistent "low residue" vertebrate pesticides has been revived. This interest has been coupled with the questionable humaneness of second generation anticoagulants in larger vertebrate pests (Littin et al. 2002; Mason and Littin 2003). More recently two new acute compounds have been investigated in Australia

and New Zealand, PAPP and sodium nitrite, and their properties are also briefly discussed below even though these compounds are not yet fully registered.

2.1.1. Zinc phosphide

Zinc phosphide was the most commonly used rodenticide worldwide until the introduction of anticoagulant compounds. It is used in the USA and Australia for field control of animal pests. In the USA its use was reviewed and supported by additional research in the 1990s (US EPA 1998). Whilst in common use in Australia for mouse plagues (Brown et al. 2002) it has not previously been used in New Zealand but is currently undergoing registration as an alternative to 1080 for possum and rodent control (Eason et al. 2008). It found favour in the USA, Australia and New Zealand because of its lack of persistence and comparatively low risk of secondary poisoning following its field use when compared with strychnine or 1080. Zinc phosphide is a quick-acting compound with death occurring generally in 3–12 h after a lethal dose. Death is mediated by a combination of cardiac and respiratory failure (Osweiler et al. 1985; Prakash 1988; Hayes and Laws 1991).

2.1.2. Sodium fluoroacetate

Sodium fluoroacetate (1080) was developed as a pesticide in the 1940s in the US (Atzert 1971). Fluoroacetate occurs naturally at lethal concentrations in poisonous plants (de Moraes-Moreau et al. 1995; Twigg et al. 1996a, 1996b). The toxin is formulated into baits to kill a range of introduced mammalian pests in Australia and New Zealand, to limit their unwanted impacts on agricultural and biological assets. In the US, 1080 is used solely for localized and very target-specific predator control in the Livestock Protection Collar (LPC). In mammals the period between the time fluoroacetate is consumed and the appearance of symptoms of poisoning is between 0.5 and 3 h, and animals receiving a lethal dose mostly die within 24 h. Inhibition of energy production in the tricarboxylic acid (Krebs) cycle results in death from heart or respiratory failure (Egeheze and Oehme 1979; Eason 2002). There is some debate about the humaneness of 1080 (Sherley 2007). Whilst it is not as humane as PAPP (see later) or cyanide (Eason et al. 2008), it is more humane than many other actives, including strychnine or anticoagulant poisons. And because of its importance for conservation and agriculture it will be retained in Australia and New Zealand until better alternatives are developed (ERMA 2007; APVMA 2008).

2.1.3. Cholecalciferol

Cholecalciferol (vitamin D_3) was developed in the 1980s in the US as a rodenticide (Marshall 1984). In New Zealand it is increasingly used as an alternative to 1080 for the field control of possums and rodents because of the relatively low risk of secondary poisoning of dogs and birds. In order to gain biological and toxicological activity, cholecalciferol must undergo metabolic conversion to 25-hydroxycholecalciferol (25OHD; Kiever et al. 1988). Death from heart failure appears to be the mode of action of cholecalciferol in the possum, as in rodents (Dorman and Beasley 1989; Jolly et al. 1993). Cholecalciferol has been explored for controlling rock squirrels, gophers, and ground squirrels in the US (Tobin et al. 1993).

2.1.4. Cyanide

Cyanide, as a vertebrate pesticide, is predominately used to control coyotes in the USA. It is delivered using the M-44 mechanical ejector (Blom and Connolly 2003; Fagerstone et al. 2004) which, when the top is pulled by a predator, ejects cyanide into the mouth of the animal. Cyanide is registered as a vertebrate pesticide in New Zealand for possum (*Trichosurus vulpecula*) control. In Australia it has been used experimentally for killing foxes (*Vulpes vulpes*; Marks and Gigliotti 1996). Of all the poisons currently used for possum control, cyanide when delivered in an optimized delivery system, is considered the most humane (Gregory et al. 1998). When developing new toxins for other vertebrate pests we are attempting to attain the standard achieved by cyanide in possums and avoid compounds with more protracted effects, such as brodifacoum (Littin et al. 2002). Cyanide disrupts energy metabolism by preventing the use of oxygen in the production of energy, causing cytotoxic hypoxia in the presence of normal haemoglobin oxygenation. When the dose is optimised the cytotoxic hypoxia depresses the central nervous system, the most sensitive site of anoxia, resulting in rapid respiratory arrest and death (Osweiler et al. 1985; Gregory et al. 1998).

2.1.5. Para-aminopropiophenone

Para-aminopropiophenone (PAPP) was originally studied as a treatment for cyanide poisoning in the 1940s (Rose et al. 1947). It is toxic to carnivores, with birds and humans being less sensitive (Savarie et al. 1983; Fisher and O'Connor 2007; Murphy et al. 2007). This is primarily due to the different metabolic pathways that occur in eutherian carnivores as opposed to other orders of animals (Wood et al. 1991). The toxin is being developed for humane control of stoat (*Mustela erminea*) and feral cats (*Felis catus*) in New Zealand, and foxes (*Vulpes vulpes*), feral cats and wild dogs in Australia (Fleming et al. 2006; Lapidge et al. 2007). The toxic effects of PAPP are related to its ability to reduce the oxygen carrying capacity of the red blood cell through the formation of methaemoglobin.

The onset of symptoms is rapid and cats and foxes are usually unconscious within 30–45 min (Marks et al. 2004). This leads rapidly to a lack of oxygen to the brain and other vital organs and death due to respiratory failure. Methylene blue will reverse the methaemoglobinaemia induced by PAPP and is considered an antidote to PAPP exposure. Research and development programmes are well advanced in both Australia and New Zealand and registration dossiers have been filed with APVMA and ERMA.

2.1.6. *Sodium nitrite*

Sodium nitrite, a meat preservative, is currently being developed as a feral pig (*Sus scrofa*) toxin in Australia (Cowled et al. 2008). Pigs are one of the most sensitive species tested to the chemical on a mg/kg basis. As with PAPP, nitrite kills through terminal hypoxia caused by methaemoglobinaemia. Time to death for feral pigs is 2–3 h with few visual symptoms (Cowled et al. 2008). Sodium nitrite is currently being investigated for its potential use for other pest species by the Invasive Animals Cooperative Research Centre (IA-CRC Australia), in collaboration with Lincoln University researchers. The IA-CRC has patented bait-delivered nitrite as a vertebrate pesticide.

2.2. *First generation anticoagulants*

First generation and second generation anticoagulant rodenticides (Table 1) have the same mode of action, i.e. interference with the synthesis of clotting factors, which results in haemorrhaging and death. The principal use of anticoagulants worldwide has been for control of commensal rodents, primarily Norway rats (*Rattus norvegicus*), ship rats (*Rattus rattus*), and house mice (*Mus musculus*). As over 10 anticoagulants have been synthesized, only three actives are reviewed below to illustrate their properties. Many of the anticoagulants listed in Table 1 are registered for commensal rodent control in the USA, Australia and New Zealand. The compounds that have been chosen for review in the section below have been identified because of their field use applications and their role in conservation programmes in the USA, Australia and New Zealand.

2.2.1. *Warfarin*

Warfarin, like pindone (see below), 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. Warfarin, like the other anticoagulants, inhibits the synthesis of vitamin K-dependent clotting factors. In addition, warfarin is reported to induce capillary damage. In general the symptoms of poisoning do not appear suddenly, and will culminate in death in rats within 5–7 days of the initial ingestion of a lethal dose. The single dose LD_{50} is 50–100 mg/kg in rats (species unspecified) versus daily doses of 1 mg/kg for 5 days (Osweiler et al. 1985) which will kill rats in 5–8 days. Warfarin has very limited use in the New World. It has recently been used for the control of feral pigs (Choquenot et al. 1990), but this use is being phased out.

2.2.2. *Pindone*

Pindone, like diphacinone, belongs to the indandione class of anticoagulants, which differ chemically from coumarin anticoagulants such as brodifacoum or warfarin. It was synthesised in 1937 (Beauregard et al. 1955) and developed as a pesticide in the early 1940s. Pindone has been used to control rodents and even possums in New Zealand but its use has decreased following the introduction of more potent anticoagulants such as brodifacoum. However it remains favoured and effective for rabbit control in Australia and New Zealand (Eason and Jolly 1993) and a single dose of approximately 18 mg/kg is sufficient to kill rabbits. In rabbits the repeat dose (7 days) LD_{50} is 0.52 mg/kg/day (Hone and Mulligan 1982). Pindone acts like the other anticoagulant toxicants by interfering with the normal synthesis of vitamin K-dependent clotting factors in the liver. The weaker potency of first generation anticoagulants such as pindone is related to a generally lower binding affinity when compared to second generation compounds (Parmar et al. 1987; Huckel et al. 1988). As with all other anticoagulant compounds, clinical signs of toxicosis in animals will usually reflect some manifestation of haemorrhage (Osweiler et al. 1985).

2.2.3. *Diphacinone*

Diphacinone is another first generation anticoagulant, of the indandione class, which differ chemically from coumarin anticoagulants such as warfarin or brodifacoum. Diphacinone is more toxic than warfarin and pindone to most rats and mice (Buckle and Smith 1994). In New Zealand it is registered primarily for field control of rodents, and it has been incorporated into fish-based bait for ferret control. In the USA it has been developed for field use and it has recently been registered by the US EPA to control rodents for conservation purposes, providing an option in addition to brodifacoum. Diphacinone, like other anticoagulants, inhibits the formation of vitamin K-dependent clotting factors. Clinical and post-mortem signs of toxicosis are as for other anticoagulants. The persistence of diphacinone in the liver is similar to pindone and both are rapidly eliminated and do not bioaccumulate like the second generation anticoagulants (Fisher et al. 2003).

2.3. Second generation anticoagulants

The second generation anticoagulants, such as brodifacoum and bromadiolone, are more toxic than first generation anticoagulant rodenticides (Eason and Wickstrom 2001). Their superior potency, and their associated greater potential to affect wildlife compared to first generation anticoagulants, is related to their greater affinity for vitamin K-epoxide reductase, and subsequent accumulation and persistence in the liver and kidneys after absorption (Huckle et al. 1988; Parmar et al. 1987). Only brodifacoum will be discussed.

2.3.1. Brodifacoum

The rodenticidal properties of brodifacoum were first described in the early 1970s (Hadler and Shadbolt 1975). Brodifacoum differs from the first generation anticoagulants in that it is very potent and only requires a single dose to induce death, if sufficient toxicant is ingested. Brodifacoum is extremely toxic in a number of animal species. Brodifacoum has been used successfully in recent rodent eradication programmes on offshore islands to protect populations of endangered indigenous birds (Taylor and Thomas 1989, 1993; Courchamp et al. 2003; Towns and Broome 2003). In addition to its use to control commensal rodents and eradicate rats from islands it is used to control possums in New Zealand.

Second generation anticoagulants, like brodifacoum, have an important role in controlling rats that have developed resistance to first generation anticoagulants. However, in Australasia they have become better known for their role in eradication of rodents from island sanctuaries (Towns and Broome 2003) and their field use in New Zealand for possum control. The field use of second generation anticoagulants has been controversial and has resulted in wildlife contamination (Stone et al. 1999; Eason et al. 2002). They have an unusual persistence because they are not fully metabolised and excreted before death. To reduce wildlife exposures and ecological risks, the US EPA is phasing in additional restrictions for second generation anticoagulant products. Except for use around livestock facilities, baits will only be applied by professional operators and applications must be made no further than 50 feet away from any building (US EPA 2008). The problems associated with persistence have been compounded by its inhumaneness when used to control larger vertebrate pests such as possums (Littin et al. 2004). Wildlife contamination extends to native birds as well as game species where there is field use of second generation anticoagulants (Young and de Lai 1997; Eason et al. 2002).

3. Past and current trends in registration activity

For the last two decades, a focus of many private and public sector organisations involved in vertebrate pest control worldwide has been on the retention of product registrations for existing pesticides and bait products (Ramey et al. 1994; Eason et al. 1999; Adams 2005; APVMA 2008). This reflects the application of more stringent product registration legislation for all classes of drugs and pesticides, including rodenticides and other vertebrate pesticides. There have also been additional requirements for new product registrations and existing products undergoing re-assessment (Ramey et al. 1992; Fagerstone and Schafer 1998; Eason et al. 2006; ERMA 2007). This has led to the development of wide ranging and detailed databases for key vertebrate pesticides in terms of chemistry, residues, efficacy and non-target species susceptibility as well as comprehensive systems of ecotoxicity, toxicology, metabolism and pharmacokinetic studies. For example, in New Zealand probably in excess of $15M has been spent by a consortium of stakeholders in the last 15 years on research, consultation with community groups and updating 1080 registration dossiers for a re-assessment of 1080 that was completed in 2007 (ERMA 2007). This was appropriate in the context of New Zealand being the largest user of 1080, and that 1080 baits are sown aerially for possum control to reduce damage to native forest and eradicate bovine tuberculosis. Likewise, a similar re-registration review has been undertaken in Australia by the Australian Pesticide and Veterinary Medicine Authority (APVMA 2008).

In the US some vertebrate pesticides are used in such small quantities, when compared to agrochemicals used in food production, that private industry cannot afford to register and produce them profitably. The Animal and Plant Health Inspection Service (APHIS) currently maintains 30 federal and state pesticide registrations, containing 11 active ingredients, with the Environmental Protection Agency (EPA) for use by Wildlife Service's personnel and cooperators. These include 1080, cyanide, strychnine and zinc phosphide. In 1988 the US Congress amended the Federal Insecticide, Fungicide, and Rodenticide Act, requiring re-registration of all active ingredients. Re-registration had an extensive impact on APHIS vertebrate pesticide products and over 400 studies, with an estimated cost of about $14 million, were requested by the EPA. Through negotiations with the EPA, placing the focus on key scientific questions, Wildlife Service's National Wildlife Research Centre (NWRC) reduced the data requirements to about 250 studies costing $3 million by resubmission of existing suitable data and obtaining data waivers for unnecessary or inappropriate studies (Fagerstone et al. 1990; Ramey et al. 1994; Fagerstone and Schafer 1998).

However, this requirement for research to build up registration dossiers on existing compounds has often been at the expense of research on new lower risk compounds (Fagerstone and Schafer 1998). In addition, the need to focus resources means that sometimes

useful compounds are lost and others with less merit are retained. As an example, cholecalciferol registrations have recently been discontinued in the European Union (EU), despite the advantages of cholecalciferol's low secondary poisoning risk versus other toxicants (Eason et al. 2000); its utility as an alternative to anticoagulants to control anticoagulant rodenticide resistance in Europe has potentially been lost. The new data requirements of the EU Biocide Directive were deemed excessive, and extremely costly to generate relative to their scientific merit and sales volume by the registrants (Knight and Cooke 2002; Adams 2005; Buckle et al. 2005).

Equally, the development of more target-specific delivery techniques for existing toxins can often result in unnecessarily protracted and expensive registration reviews. A recent example is with the PIGOUT® bait in Australia, a specifically-designed grain-based feral pig bait for Australian conditions that delivers the already registered (in much higher doses) toxin 1080 in an internal core (to centralise the 1080 in the 250-g bait) to improve feral pig dose compliance and non-target safety. National registration of this product took 17 months, 7 months more than the statutory guidelines of the APVMA, despite the product increasing feral pig control efficacy (Cowled et al. 2006a) and significantly reducing non-target hazard (Cowled et al. 2006b) and operator safety versus existing products. In New South Wales, the product's biggest market, PIGOUT® was further delayed from sale for an additional 10 months due to it not being specifically listed (although 1080 and grain were) on the state Pesticide Control Order. During this 27 month registration process the non-specific and inhumane feral pig toxicants yellow phosphorous and warfarin continued to be used, likely to the detriment of animal welfare and the environment. This and other examples, highlight how rigid regulatory structures can stifle innovation to the detriment of what the process is attempting to protect. Such delays are incredibly costly to private industry who are likely to invest elsewhere rather than in improving this industry, and it makes products with limited profitability unviable.

Nevertheless, environmental protection agencies in the New World encourage the replacement of persistent or unpopular vertebrate pesticides or delivery techniques with more humane or less persistent alternative toxicants, more species-targeted delivery techniques or non-lethal means of control (EPA 2002; ERMA 2007; APVMA 2008). On the positive side PAPP is being developed for the control of foxes and feral cats in Australia and stoats and feral cats in NZ. If the research and registration of PAPP baits are successfully completed it will be the first new vertebrate toxicant developed for mammalian pest control since the 1980s (Murphy et al. 2007), and the only one developed with target specificity, humaneness and low residue risk as priority features. A similar push is also now occurring with nitrite for feral pig control (Cowled et al. 2008) and a canine-tailored toxicant (methylxanthines) in the USA (Johnston 2005). Furthermore, global harmonisation in registration requirements and collaboration in vertebrate pesticide product development is being encouraged in the field of invasive species management and product development (Lapidge et al. 2007), and is already occurring in the old world (Knight and Cooke 2002; Buckle et al. 2005), which is an encouraging step.

As indicated by the USA experience cited above (Fagerstone et al. 1990; Ramey et al. 1994; Fagerstone and Schafer 1998), it is also important to note when considering the continued registration of existing products or new product registration that authorities are increasingly focusing on key scientific questions. This is further illustrated by the attention given to pharmacokinetics, persistence in sub-lethally dosed animals and the relative tendency of pesticides to bioaccummulate (EPA 2004a). In the USA this focus has resulted in today's pesticide regulatory framework first established in 1972, and amended several times over subsequent years. A significant overhaul of pesticide regulation occurred with the enactment of the 1996 Food Quality Protection Act (FQPA). The key concept of FQPA is the evaluation of aggregate risk to humans of a pesticide by all routes of exposure, and the cumulative risk of pesticides having a common mechanism of action. A recent action by the EPA with consequence for vertebrate control products was the issuance of the 'Rodenticide Mitigation Decision for Ten Rodenticides' (US EPA 2008). The mitigation measures are intended to minimize children's exposure to rodenticide products in homes, and to decrease wildlife exposure and ecological risk. Principal mitigation measures for second generation rodenticides include limiting sales of 'consumer size' (in and around the home) products to non-refillable bait stations containing no more than 454 g (1 lb) of bait or in 1.4 kg quantities sold with refillable bait stations. In addition, 'consumer size' products are limited to bait block formulations. Since field use of anticoagulant rodenticides is very limited in the USA, mitigation measures will have little impact on field applications or the use of brodifacoum and diphacinone bait pellets for eradicating rodents on islands. Encouragement to develop and register vertebrate pesticide products for routine use, that do not bioaccumulate, and do not cause secondary poisoning, is a logical step which mirrors developments with other classes of pesticides.

4. The rationale for data

This section focuses on the traditional rationale for data requirements by regulatory agencies. Registering insecticides, herbicides, fungicides and vertebrate pesticide products has commonalities throughout the New World and Australasia; whether it be through the APVMA, the US EPA, or the NZ ERMA and Food Safety Authority

(NZFSA), and data requirements for registering a new product or re-registering existing actives and products are somewhat analogous (Lapidge et al. 2007).

Registration is now a sophisticated evaluation process applied to new products or older products undergoing a re-assessment which in itself lends a large degree of safety to pesticide products. Before a pesticide product can be marketed and used to manage a wildlife damage problem, the product must be registered with the agency responsible for regulating the sale, distribution and use of pesticide products. Originally, registration of pesticides was required to protect the consumer from fraudulent use claims. However, as awareness developed of the potential impacts of pesticides on humans and the environment, the registration process has become a means not only for regulating the use patterns of pesticide products, but also for ensuring that human safety and environmental health are considered (Fagerstone et al. 1990). To assist in this process regulatory toxicology studies in animal or *in-vitro* test systems are usually conducted before the registration of new products. Alternatively, they may be conducted on older compounds, such as with sodium fluoroacetate, in anticipation of a re-assessment process (Eason and Turck 2002). The principles that have underpinned the development of regulatory testing of pesticides to assess the risk to humans are listed below:

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

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

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

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

In 2007 the US EPA revised the data requirements for pesticide registration applications (US EPA 2007). The data requirements fall into 8 general categories and these requirements are similar in other countries:

1.	Product chemistry	Provides a profile of the physical and chemical characteristics of the product.
2.	Product performance	Demonstrates efficacy under laboratory and field conditions.
3.	Environmental fate	Provides a profile for assessing the movement, degradation and metabolism of the pesticide in soil, water and air.
4.	Residue chemistry	Provides information on pesticide residues in plants or animals, leading to issuance of tolerances that specify acceptable residue levels in human food and animal feed items.
5.	Studies that determine hazard to humans and domestic animals	Allows the assessment of hazards to humans and domestic animals through acute, subchronic, and chronic toxicity tests, mutagenicity tests, and pesticide metabolism.
6.	Studies that determine hazard to non-target organisms	Data required for the assessment of hazards to humans and domestic animals are derived from a variety of acute, subchronic, and chronic toxicity tests, and tests to assess mutagenicity and pesticide metabolism. Provides acute and chronic toxicity information for assessing risk to non-target terrestrial and aquatic organisms.
7.	Applicator/user and post-application exposure	Provides for the protection of pesticide applicators and farm workers.
8.	Spray drift	Provides data for the assessment of risk of off-field risk to non-target organisms resulting from aerosolized applications. These data are not normally required for vertebrate pesticides.

In NZ the requirements of the Hazardous Substances and New Organism (HSNO) legislation must be met, along with the requirements of the Agricultural Chemistry and Veterinary Medicines (ACVM) act. The registration process is challenging as approvals

are required from both the Environmental Risk Management Agency (ERMA) and the New Zealand Food Safety Authority (NZFSA); consultation with Maori is a prerequisite, and welfare considerations are a key component of the registration assessment process for vertebrate pesticides. However, the overall requirements are similar to those of the US EPA and the APVMA. This paper is not, however, focused on the protocols for these studies or the precise guidelines for the US EPA and the Australian APVMA *per se*, nor with comparisons with NZ registration requirements. Such information can be found on the websites of the different agencies: US EPA, http://www.epa.gov/; APVMA, http://www.apvma.gov.au/; NZ ERMA, http://www.ermanz.govt.nz/, and is well summarised within Knight and Cooke (2002).

As with the US EPA a typical regulatory toxicology package for any country for a new agrochemical may include relevant studies of acute toxicity (oral, dermal, inhalation), mutagenicity, sub-chronic 3-month rodent feeding studies, chronic long-term rodent feeding (including carcinogenicity) studies, developmental toxicity (teratogenicity, reproduction toxicity) in rabbits/rats, metabolism, ecotoxicology in terrestrial and aquatic invertebrates, vertebrates and plants, and environmental fate and residues. In addition, when conducting safety evaluation it is also important to consider the implications of pharmacokinetics, mechanisms of toxicity and receptor interactions using sound scientific judgement as well as satisfying legislative requirements.

These scientific principles are particularly relevant for vertebrate pesticides which are designed to be toxic to mammals but used in small amounts when compared with agrochemicals. As current pesticide registration requirements have principally been developed to target broad scale agricultural applications of agrochemicals onto food crops, there should be a different focus when dealing with vertebrate pesticides (many of which are used in minor amounts with focused delivery systems) that determines which scientific data are relevant and allows for waivers of other data requirements. For vertebrate pesticides it has been recognised that understanding the likely exposure risk of non-target species determined by well designed field trials will be as, if not more, important than completion of guideline laboratory studies defining hazards.

5. Pesticide use patterns

Australia and NZ are often considered to rely heavily on vertebrate pesticides in comparison with other countries. This is primarily due to the large number of introduced mammals disrupting native ecosystems and putting endemic species at risk. However, even in these countries vertebrate pesticide containing products are considered 'minor use products' in terms of the amounts used. For example in NZ 3,500 tonnes of pesticide active ingredient are used annually, most of which are in the form of herbicides (Manketelow et al. 2005). In comparison to insecticides, fungicides and herbicides, probably in the order of 0.1–0.2% (3.5–7 tonnes) of vertebrate pesticides are used annually, with this figure approaching 0.4% (14 tonnes) of total active ingredient used per annum if household rodenticides are included. Even though NZ is the largest user of 1080 in the world, the amount of active ingredient used per year is approximately 1.0–3.5 tonnes (Innes and Barker 1999), which is less than 0.1% of the total pesticide active ingredient used per annum in NZ.

In the USA vertebrate pesticides also constitute a low volume of use compared to insecticides, fungicides and herbicides. For example, the EPA has reported that total use of pesticides in the USA was approximately 544 million kg (1.2 billion pounds) in 2001 (EPA 2004b). Fungicide use was 6% of the total (33 million kg), herbicide use was 46% (250 million kg), insecticide use was 9% (48 million kg), and other pesticide use was 39% (214 million kg). The category 'other' includes conventional pesticides (excluding chlorine hypochlorite, wood preservatives and biocides) (EPA 2004b). In contrast, vertebrate pesticide use is very small. The State of California maintains the most extensive publically available pesticide use reporting system in the USA. Reportable uses include most agricultural and commercial pest control uses; and excludes home and garden uses, and most industrial and institutional uses. In 2001, California reported 68.5 million kg (approximately 151.1 million pounds) of pesticide active ingredient used (California DPR 2002), or approximately 12.6% of the total EPA estimated pesticide use nation-wide during the same year. In 2006, reported pesticide use in California was 86.0 million kg (approximately 189.6 million pounds) (California DPR 2007). Using the 2006 California data, it is estimated that 30,390 kg (approximately 67,000 pounds) of active ingredient from EPA registered products was used for vertebrate control, or $<0.04\%$ of the total State-wide reportable pesticide use. While California may or may not be representative of the US as a whole, these data indicate that the proportion of pesticide application targeting vertebrates is extremely small.

At a practical field application level the target pest density of weeds and pests for common agrochemicals is far greater than the pest density for vertebrate pests e.g. voles on farmland in the USA, feral cats and foxes in Australia or possums in NZ, which might number 3–15 per ha. There are key differences in amounts used, use patterns and delivery systems for conventional agrochemicals versus vertebrate pesticide products which target terrestrial mammals (including invasive species). Vertebrate pesticides are rarely used to control pest animals in food crops. Agrochemicals are frequently delivered as sprays whereas vertebrate pesticides are usually applied in solid or paste baits, and often by discrete application methods. And, when

vertebrate pesticides are used in agriculture they are rarely applied directly to food crops.

Because different deployment methods are used, a different risk picture emerges for various application techniques, which range from discrete ground control in baits in secure bait stations, using specially designed baits eaten by individual pests, versus agrochemicals that are sprayed over wide areas. On the occasions that vertebrate pesticide products are applied from the air, the amounts of active ingredient used are small. For example approximately 5–10 g/ha of 1080 is used when aerial baiting inaccessible bush in NZ for possums, and rates of anticoagulants used in the USA for rodent eradication projects on islands can be as low as 0.45 g/ha.

Delivery and formulation considerations can eliminate a significant amount of risk, as can stringent occupational health and safety protocols, and should be given a greater weighting in vertebrate pesticide risk assessment, just as risk versus benefit is taken into account in the registration process. For example in NZ, introduced stoats are devastating native flightless birds, including the iconic kiwi (*Apteryx* spp.) whose numbers have been declining throughout the country (Innes and Barker 1999). Killing stoats with poisoned baits in custom-designed bait stations in remote NZ forest ecosystems obviously presents different risk benefit scenarios from spraying insecticides and herbicides on food crops. The USA pesticide regulations already require EPA to conduct a risk benefit analysis as an element of the product registration process and a similar process is followed by ERMA, which includes a tiered approach to assessing changes in the risk profile of a substance linked to the application method.

6. Use pattern as a basis for assigning science-based data requirements

In this section a hierarchy or sliding scale of typical data requirements is presented relative to vertebrate pesticide application techniques to help clarify an evolving approach. So far in this paper we have focused on vertebrate pesticides which are delivered using baits. At this stage we include other wildlife management tools mentioned in Table 1, as well as agrochemicals for comparative purposes to aid in the development of a hierarchy of data requirements (see Table 2). A full list of all possible studies required for the registration of a new agrochemical to be used on food crops is provided in Table 3 for reference. This listing is recognized as being well beyond the scope of requirements for vertebrate pesticides.

The precise and full list of studies required for vertebrate pesticides in any particular application technique is difficult to define; although some studies are overtly essential others are not, and a degree of discretion and expert judgment is necessary. The US EPA has previously demonstrated such discretion (Fagerstone and Schafer 1998). In the preparation of this summary table we have considered the actual datasets (i.e. lists of completed studies) required by different New World registration authorities and have identified those areas where there is minimal flexibility and requirements are prescriptive (e.g. chemistry and manufacturing), and those where there is more flexibility (e.g. ecotoxicology and environmental fate). We have attempted to capture and list rational science-based requirements for different agents and use patterns. The data requirements are tailored according to the intended 'use pattern' (e.g. ground versus aerial application) which were consistent with our collective experience in vertebrate pesticide registration. The tabulation in Table 2 seeks to focus attention on the types of studies needed, and highlight those that have real merit for a particular use pattern.

By comparing the requirements for an aerially applied insecticide at one end of the scale with the requirements for contraceptive vaccines at the other, we are able to assign data requirements for other use patterns between these two extremes. Examples of considerations when developing Table 2 are as follows:

- Forcing products into agrochemical models when the use pattern, delivery and formulations do not fit is not science based.
- Toxicology data will be required for all agents for worker protection in manufacturing plants. Hence, all delivery mechanisms (except injectable) begin with some requirement for acute and chronic toxicity. However, the depth of chronic data requirements will vary.
- Acute toxicity is less relevant for fertility control agents especially when the compounds are native to the target organism and non-target species (e.g. proteins such as GnRH, which are non-toxic irrespective of concentration).
- Toxicities associated with impurities in an active ingredient may not be required to the same level of scrutiny as for a veterinary drug or a pesticide that may enter the food chain if the active is contained in a bait station or similar.
- Terrestrial invertebrate risk from underground baiting or bait stations is minimal and localized, and waivers for ecotoxicity and fate data are appropriate.
- Bait station use also limits the need for extensive terrestrial plant and animal toxicology, and obviates the need for aquatic toxicity studies (unless the bait stations are used in sewers).
- Chronic terrestrial non-target data requirements are less relevant where vertebrate pesticides are used infrequently, such as in Australia and NZ.
- Island conservation uses or other single application scenarios present a unique risk picture. Chronic data requirements are not appropriate because of the duration of exposure, whereas

Table 2. Proposed data needs relative to different pesticide application techniques. The number of plus signs indicates the relative importance.

	Aerial broad-spectrum insecticide	Aerial broad cast bait	Ground broad cast bait	Exposed (spot) bait	Open bait station	Enclosed bait station	Underground bait application	Burrow fumigants	Injectable contraceptive vaccine
Product chemistry									
Product components and manufacture	+++	+++	+++	+++	+++	+++	+++	+++	+++
Analytical methodology	+++	+++	+++	+++	+++	+++	+++	+++	+++
Physical characteristics	+++	+++	+++	+++	+++	+++	+++	+++	+++
Product performance									
Laboratory efficacy	+++	+++	+++	+++	+++	+++	+++	+++	+++
Field efficacy	+++	+++	+++	+++	+++	+++	+++	+++	+++
Worker protection									
Exposure monitoring	+++	+++	+	+	+	+	+	+	
Toxicology									
Acute toxicity	+++	++	++	++	++	++	++	++	+
Sub-chronic toxicity	+++	++	++	++	++	++	++	++	+
Chronic toxicity	+++	++	+	+	+	+	+	+	
Genotoxicity	+++	++	++	++	++	++	++	++	
Terrestrial vertebrate non-target organisms									
Acute	+++	+++	++	++	++	+	+	+	
Chronic	+++	+							
Terrestrial invertebrate non-target organisms									
Acute	+++	++	+	+	+				
Chronic	+++								
Fate									
Terrestrial mobility and biodegradation	+++	++	++	++			++		
Aquatic mobility and biodegradation	+++	+		+			+		
Residue chemistry									
Food or feed tolerance	+++	++	++						
Aquatic freshwater non-target organisms (invertebrate and vertebrate)									
Acute	+++	++							
Chronic	+++								
Aquatic marine non-target organisms (invertebrate and vertebrate)									
Acute	+++								
Chronic	+++								
Non-target plants									
Acute toxicity	+++								
Spray drift	+++	+							

Table 3. Registration studies for agrochemicals and typical costs from contract facilities in Europe and the USA (Bennet 2008).

	Registration only in EU	Registration only in USA	Registration in EU and USA
1. Identity of the active substance			
Analytical profile of batches (5-Batch Analysis)	$30,000	$30,000	$30,000
2. Physical and chemical properties of the active substance			
Melting point/freezing point	$2,000	$2,000	$2,000
Boiling point	$2,500	$2,500	$2,500
Relative density	$2,000	$2,000	$2,000
Vapour pressure	$11,000	$11,000	$11,000
Volatility (Henry's law constant)	$42,000	$42,000	$42,000
Colour, physical state	$1,100	$1,100	$1,100
Odour	$500	$500	$500
UV/Vis spectra	$4,000	$4,000	$4,000
IR, NMR, MS spectra	$10,000		$10,000
Solubility in water including effect of pH (4 to 10) on solubility	$8,000	$8,000	$8,000
Solubility in organic solvents including effect of temperature on solubility	$10,000	$10,000	$10,000
Partition coefficient n-octanol/water including effect of pH (4 to 10)	$8,000	$8,000	$8,000
Hydrolysis	$40,000	$40,000	$40,000
Direct phototransformation if e > 10 at l > 290 nm	$75,000	$75,000	$75,000
Quantum yield of direct phototransformation	$25,000	$25,000	$25,000
Dissociation constant in water (pKa) (OECD 112)	$7,500		$7,500
Stability in air, photochemical degradation, identity of breakdown product(s)	$75,000	$75,000	$75,000
Auto-flammability of liquids	$1,860		$1,860
Flash point (2 tests, a.s. and formulation)	$2,500		$2,500
Explosive properties	$3,000		$3,000
Surface tension if solubility > 1 mg/L	$1,200		$1,200
Oxidizing properties	$5,000		$5,000
1-Yr shelf-life study included in phys-chem		$10,000	
2-Yr shelf-life study included in phys-chem	$10,000		$10,000
Radiolabelled material preparation	$50,000	$50,000	$50,000
3. Analytical methods			
Determination of pure active substance in technical product		$5,000	$5,000
Determination of pure active substance in technical product : ILV	$5,000		$5,000
Determination of significant/relevant impurities and additives in technical product			
Residues in and/or on plants	$20,000	$20,000	$20,000
Inter-Laboratory Validations (ILV) Methods	$20,000		$20,000
Residues in soil	$25,000		$25,000
Residues in water	$25,000		$25,000
Residues in air	$25,000		$25,000
4. Toxicological and metabolism studies on the active substance			
Comparative metabolism	$500,000		$500,000
Acute skin sensitization (Buehler – USA; Magnusson and Klingman – EU)	$4,000		$4,000
Oral 90-day study rat	$200,000		$200,000
Oral 90-day study dog	$309,000		$309,000
Multi-generation studies = 2 generation rat/inhalation	$1,200,500	$1,200,500	$1,200,500

(*continued*)

Table 3. (*Continued*).

	Registration only in EU	Registration only in USA	Registration in EU and USA
90 days subchronic neurotox inhalation		$450,000	$450,000
Plant Metabolism	$200,000	$200,000	$200,000
Animal Metabolism (Goat)	$200,000	$200,000	$200,000
Supplementary studies on the active substance (Cattle Feeding, etc.)	$450,000	$450,000	$450,000
5. Residues in or on treated products, food and feed	$500,000		$500,000
6. Fate and behaviour in the environment			
Aerobic degradation for EU (route and rate)	$150,000		$150,000
Aerobic degradation for USA (final phase)		$100,000	$100,000
Anaerobic degradation (route and rate)	$80,000	$150,000	$150,000
Soil photolysis		$75,000	$75,000
Field dissipation (2 sites USA)		$600,000	$600,000
Adsorption and desorption	$60,000		$60,000
'Ready biodegradability'	$60,000		$60,000
Route and rate of degradation in air (as far as not covered by point 2.10)	$800,000		$800,000
7. Ecotoxicological studies on the active substance			
Acute toxicity to birds by inhalation (2 species for EU, 1 for USA)	$183,000	$91,500	$183,000
Subchronic toxicity to birds and reproduction/inhalation (2 species)	$250,000		$250,000
Acute toxicity to fish	$35,200	$35,200	$35,200
Acute toxicity to aquatic invertebrates	$15,000	$15,000	$15,000
Effects on algal growth	$11,000		$11,000
Acute toxicity to bees	$40,000		$40,000
Other arthropods (2 species min)	$80,000		$80,000
Acute toxicity to earthworms	$8,000		$8,000
Sublethal effects to earthworms	$25,000		$25,000
Probable study of recolonisation in the field (cost per 2 sites)	$60,000		$60,000
Effects on soil non-target micro-organisms	$22,000		$22,000
Effects on other non-target organisms (litter bag)	$45,000		$45,000
Effects on biological methods for sewage treatment	$6,500		$6,500
	$6,500		$6,500
8. Other: consultancy ...			
Water/Air modelling USA		$100,000	$100,000
Study monitoring costs USA		$50,000	$50,000
Regulatory costs USA		$650,000	$650,000
Regulatory costs EU submission	$450,000		$450,000
Regulatory costs EU Member states	$500,000		$500,000
Monitoring costs EU (for 5-year program)	$528,000		$528,000
Redaction of the dossier	$100,000		$100,000
E-fate modelling	$30,000		$30,000
Special studies		$75,000	$75,000
Total	$7,649,360	$4,863,300	$9,824,360

repeated aerial applications in an agricultural field may lead to situations where repeated or chronic exposures may be a real possibility.

We recognize that exposure is not the only concern regarding pesticide use. Both exposure and toxicity are factors in assessing risk. However, our premise is that delivery and formulation (including worker protection) considerations can eliminate a significant amount of environmental and human health exposure, thus reducing risk. Therefore, product delivery and formulation must be given appropriate consideration in vertebrate pesticide product registration. This is best conceptualized as a balance between inherent hazards presented by the active ingredient and the delivery method, illustrated by comparative exposure risk associated with an aerial application of a pesticide versus a bait station application of a rodenticide.

Formulation is a key part of risk mitigation, as vertebrate pesticide products can be designed to be safe to handle and to be attractive to target individual pest animals rather than to non-target species (Cowled et al. 2006b). Delivery systems that facilitate contact with target species and minimize non-target species exposure are critical. Hence evidence of an understanding of the ecology and behaviour of pest animals and non-target wildlife is important. As mentioned earlier, in New Zealand stoats are devastating native flightless birds, whose numbers are falling throughout the country (Innes and Barker 1999). Killing stoats with baits in bait stations (Parkes and Murphy 2004) not only presents quite different risk benefit scenarios from conventional agrochemicals but is also unique, as the damage caused by the stoat outweighs the real or perceived risks from the toxicant. Without the vertebrate pesticide product, biodiversity is compromised and the native ecosystem is unprotected.

7. Conclusions

We have attempted to consolidate a science-based strategy for the application of different data requirements for vertebrate pesticide products. Registration requirements for common herbicides and insecticides have been developed to target broad-scale applications of these agrochemicals sprayed onto food crops. Although the core components of registration dossiers are similar for agrochemicals and vertebrate pesticides, different data requirements for the latter have evolved in recognition of the relatively small amounts and discrete application methods used. However, in areas such as toxicology, ecotoxicology or environmental toxicology and fate there is still a need for greater flexibility and the opportunity to link data requirements to how the products are used. In-depth ecotoxicology data, such as aquatic and plant non-target toxicity and some terrestrial non-target and fate studies are deemed of limited or no value when baits are used in secure bait stations. Field observation of non-target species interaction with the baits and bait stations is recognised as having greater value than completing a checklist of GLP studies for potential non-target species. Hence, we have defined a hierarchy or sliding scale of data needs in this paper relative to vertebrate agent application techniques to help clarify an evolving science-based approach which is being adopted for the registration of vertebrate pesticides. An emphasis on risk assessment linked to the likelihood of exposure that still provides for human health and environmental safety is a rational development.

Product innovation needs to be stimulated to encourage alternatives to the current suite of vertebrate pesticides, as a number of these are associated with secondary poisoning or bioaccumulation or they are viewed as inhumane (Mason and Littin 2003; Sherley 2007). The value of this review paper is in drawing attention to the ultimate registration requirements for different types of products and applications. We have sought to go beyond describing some of the impediments to re-registration of existing products and new product applications, and sought to provide some clearer guidance and recommendations for registration data requirements. Ideally researchers need to work more closely with regulators, without compromising scientific integrity, to ensure that vertebrate pest product registrations are not stifled to the detriment of agriculture and the environment.

The progression of product development is also often aggravated by a lack of understanding amongst research providers and scientists with regard to data requirements and the registration processes for vertebrate pesticides. Research groups must be aware of the generic guidelines cited above, as too often effective vertebrate pesticide products are developed that have never been submitted for registration due to the uncertainty over data requirements and product responsibilities. However, there is a huge difference between being aware of these guidelines and focusing research on what is essential, having defined a complete and concise list of data requirements and study types that will enable a new product to achieve full registration approval in a timely manner. Research groups frequently focus on efficacy and insufficient attention is given to the chemistry and manufacturing dossiers which are the platform for a successful registration. It is hoped that this paper might inform researchers and form the basis for future discussion with regulatory agencies who are increasingly applying tiered approaches to assessing risk profiles based on the method of application of different vertebrate pesticide formulations.

In the New World and Australasia there is an emphasis on retaining the best of existing vertebrate pesticides whilst at the same time seeking to develop improved actives, in contrast with the EU which is retaining only anticoagulants.

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