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SECONDARY AND TERTIARY POISONING RISKS ASSOCIATED WITH BRODIFACOUM

Summary: The field use of brodifacoum baits (Talon® and Pestoff®) to control brushtail possums (*Trichosurus vulpecula*) has increased in recent years. This has raised concerns of secondary and tertiary poisoning, resulting from the transfer of this toxicant through the food chain. In New Zealand, feral pigs (*Sus scrofa*) are known to scavenge possum carcasses and may also gain access to bait stations containing possum baits. We have determined the concentrations of brodifacoum in muscle and liver tissue from captive pigs after primary and secondary poisoning. Highest concentrations were found in the liver. Pigs eating 500 to 1776 g of brodifacoum bait containing 20 mg kg^{-1} had muscle concentrations ranging from 0.02 to 0.07 mg kg^{-1} and liver concentrations ranging from 0.72 to 1.38 mg kg^{-1} . Both appeared to be independent of the amount of bait eaten. Possums fed 400 g of bait had similar liver concentrations (0.52–1.20 mg kg^{-1}). Pigs that had eaten the soft tissue from eight poisoned possums had brodifacoum concentrations of 0.32 to 0.80 mg kg^{-1} present in the liver and the concentration increased in a dose-dependent manner. Brodifacoum was detected in muscle from only one of these animals. In a preliminary field survey, 11 of 21 wild pigs sampled from areas where possum control had been undertaken were contaminated with brodifacoum concentrations in the liver ranging from 0.007 to 1.7 mg kg^{-1}. In view of the potential impact on pig hunters and dogs consuming wild pig meat and offal, some restrictions on the wide-scale field use of brodifacoum baits appears to be warranted.

Keywords: Anticoagulant; baits; non-target species; pigs; possums.

Introduction

Brodifacoum (3- [3-(4' - bromobiphenyl-4-yl) -1, 2, 3,4- tetrahydro-1-naphthyl] -4- hydroxycoumarin), is a potent, second-generation, anticoagulant rodenticide developed in the mid-1970s, which causes concern because of its extreme persistence in target and non-target species (Eason, Wright and Batcheler, 1996). It has been used with success in recent rodent eradication programmes on New Zealand's offshore islands to protect populations of endangered indigenous birds (Taylor and Thomas, 1993; Buckle and Fenn, 1992; Robertson, Colbourne and Nieuwland, 1993; Towns, McFadden and Lovegrove, 1993). In addition to its world-wide use to control and eradicate rats, brodifacoum has also been used to eradicate rabbits (*Oryctolagus cuniculus* L.) from offshore islands (Merton 1987; Towns *et al.*, 1993). It is now commonly used in New Zealand to control brushtail possums (*Trichosurus vulpecula* Kerr) (Eason *et al.*, 1993).

Brodifacoum differs markedly in its mode of action when compared to the fast-acting toxins, such as sodium monofluoroacetate (1080) or cyanide, since possums may take 3 or more weeks to die after eating a lethal dose of brodifacoum bait (Eason *et al.*, 1994). The reported LD$_{50}$ for brodifacoum in possums is 0.17 mg kg^{-1} (equivalent to 20 g of bait containing 20 mg kg^{-1} for a 2–3 kg possum) (Godfrey, 1985). However, because of the slow onset of action of brodifacoum, some possums will eat more than 1 kg of bait before dying, which can make the use of brodifacoum expensive compared with 1080 (Eason *et al.*, 1994; Henderson *et al.*, 1994). Nevertheless, this toxicant can be cost-effective when used after 1080, cyanide, or trapping, to maintain possum numbers at very low levels.

During the last 2 or 3 years there has been an increasing use of cereal bait containing 20 mg kg^{-1} brodifacoum (Talon® and Pestoff®) for killing possums. The difficulties with using 1080, including the increasing public concerns and the legal consents process and notifications required before using 1080, are probably contributing to this increased user-preference for brodifacoum bait.

This wide-scale field use of brodifacoum in New Zealand is in itself unusual: in the USA and UK, the toxicant is used only for commensal rodent control (A. Buckle, *pers. comm.*). Even this comparatively restricted use, around farm buildings, causes concern in regard to secondary poisoning of birds and mustelids (Duckett, 1984; Hegdal and Colvin, 1988; Newton, Wyllie and Freestone, 1990; Colvin, Jackson and Hegdal, 1991).

The toxicology of brodifacoum and the species at risk from primary and secondary poisoning in New Zealand have been reviewed elsewhere (Eason *et al.*, 1993; Eason and Spurr, 1995). The acute toxicity of brodifacoum in birds varies from an LD_{50} of <1 mg kg^{-1} in pukeko (*Porphyrio p. melanotus* Temminck) to >20 mg kg^{-1} in paradise shelduck (*Tadorna variegata* Gmelin). In several species of mammals, including rodents, pigs and possums, the LD_{50} is < 0.4 mg kg^{-1}. Because of its toxicity, all vertebrates that eat baits or poisoned prey containing brodifacoum residues are at risk, including humans. There are numerous documented cases of deliberate or inadvertent poisoning of humans (Barlow, Gay and Park, 1982; Jones, Groew and Naiman, 1984; Lipton and Klass, 1984; Chong, Chan and Ho, 1986; Hoffman, Smilkstein and Goldfrank, 1988; Weitzel *et al.*, 1990; Wallace *et al.*, 1990; Kruse and Carlson, 1992; Tasheva, 1995). For example, in one fatal incident villagers in South Sumatra, Indonesia, used a 50 ppm brodifacoum rice grain bait as a food source. They attempted to remove the rodenticide by repeated washing, rinsing, and cooking before eating the rice. Because of the delay in the appearance of symptoms, it appeared to the villagers that they had been successful, thus encouraging others to eat the rice, resulting in several deaths (Tasheva, 1995).

To date there are no recorded incidents of humans being poisoned after eating contaminated meat. However, a risk exists which is compounded by the unusual persistence of this toxicant and other second generation anticoagulants in vertebrate species compared with first generation anticoagulants (Parmar *et al.*, 1987), or most other xenobiotics which are usually excreted in a matter of hours or days (Eason, Bonner and Parke, 1990), rather than weeks or months. For example, brodifacoum has been shown to persist in the liver of sheep (*Ovis aries* L.) for 16 weeks (Laas, Forss and Godfrey, 1985) and possums for 9 months (Eason, *et al.,* 1996), respectively. However, little consideration has been given to the potential dangers to humans arising from brodifacoum residues in possum carcasses, or to other wildlife, including game species. Pigs are one of a number of species that may scavenge possum carcasses, and possums dying up to 1 year after being exposed to sublethal amounts of brodifacoum will contain residues, particularly in the liver, which could be transferred through the food chain (Eason, *et al.,* 1996).

In this paper we report our findings on the concentration of brodifacoum in pig serum and tissue (liver and muscle) after the primary poisoning and secondary poisoning of captive pigs. The risks of secondary poisoning to humans and pets associated with brodifacoum use in New Zealand are discussed alongside some preliminary data from samples taken from feral pigs.

Method

Standard Pestoff® possum bait containing 20 mg kg^{-1} brodifacoum and a fortified bait containing 100 mg kg^{-1} brodifacoum were obtained from Animal Control Products, Wanganui. Possums were captured from the wild, housed singly in cages and fed cereal pellets and vegetables with water available *ad libitum*. Domestic pigs (weighing between 17 and 28 kg) were obtained from a local breeder and penned in groups of four on a concrete floor covered with straw. Pigs were fed twice daily with weaner pig pellets (Archers, Rangiora) and greens, and offered water *ad libitum*. This investigation was carried out with the approval of the Landcare Research Animal Ethics Committee.

Primary poisoning of pigs

Sixteen pigs held in captivity were divided into four groups of four each. Group 1 received non-toxic pellets; Group 2 were fed 500 g (± 31.2 g), Group 3 were fed 937 g (± 34.2 g), and Group 4 were fed 1776 g (± 81.4 g) of brodifacoum bait, respectively. All groups were fed the pellets over a 2-day period. Pigs in the medium and high dose groups received between 5 and 200 g of fortified (i.e., 100 mg kg^{-1}) brodifacoum on the second day to elevate total intake to the required levels and minimise the within-group variation in the amount of brodifacoum ingested. The rationale for the dosages used is as follows. The published LD_{50} values for brodifacoum in pigs vary from 0.1 mg kg^{-1} (Godfrey, 1985) to 0.5–2.0 mg kg^{-1} (Dublock and Kaukeinen, 1978). Since possum baits contain 20 ppm (or 20 mg kg^{-1}), a 20-kg pig would need to eat 1 kg of bait to ingest 1 mg kg^{-1} of brodifacoum, which would be approximately equivalent to an LD_{50} dose. Half this would be approximately an LD_{25} dose, and double this would be approximately equivalent to an LD_{90}. Furthermore, these amounts could approximate the quantity of bait wild pigs might readily obtain if they fed directly from possum bait stations. Some of these would be expected to survive, and even those eating lethal amounts of bait could be hunted and eaten prior to the toxicant taking effect.

All the pigs were humanely killed 5 days after they had started eating toxic bait, prior to the onset of major clinical signs associated with anticoagulant toxicosis. Serum, liver and muscle tissue (hind limb) samples were taken and stored at -20°C until analysis.

Secondary poisoning experiment

Fifty possums were offered standard brodifacoum bait (20 mg kg^{-1}) for 4 days to achieve an average of 400 g intake per possum. A small percentage of possums were offered fortified brodifacoum (100 mg kg^{-1}) on the fourth night to minimise the variation in the amount of brodifacoum ingested. The possums were humanely killed 5 days after they had started eating bait, samples of liver and hind limb were taken from six possums and retained at -20°C until analysis.

Edible soft tissue from the possum preferred by pigs, including liver, kidney, heart, and muscle, and portions of the small intestine, were retained.

Another sixteen pigs were divided into five groups and fed possum tissue over a 2-day period. Group 1 were fed possums that had not been dosed with brodifacoum (n=4). Pigs in Group 2 were each fed soft tissue from one poisoned possum carcass each (n=3). Pigs in Group 3 were each fed soft tissue from two poisoned carcasses (n=3), pigs in Group 4 were each fed soft tissue from four carcasses (n=3), and pigs in Group 5 (n=3) were each fed soft tissue from the equivalent of eight possum carcasses each. Five days after the pigs had first started eating the possum meat and organs, they were humanely killed. Liver and hind limb samples were taken and stored at -20°C.

Field survey of feral pigs

Samples of liver were collected from 20 feral pigs that were shot and from one pig found dead in areas where brodifacoum was currently in use for possum and rat control. All samples were stored frozen at -20°C.

All analyses, on the baits used and on the liver and muscle tissue, were undertaken by high-performance liquid chromatography with fluorescence detection using published methods for determining brodifacoum residues (Hunter, 1983).

Statistics

Differences in group mean concentrations of brodifacoum in liver, muscle and serum were tested using analysis of variance (ANOVA). Significant effects were further investigated using Bonferoni adjusted pairwise comparisons. The data were square root transformed to meet assumptions of the analysis. Where the data could not be transformed to meet the assumptions of ANOVA, Kruskal-Wallis tests were used.

Results

The standard possum baits used in these studies had a concentration of 21.4 mg kg^{-1} which was close to the nominal concentration of 20 mg kg^{-1}, and fortified bait was confirmed to contain 100 mg kg^{-1}.

Primary poisoning of pigs

The concentration of brodifacoum in the livers and muscle of pigs that had eaten toxic bait appeared to be independent of the amount of bait eaten over the range 500 to 1776 g per pig. Serum concentrations of brodifacoum appear to increase with increasing dosage, but this was not a statistically significant increase. The concentration of brodifacoum in the liver was over 20 times that in the muscle (Table 1).

Secondary poisoning of pigs

Possums ate an average 388 ± 41.5 (S.E.) g of bait [or 3.12 ± 0.09 (SE) mg kg^{-1} of brodifacoum] over 4 nights. The concentration of brodifacoum in the possum tissues fed to pigs varied from 0.84 mg kg^{-1} (range 0.52 to 1.20) in the liver to 0.065 mg kg^{-1} (range 0.013 to 0.094) in the muscle.

Table 1: *The average amount of Pestoff® bait eaten (g/Pig ± S.E.) and corresponding average dose of brodifacoum (mg kg^{-1} ± S.E.) and the concentration of brodifacoum in pig liver, muscle and serum (mg kg^{-1} ± S.E.). * Denotes some low level exposure in control pigs that escaped and ate some toxic bait before recapture.*

Group	Bait eaten	Brodifacoum ingested (mg kg^{-1})	Mean concentration ± S.E.		
			Liver[+]	Muscle[+]	Serum
1	Control non-toxic	0 negligible*	0.04 ± 0.02*	0	0
2	Pestoff® 500 g/pig (± 31.2 g)	0.57 ± 0.06	1.13 ± 0.07	0.05 ± 0.006	0.17 ± 0.06
3	Pestoff® 937 g/pig (± 34.2 g)	0.96 ± 0.03	1.08 ± 0.14	0.05 ± 0.01	0.25 ± 0.04
4	Pestoff® 1776 g/pig (± 81.4 g)	1.94 ± 0.09	1.05 ± 0.06	0.05 ± 0.003	0.38 ± 0.06

[+] concentrations in muscle range from 0.02 to 0.07 and in liver from 0.72 to 1.38 mg kg^{-1}

The concentration of brodifacoum in the liver of pigs that ate the soft tissues from poisoned possums increased in a dose-dependent manner, ($H_4 = 14.045$, $P = 0.007$) with the highest concentrations present in pigs that had eaten the soft tissue and muscle from eight possums (Fig. 1). The concentration of brodifacoum in serum and in pig muscle tissue was below the limit of detection except for one animal, which had a concentration of 0.01 mg kg^{-1} in muscle (and 0.8 mg kg^{-1} in the liver). The liver concentration of 0.8 mg kg^{-1} was the highest detected in this group of pigs.

Field survey of feral pigs

Ten out of 21 pigs (approx. 50%) were not contaminated. The remaining 11 pigs, including one which was found dead, were found to be contaminated with brodifacoum at concentrations ranging from 0.007 to 1.7 mg kg^{-1} (Table 2). Only three of the contaminated pigs contained liver concentrations of brodifacoum less than 0.1 mg kg^{-1}.
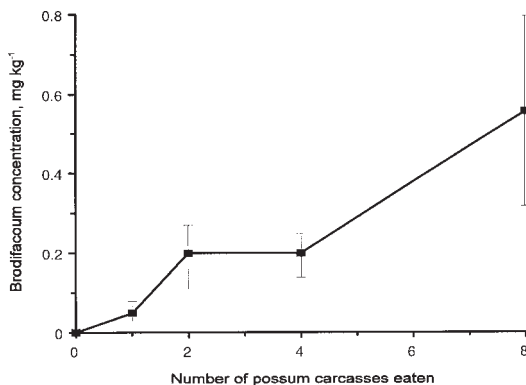

Figure 1: *Brodifacoum concentrations (mg kg^{-1}) in pig liver 5 days after eating possum tissues. Range is presented as bars (in preference to S.E.) as these data do not assume a normally distributed error.*

Discussion

The presence of high liver concentrations of brodifacoum in pigs highlights the potential secondary and tertiary risks associated with brodifacoum. It is apparent that pigs scavenging dead possums (or rats) are at risk of poisoning and subsequent transfer of brodifacoum residues on to humans, particularly if people eat the livers of feral pigs. These risks are compounded by the unusual persistence of brodifacoum and will be heightened in people who repeatedly eat possums or pigs. Such multiple exposures of second-generation anticoagulants are most likely to lead to accumulation in the liver of any vertebrate species. To date, we have such information only from rats (Huckle, Hutson and Warburton, 1988).

Our studies with captive animals have demonstrated the presence of low levels of residues in muscle tissue in possums and pigs albeit at concentrations about 20 times lower than those found in the liver. Even if brodifacoum use were to cease immediately, it could persist in the food-chain for several years, hence a sensible precaution to reduce risk to humans would be to recommend to hunters that the liver from all game be discarded.

In an earlier paper (Eason, Wright and Batcheler 1996) we reported mean liver concentrations of approximately 0.1 mg kg^{-1} in possums after administration of 0.1 mg kg^{-1} brodifacoum, which persisted in possum liver for the 9-month duration of the experiment. This concentration was associated with bleeding disorders and death in two out of 36 possums. In the feral pig survey, only three of the 11 contaminated animals had concentrations in the liver of <0.1 mg kg^{-1}. It is difficult to predict whether pigs or humans would respond similarly. In risk assessment a precautionary approach is normal, hence we should assume that concentrations of ≥0.1 mg kg^{-1} are of considerable concern in any non-target species. In our earlier paper on this issue (Eason, *et al.,* 1996) we estimated, based on an LD$_{50}$ value of 3.5 mg kg^{-1} for brodifacoum in dogs, that a 15-kg dog would need to eat 500 kg of possum liver to receive a lethal dose of brodifacoum. However, we have since found a wide range of literature values for

Table 2: *Brodifacoum concentrations (mg kg^{-1}) in the livers of feral pigs and number contaminated over the range 0 to 2 mg kg^{-1}*

Range (mg kg^{-1})	Number of pigs	Actual liver concentration (mg kg^{-1})
0	10	–
0 – 1.0	8	0.007, 0.009, 0.04, 0.13, 0.15, 0.21, 0.24, 0.31
1.0 – 2.0	3	1.09, 1.6, 1.7[+]

[+] found dead, all other samples taken from shot pigs.

the LD_{50} of brodifacoum in dogs (0.25 to 3.25 mg kg^{-1}) (Hone and Mulligan,1982). Taking a more conservative figure (LD_{50} 0.25 mg kg^{-1}), a 15-kg dog would need to eat 37.5 kg of possum liver containing 0.1 mg kg^{-1}, or 3.75 kg of liver containing 1 mg kg^{-1}. If the LD_{50} for humans and dogs is similar (and for most species the LD_{50} is <1 mg kg^{-1}), a 60-kg man would need to eat approximately 15 kg of liver containing 1 mg kg^{-1} to receive an LD_{50} dose, assuming the LD_{50} for brodifacoum in humans is similar to that in dogs.

In overseas studies, liver concentrations of 1.0 to 1.9 mg kg^{-1} brodifacoum were commonly found in rats. However, concentrations between 2 and 5 mg kg^{-1} occurred with a lower frequency and, in some instances, concentrations of > 7 mg kg^{-1} of brodifacoum in rat liver were detected (Brown, 1994). Repeated dose studies in rats with flocoumafen (another second-generation anticoagulant closely related to brodifacoum) have demonstrated that concentrations in the liver of rats can reach a maximum of 3-5 mg kg^{-1}, at which time lethal anticoagulant effects occur in most animals (Huckle *et al.*, 1988).

In our study the concentration of brodifacoum showed a dose-dependent increase in pigs that consumed possum tissue containing brodifacoum concentrations of < 1 mg kg^{-1}. No dose-dependent increase was observed in pigs receiving larger amounts of bait over 2 days. This is likely to be due to short-term saturation of absorption or binding processes, and does not preclude the potential for further accumulation in the liver on repeated exposure, which would reduce the amount of liver a dog or human would have to eat to receive a toxic dose of brodifacoum.

We believe the levels of brodifacoum present in pig livers could represent a risk to humans as well as to other predators and to farm dogs; this risk is magnified by the persistence of the compound, which could lead to accumulation on repeated exposure. In this regard it is important to remember that a sublethal dose well below the LD_{50} will produce significant clotting abnormalities and some haemorrhaging (Eason, *et al.,* 1996). Humans that are already on antithrombotic therapy (e.g., warfarin treatment or aspirin) may be at special risk because of possible adverse drug interactions.

In the absence of more extensive field data, some restrictions on the wide-scale use of brodifacoum baits appears warranted particularly in areas where game, including possums, might be eaten by humans. To date, the highest known concentration of brodifacoum in the liver of wild pigs is 1.7 mg kg^{-1}. This finding, and the detection of brodifacoum residues in a range of wildlife including native birds such as kiwi (Robertson *et al.* 1999), raises serious concerns about the long-term effects of broad-scale field use of brodifacoum in New Zealand.

Acknowledgements

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