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NON-TARGET AND SECONDARY POISONING RISKS ASSOCIATED WITH CHOLECALCIFEROL

C.T. EASON[1], M. WICKSTROM[2], R. HENDERSON[3], L. MILNE[1] and D. ARTHUR[4]

[1]*CENTOX Centre for Environmental Toxicology, Landcare Research, PO Box 69, Lincoln 8152, New Zealand*
[2]*University of Saskatchewan, 44 Campus Drive, Saskatoon, SK S7N 5B3, Canada*
[3]*Drains Road, Leeston, New Zealand*
[4]*Labworks Laboratory, PO Box 113, Lincoln University, Lincoln, New Zealand*

ABSTRACT

In New Zealand cholecalciferol-containing baits are used for possum and rodent control. We have assessed the primary and secondary non-target hazards associated with these baits. At 2000 mg/kg cholecalciferol had no adverse effects in ducks, but some chickens and canaries died. Weta and weka were not affected by eating bait containing cholecalciferol. In secondary poisoning studies most dogs and cats fed carcasses of possums poisoned with cholecalciferol were unaffected, but repeat exposures for 5 days induced some reversible signs of toxicosis in dogs. The most distinguishing feature of cholecalciferol is a lower risk of secondary poisoning when compared with 1080 and brodifacoum.

Keywords: vertebrate pesticide, cholecalciferol, non-target species, risk assessment.

INTRODUCTION

Cholecalciferol (Vitamin D3) was first used as a rodenticide in the 1980s (Marshall 1984). It was initially registered in the USA. In Europe it has been added to baits (containing first-generation anticoagulants) to overcome anticoagulant resistance in rats and mice (Tobin *et al.* 1993; Pospischil and Schnorbach 1994). In 1995 a cereal-based pellet containing cholecalciferol was registered for the control of brushtail possums (*Trichosurus vulpecula*) in New Zealand. Possum baits contain cholecalciferol at 0.8%, approximately 10 times more active ingredient than in rodenticide formulations, to compensate for possums' larger sizes (Eason 1991).

Animals that ingest a lethal dose of cholecalciferol bait die usually within 4–7 days. Clinical signs commonly expressed include loss of appetite, constipation, lethargy and death. In order to gain biological and toxicological activity, cholecalciferol must undergo metabolic conversion to 25-hydroxycholecalciferol (25OHD). At toxic doses 25OHD disrupts calcium homeostasis by increasing its absorption from the small intestine and mobilisation from bones into the blood stream, as well as decreasing calcium excretion by the kidneys (Jolly *et al.* 1993; Beasley *et al.* 1997). Mineralisation and blockage of blood vessels, with death probably from heart failure, appears to be the mode of action of cholecalciferol in rodents and possums (Jolly *et al.* 1993). In other species, including cats and dogs, renal failure (caused by vessel blockage and nephrocalcinosis) and gastrointestinal haemorrhage appear more prominent (Haschek *et al.* 1978; Gunther *et al.* 1988; Moore *et al.* 1988; Jolly *et al.* 1993).

The single-dose LD_{50} for cholecalciferol in Norway rats (42.5 mg/kg) and house mice (43.6 mg/kg) is very similar, but there is some species variation in susceptibility amongst other mammals. Possums and rabbits are particularly sensitive to cholecalciferol (Eason 1991, 1993; Jolly *et al.* 1995). Cholecalciferol has also proved effective in the US in controlling rock squirrels, gophers and ground squirrels (Beard

et al. 1988; Tobin *et al.* 1993), and is currently under investigation in New Zealand for the control of stoats (E.B. Spurr, pers. comm.). Cats are less susceptible than possums, and toxicity is less consistent, with some cats surviving doses up to 200 mg/kg, while others died after doses of 50 mg/kg (Eason 1991). Some fish-eating marine mammals, such as seals, which are exposed to high dietary levels of cholecalciferol, are quite resistant (Keiver *et al.* 1988).

Because vitamin D3 is naturally occurring and involved in calcium homeostasis, there has on occasion been a tendency to consider baits containing cholecalciferol as safe to non-target species. In this paper we report data from acute toxicity studies in non-target species and secondary poisoning assessment in dogs and cats. The later, secondary poisoning builds on earlier work where Marshall (1984) showed no signs of toxicosis in dogs eating rodents killed with baits containing 0.015% cholecalciferol.

METHODS

Non-target acute toxicity

Non-target species were exposed as follows: groups of six mallard ducks (*Anas platyrhyndos*), four domestic chickens (*Gallus gallus*), and four canaries (*Serinus canarius*) were dosed orally with cholecalciferol concentrate at 2000 mg/kg in corn oil. Control groups received corn oil alone. Sixteen weka (*Gallirallus australis*) were allowed to voluntarily ingest bait containing 0.1% cholecalciferol (concentration similar to rodenticide formulations).

Two groups of six ground weta (*Hemideina* spp.) were orally dosed with cholecalciferol concentrate in corn oil at 125 mg/g and 250 mg/g. A control group received corn oil alone. All animals in these acute toxicity studies were observed for 30 days after dosing, and clinical signs of poisoning and mortality noted.

Secondary-poisoning feeding studies in cats and dogs

Possums were chosen for the secondary-poisoning studies because the concentration of cholecalciferol in possum bait is more than 10 times greater than that used for rodents. Hence, possums poisoned with these baits are likely to provide a 'worst-case' scenario in terms of the potential secondary poisoning risks associated with use of rodent baits.

Twelve feral cats were fed whole carcasses of cholecalciferol-poisoned possums as their only food for 5 consecutive days. Appetite and body weight were monitored daily for 63 days, and blood samples were taken at regular intervals for serum calcium measurements, prior to the experiment and after the 5-day treatment period. Further blood samples were taken 1 and 7 weeks after cessation of treatment.

To assess the secondary poisoning risks to domestic dogs in a more comprehensive manner, six groups of dogs were fed tissue from cholecalciferol-poisoned possums or control meat (Table 1). Possums were divided into two groups and given an LD95 dose of cholecalciferol-treated cereal bait. The first group of possums was monitored until death occurred from poisoning (typically within 5–7 days). Dogs fed these carcasses were therefore exposed to the concentration of 25OHD residues usually encountered by scavengers after possum-poisoning operations. In addition, in order to create a worst-case secondary poisoning scenario, a second group of possums was humanely killed 48 h after dosing with cholecalciferol. These carcasses would be expected to contain high levels of tissue 25OHD (Keiver *et al.* 1988; Dougherty *et al.* 1990), plus residual bait material in the gastrointestinal tract. Possums that were used as controls were undosed.

Twenty-two stray dogs, scheduled for euthanasia, were obtained from a pound and allocated to six different treatment groups (see Table 1). Dogs were fed one poisoned carcass for 1, 2 or 5 consecutive days. Control dogs were fed carcasses of undosed possums. Blood samples were collected from all dogs to monitor changes in serum calcium and urea nitrogen. Dogs were humanely euthanased after 14 or 28 days, and subjected to complete post-mortem and histopathological examination. Animal Ethics approval for these studies was obtained from the Landcare Research Animal Ethics Committee.

TABLE 1: Dog treatment groups, animal numbers and mean dog body weights at the onset of dosing.

Treatment	No. of carcasses	Mean body weight (kg)	Sample size
carcass (died)[1]	1	15.3	2
carcasses (died)[1]	2	21.0	2
carcasses (died)[1]	5	20.2	6
carcass (killed)[2]	1	20.5	2
carcasses (killed)[2]	5	24.5	6
undosed carcasses[3]	5	20.5	4

[1]Possums which died 5–7 days after dosing.
[2]Possums euthanased 48 h after dosing prior to death.
[3]Undosed possums gavaged with water only.

RESULTS

Mallard ducks were not affected by oral dosing with cholecalciferol at 2000 mg/kg. However, 25% (1/4) of canaries and 75% (3/4) of domestic chickens died following exposure to the same dose.

In the studies using native New Zealand non-target species, 10/16 weka ate bait containing 0.1% cholecalciferol. The maximum amount eaten by weka was 58 g of bait, while seven birds ate less than 10 g. No weka exhibited signs of cholecalciferol toxicosis. There also appeared to be no treatment-related adverse effects in weta dosed orally with cholecalciferol (1/6 died in each group).

Each of the 12 cats ate approximately 1 kg of possum tissue containing residues of cholecalciferol over the 5-day period. No cats died, and at the end of 5 days, and in all subsequent samples, mean serum calcium concentrations remained within, or very close to, the normal range for cats (2.0–2.7 mmol/litre) (Table 2). This mild deviation is not clinically significant, as also evidenced by the lack of effect on appetite and body weight of treated cats (Fig. 1).
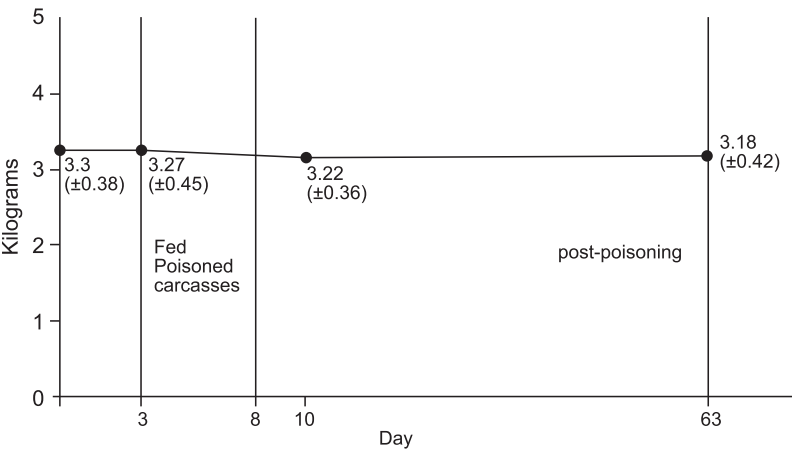

FIGURE 1: Mean body weight (kg ± SD) in cats before, during and after feeding on the carcasses of cholecalciferol-poisoned possums.

TABLE 2: **Mean total serum calcium (± SE) concentrations (mmol/litre) in cats.**

Pre-treatment	After 5 days	1 week later	7 weeks later
2.54 (0.06)	2.75 (0.10)	2.72 (0.07)	2.64 (0.03)

Mean total serum concentrations of calcium in dogs fed daily (for 5 days) with a possum that died and dogs fed killed possums increased by a maximum of 18% and 39% respectively within a week of starting to feed on contaminated possums, and remained above the normal canine range for a further 1–2 weeks (Table 3). Mean serum urea nitrogen concentrations in dogs fed five poisoned carcasses from both the acute and chronic groups also exceeded normal values by day 4, indicative of either toxin-induced renal damage or dehydration secondary to anorexia (Table 4). Serum urea nitrogen returned to normal by day 28 after dosing in all animals. No toxin-related changes were observed in the haematology in any treatment group, and no dogs died.

All dogs that were fed five possum carcasses from the 'acute' group exhibited partial anorexia and varying degrees of lethargy from day 4 to day 14 after dosing. By day 7, mean body weights had decreased by 5% compared to pre-treatment values. All affected dogs began to recover without veterinary intervention or treatment by about 14 days after the onset of exposure. Appetite and body weight gradually returned to pre-treatment levels.

Histopathological examination revealed dystrophic mineralisation of the kidneys consistent with cholecalciferol toxicosis in all dogs euthanased on day 14 that had been hypercalcaemic, with the most severe lesions observed in animals fed 'acute' possums. No toxin-induced lesions were observed in dogs euthanased on day 28, possibly indicating recovery from toxin-induced renal damage.

TABLE 3: **Mean (± SE) total serum calcium concentrations (mmol/litre) in dogs fed possum carcasses for 5 consecutive days as a function of time after the onset of exposure[1].**

Treatment	day 0	day 1	day 2	day 3	day 4	day 5	day 6	day 7	day 8	day 10	day 12	day 14	day 21	day 28
Control	2.59 ±12	2.66 ±16	2.66 ±15	2.54 ±18	2.57 ±15	2.64 ±19	2.52 ±15	2.69 ±19	2.72 ±13	2.73 ±11	2.64 ±16	2.64 ±16	2.58 ±12	2.53 ±18
Acute	2.75 ±11	2.88 ±13	3.02 ±11	3.22 ±20	3.50 ±22	3.70 ±35	3.53 ±22	3.86 ±21	3.59 ±26	3.71 ±26	3.30 ±22	3.19 ±18	2.63 ±19	2.70 ±18
Chronic	2.76 ±09	2.79 ±07	3.02 ±12	2.93 ±18	3.16 ±27	3.13 ±20	3.09 ±25	3.31 ±37	3.16 ±18	3.16 ±22	2.94 ±15	2.88 ±11	2.74 ±09	2.62 ±12

[1]Normal values for total serum calcium concentrations in dogs are 2.0–3.0 mmol/litre.

TABLE 4: **Mean (± SE) serum urea nitrogen concentrations (mmol/litre) in dogs fed possum carcasses for 5 consecutive days as a function of time after the onset of exposure[1].**

Treatment	day 0	day 4	day 7	day 14	day 28
Control	6.4 ± 0.9	6.2 ± 0.8	6.3 ± 0.7	6.0 ± 0.8	6.2 ± 0.7
Acute	5.6 ± 0.8	10.6 ± 2.2	11.6 ± 2.6	9.0 ± 2.0	6.7 ± 0.8
Chronic	6.4 ± 0.6	7.2 ± 1.5	8.4 ± 1.9	5.4 ± 0.7	6.0 ± 0.7

[1]Normal values for serum urea nitrogen in dogs are 3.6–7.8 mmol/litre.

DISCUSSION

Mallard ducks and some chickens and canaries dosed with cholecalciferol at 2000 mg/kg survived, as did all weka eating baits containing 0.1% cholecalciferol. These results are consistent with earlier studies in ducks and quail (Marshall 1984).

A duck would only need to eat one 0.15% 1080 bait (5–10 g) to receive a lethal dose, compared with 200 g of 20 mg/kg brodifacoum bait, or more than 200 g of 0.8% cholecalciferol (as used for possum control) or 2000 g of 0.08% cholecalciferol (as used for rat control). Nevertheless it is apparent that the sensitivity of different bird species to cholecalciferol varies considerably, and care must be taken to minimise exposure to birds when baiting in the field. Like brodifacoum but unlike 1080, cholecalciferol showed no insecticidal effects when weta were dosed.

Our feeding study with feral cats appeared to confirm an earlier secondary-poisoning study with dogs (Marshall 1984), which indicated that the risk of secondary poisoning with cholecalciferol is very low. However, our assessment in dogs indicates that there is a risk of hypercalcaemia and adverse effects on target organs such as the kidney in dogs repeatedly eating carcasses of animals poisoned with cholecalciferol baits.

Marshall (1984) reported no signs of cholecalciferol intoxication in dogs fed rats for 14 days, but included no data on food consumption, body weights, blood chemistry, or pathology. Hence it is not possible to compare the Marshall (1984) secondary-poisoning study with the toxicosis observed in our study. The toxicosis we observed in dogs could have been a factor of a more detailed toxicological assessment of general health, body weight, and pathology, or a result of the higher concentration of cholecalciferol (0.8%) used in possum baits versus rodent baits (0.075%).

Regardless of this, we can conclude that baits containing cholecalciferol have a lower risk of causing secondary poisoning of pets when compared with 1080 or brodifacoum. This is the most distinguishing feature of cholecalciferol when compared to other commonly used vertebrate pesticides. However, low risks of secondary poisoning with cholecalciferol does not imply no risk, and all pets and farm dogs should be discouraged from eating animals that have been poisoned with cholecalciferol. Since we have shown that mild toxicosis can occur in dogs eating possum meat, it would be extremely unwise for hunters to take game from areas where cholecalciferol has been used in the last 1–3 months. The potential hazard to humans would be exacerbated if game species gain direct access to bait.

Persistence studies with cholecalciferol indicate that elevated concentrations of 25OHD are likely to persist for several weeks in possums that receive sub-lethal doses (Eason *et al.* 1996a) and similar persistence may be anticipated in feral game species if they consume bait. In comparison to other examples in the literature, the clearance of elevated 25OHD in poisoned possums appeared to be quite slow. This is perhaps not surprising since it has been shown in other animals that clearance of 25OHD is dose-dependent (Keiver *et al.* 1988), and target animals poisoned with cholecalciferol received extremely high near-lethal doses. For example, the plasma elimination half-lives of 25OHD were 15–36 days in humans when vitamin D status was normal, but increased to 25–68 days in humans and cows experiencing vitamin D toxicosis (Keiver *et al.* 1988). Clearly 25OHD is more persistent than rapidly eliminated poisons like 1080 (Eason *et al.* 1996a), but is less persistent than second-generation anticoagulants like brodifacoum (Eason *et al.* 1996b). Research in rats has demonstrated that 25OHD, whilst active when administered orally (Rambeck *et al.* 1990), is partially degraded in the intestinal tract (Frolick and Deluca 1973). Hence not all the 25OHD present in poisoned carcasses will be bioavailable to animals eating poisoned carcasses. At present there are no data on the persistence of cholecalciferol in the carcasses of dead possums.

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