ORAL TOXICITY OF p-AMINOPROPIOPHENONE TO BRUSHTAIL POSSUMS (TRICHOSURUS VULPECULA), DAMA WALLABIES (MACROPUS EUGENII), AND MALLARDS (ANAS PLATYRHYNCHOS)

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ORAL TOXICITY OF *p*-AMINOPROPIOPHENONE TO BRUSHTAIL POSSUMS (*TRICHOSURUS VULPECULA*), DAMA WALLABIES (*MACROPUS EUGENII*), AND MALLARDS (*ANAS PLATYRHYNCHOS*)

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ABSTRACT: Development of *p*-aminopropiophenone (PAPP) as a toxicant for pest predator management in New Zealand and Australia prompted investigation of its toxicity to potential nontarget species. Acute oral toxicity of PAPP in brushtail possums (*Trichosurus vulpecula*), dama wallabies (*Macropus eugenii*), and Mallards (*Anas platyrhynchos*) was estimated in pen trials, carried out between February 2000 and September 2001. The susceptibility of possums ($LD_{50} \geq 500$ mg kg^{-1}) and wallabies (LD_{50} 89 mg kg^{-1}) to PAPP was low in comparison to noncarnivorous placental mammal species, but ducks (LD_{50} 38 mg kg^{-1}) were more susceptible than other bird species. These results suggest that the nontarget hazard to possums and wallabies from PAPP bait applied for pest predator control would be low. However, future development of PAPP as a vertebrate pest control agent should include rigorous assessments of the hazard posed by bait formulations to bird species and provision for delivery techniques that could mitigate exposure of nontarget birds.

Key words: Duck, marsupial, nontarget, *p*-aminopropiophenone, PAPP, possum, toxicity, wallaby.

INTRODUCTION

Mammalian carnivores appear generally more susceptible to oral doses of the aryl amine compound *p*-aminopropriophenone (PAPP) than either rodents or birds (Table 1) as found by Savarie et al. (1983) in an investigation of PAPP as a potentially selective coyote (*Canis latrans*) toxicant. Currently there is renewed interest in its potential as a toxicant for the management of introduced pest predators such as feral cats (*Felis catus;* Australian Pesticides & Veterinary Medicines Authority 2006 www.apvma.gov.au/chemrev/1080_faq.shtml) and canids (*Vulpes vulpes, Canis familiaris*) in Australia (Marks et al., 2004; Fleming et al., 2006) and stoats (*Mustela erminea;* Murphy et al., 2005) and ferrets (*Mustela furo*) in New Zealand (Fisher and O'Connor, 2007).

This interest has raised a number of new nontarget issues in Australia and New Zealand. The brushtail possum (*Trichosurus vulpecula*) and dama wallaby (*Macropus eugenii*) are both native to Australia and thus are considered nontarget species of pest animal control operations in that country. Conversely these two species are introduced pests in New Zealand and are controlled using a range of techniques, including poison baiting. In the absence of published PAPP toxicity data for marsupials in general, it was therefore important to assess the relative susceptibility of marsupial herbivores as part of the ongoing development of PAPP bait formulations for pest predator control in New Zealand (to determine the potential of PAPP as a toxicant for marsupial pests) and Australia (to estimate nontarget hazard to marsupial wildlife).

Savarie et al. (1983) found avian species to be far less susceptible than mammals in captive trials with relatively small samples of American bird species (see Table 1). More refined toxicity estimates in a wider range of bird species would provide greater confidence to underpin risk assessments for nontarget bird species and newly developed PAPP bait formulations in both New Zealand and Australia. We selected the Mallard (*Anas platyryhnchos*)

TABLE 1. Reported oral lethal dose (LD_{50}) values for PAPP. Where available the sex, species, and strain of the animals tested are given and 95% confidence limits shown in brackets. In the absence of these in some references, "mouse" was assumed to be laboratory *Mus musculus* and "rat," laboratory *Rattus norvegicus*.

Species	LD_{50} (mg kg^{-1})	Reference
Dog (*Canis familiaris*)	7.5	Coleman et al., 1960
Coyote (*Canis latrans*)	5.6	Savarie et al., 1983
Kit fox (*Vulpes velox*)	14.1	Savarie et al., 1983
Red fox (*Vulpes vulpes*)	<25.2[a]	Marks et al., 2004
Cat (*Felis libyca domestica*)	5.6	Savarie et al., 1983
Bobcat (*Lynx rufus*)	10	Savarie et al., 1983
North American badger (*Taxidea taxus*)	~100	Savarie et al., 1983
Raccoon (*Procyon lotor*)	142	Savarie et al., 1983
Striped skunk (*Mephitis mephitis*)	>400	Savarie et al., 1983
Stoat (*Mustela erminea*)	9.3 (n.d.–11.8)	Fisher et al., 2005
Ferret (*Mustela furo*)	15.52 (14.13–17.42)	Fisher and O'Connor, 2007
Guinea pig (female) (*Cavellio porcinus*)	1,020	Scawin et al., 1984
Mouse (albino)	223	Savarie et al., 1983
Mouse (female)	>5,000	Scawin et al., 1984
Mouse (male) (Swiss Webster strain)	168	Pan et al., 1983
Rat (female) (Porton Wistar strain)	223.7	Scawin et al., 1984
Rat (male)	475	Scawin et al., 1984
Rat	177	Savarie et al., 1983
Rat (male) (Sprague-Dawley)	221	Pan et al., 1983
Golden eagle (*Aquila chrysaetos*)	>50	Savarie et al., 1983
Coturnix quail (*Coturnix coturnix*)	>316	Savarie et al., 1983
Starling (*Sturnus vulgaris*)	>316	Savarie et al., 1983
Red-winged Blackbird (*Agelaius phoenicus*)	133	Savarie et al., 1983
Black-billed Magpie (*Pica pica*)	178	Savarie et al., 1983
Common Crow (*Corvus brachyrhynchos*)	≥178	Savarie et al., 1983

[a] Lowest oral dose causing death.

as a representative bird species for oral toxicity testing in a study in April to September 2001. Trials with captive wallabies and possums were carried over September 2000 to June 2001.

METHODS

Oral toxicity of PAPP to brushtail possums

Wild-caught brushtail possums (nine male: nine female; mean weight 3.3±0.2 kg) were brought into captivity at the Landcare Research animal facility, Lincoln, New Zealand. They were individually housed in wire cages (350×200×200 cm) in temperature-controlled rooms (19±5 C) under natural-day-length lighting. They had free access to water and cereal-based pellets (Weston Animal Nutrition, Rangiora, New Zealand), supplemented weekly with fruit and vegetables. After acclimation to these conditions for at least 2 wk, possums were randomly allocated to three treatment groups, each of three males and three females. The treatments were gavage delivery of either 0 (control), 250, or 500 mg PAPP per kilogram of possum body weight.

Dosing solutions of the hydrochloride form of PAPP (4′-aminopropiophenone; Merck, Darmstadt, Germany) were prepared fresh for each group in monopropyleneglycol (MPG; BDH Ltd., England) and water to 50 mg ml^{-1}. Possums were placed under light fluothane anesthesisa, weighed, and gavage dosed using a stomach tube. The 250 mg kg^{-1} and control treatments were dosed first, with a maximum dose volume of 10 ml kg^{-1} for the PAPP treatment and control possums receiving 5 ml MPG. All possums were

TABLE 2. Mortality in groups (n=6) of male dama wallabies administered doses of PAPP or control treatment (MPG) by gavage.

Dose (mg kg^{-1})	No. wallabies dosed	Mortality
0 (control)	6[a]	0
	6	0
	6	0
31.25	6	0
62.5	6	2/6 (~33%)
125	6[a]	5/6 (~83%)
	6	5/6 (~83%)
250	6[a]	6/6 (100%)

[a] Intramuscular injection of Zoletil used to immobilize wallabies in these groups.

closely monitored over the hour following dosing and then at half-hourly intervals over the next 12 hr. Survival was determined after 3 days in possums dosed with 250 mg kg^{-1}. One week later the 500 mg kg^{-1} group was dosed and observed in the same manner. All procedures were carried out at ambient room temperature (~19 C).

Oral toxicity of PAPP to dama wallabies

Forty-eight wild male dama wallabies (*M. eugenii;* mean weight 5.5±0.4 kg) were captured in the Rotorua district and transported to a captive facility at Te Puke (Aotearoa Wildlife Export). Wallabies were individually identified by numbered plastic ear tags, which were threaded on a string "collar" around their necks. They were group housed in a fenced pasture pen with an enclosed shed (6×2 m) with sawdust bedding for shelter. Pasture diet was supplemented with calf muesli and vegetable food freely available during a 2-wk acclimation period and the trial.

Dosing solutions of PAPP for administration by gavage were prepared as previously described, to concentrations of 12.5–50 mg ml^{-1} depending on the required dose for each treatment group of six (Table 2). Maximum dose volume was 35 ml, and control wallabies received 10 ml MPG only. Wallabies in the first three treatment groups (250, 125, or 0 mg kg^{-1} as control; Table 2) were immobilized by intramuscular injection of approximately 10 mg kg^{-1} Zoletil® (tiletamine and zolazepam; Virbac, Auckland, New Zealand) for weighing and dosing. However, the relatively long duration of recovery from Zoletil® masked behavioral signs of the onset of PAPP toxicosis (see Results). After this, portable veterinary equipment was used to induce fluothane anesthesia for weighing and dosing; three groups were dosed on one day with either 125, 62.5, or 0 mg kg^{-1}, and further groups dosed 2 days later with either 31.25 or 0 mg kg^{-1} (Table 2). After dosing, wallabies were returned to the shelter, with access to the pasture pen, and closely monitored for recovery from anesthesia and for signs of toxicosis for the following 8 hr and then twice daily over the next 3 days. Mean temperature on dosing days was 15 C to 23 C. A lethal dose (LD_{50}) value with 95% confidence intervals was estimated using logistic regression models (SYSTAT 7.0, SPSS Inc., Chicago, United States).

Oral toxicity of PAPP to Mallards

Domestic ducks (*A. platyrhynchos,* Pekin breed; nine male and 15 female, mean weight 2.34±0.1 kg) were group housed in enclosed outdoor pens (32×3×2 m) with shelter at the Landcare Research animal facility. They had free access to grain mix, duck pellets, and water throughout a 2-wk acclimation period. Ducks were individually identified by leg bands and randomly allocated to treatment groups of six, with a "step up or down" dosing schedule, where mortality observed in one dose group dictated the next dose administered (Table 3). This design was used to achieve a suitable spread of mortality across dose groups, enabling more precise calculation of an LD_{50} value, which was estimated with 95% confidence intervals using logistic regression models (SYSTAT 7.0).

Fresh dosing solutions for gavage administration were prepared for each treat-

TABLE 3. Mortality in groups ($n=6$) of ducks administered doses of PAPP or control treatment (MPG) by gavage. Groups were treated on different days at varying intervals, and the order in which the groups were dosed is shown in brackets next to the treatment.

Dose PAPP (mg kg^{-1}) (order of dose groups)	No. ducks dosed (sex)	Mortality
0 (1)	6 (3M, 3F)	0
0 (5)	6 (3M, 3F)	0
15.63 (6)	6 (3M, 3F)	1/6 (~17%)
31.25 (5)	6 (2M, 4F)	4/6 (~67%)
62.5 (4)	6 (3M, 3F)	6/6 (100%)
125 (3)	6 (3M, 3F)	5/6 (~83%)
250 (2)	6 (1M, 5F)	6/6 (100%)
500 (1)	6 (2M, 4F)	6/6 (100%)

ment group as previously described, to final concentrations of 6.25–50 mg ml^{-1} depending on the PAPP dose required. Each group was dosed on a different day, with dose volumes of 5–10 ml kg^{-1} depending on the PAPP treatment. Two control groups were dosed (5 ml MPG kg^{-1}) on the days of the 500 and 31.25 mg kg^{-1} treatments (Table 3). Ducks were manually restrained during weighing and gavage, then were returned to their outdoor housing and closely observed over the following 8 hr for signs of toxicosis, left overnight, and checked early the following morning. The mean 24-hr temperature on the days of testing ranged from 2.7 C to 17.6 C, with some relatively cold overnight conditions (−2 C to 4 C).

RESULTS

Oral toxicity to brushtail possums

All control and PAPP-dosed possums recovered full coordination and alertness within 10 min of anesthesia and dosing. Four of the six possums dosed with 250 mg kg^{-1} had visibly cyanotic skin on the nose and ear by 30 min after dosing, but all six retained normal movements and responses to stimuli, as did all the control possums throughout the observation period. The next morning one of the PAPP-dosed possums retained a deeply cyanotic appearance, was sluggish in responses to noise and touch, and had rapid respiration, and blood was observed around the anus and in urine passed overnight. This visibly affected possum had returned to normal appearance and movements by the following morning, that is, two nights after dosing. The other possums that had been dosed with PAPP appeared normal on the morning after dosing and readily consumed their ration of food.

In the 500 mg kg^{-1} group, 30–60 min after dosing all possums first showed the distinctive cyanotic appearance seen in the 250 mg kg^{-1} group. Impaired coordination of movement and shaking was observed in three possums 4–6 hr after dosing; this progressed to outright prostration in two possums. Both of these died overnight, and the other died approximately 32 hr after dosing. Bleeding from the nose was observed the morning after dosing in one of the possums that survived, and the remaining two possums appeared to have fully recovered on the second day after dosing. Although no possums dosed with 250 mg kg^{-1} died, four of the six dosed were visibly affected by PAPP. All six possums dosed with 500 mg kg^{-1} were visibly affected, and three died, resulting in an oral LD_{50} estimate of PAPP in possums of $\geq$500 mg kg^{-1}.

Oral toxicity to dama wallabies

All wallabies in the control groups and the 31.25 mg kg^{-1} PAPP treatment group survived. All six wallabies dosed with 500 mg kg^{-1} died, with some mortality also in the 125 and 62.5 mg kg^{-1} groups (Table 2). Using these data, an oral LD_{50} for PAPP in wallabies was estimated as 89 mg kg^{-1} (95% CI: 63–118). Control wallabies injected with Zoletil® took up to 4 hr to regain normal coordination and alertness. In wallabies orally dosed with 250 or 125 mg kg^{-1} PAPP, the effects of Zoletil disguised early signs of toxicosis before progression into the prone stage of toxicosis (see below). In contrast, control

and dosed wallabies anesthetized with fluothane recovered normal movement and alertness within approximately 10 min. Because wallabies recovered relatively quickly from fluothane anesthesia, close observation of some animals was difficult without disturbing them. Close observation was easier in those wallabies where reduced movement was an effect of PAPP. In those wallabies that could be adequately observed, cyanosis around the mouth was evident, especially in the 125 and 62.5 mg/kg treatment groups. Cyanosis was generally seen within 50 min of dosing and often accompanied by excessive salivation. Progressive signs included a gradual reduction of activity, impaired coordination, and lying down but conscious within 6–10 hr of dosing. Wallabies then became more prone over the following 2–5 hr, with breathing becoming more shallow and irregular. By this stage wallabies appeared to be unconscious, or to have intermittent consciousness, with occasional limb flexing that may have been involuntary. They remained in this state until death, which on average occurred 20±6 hr after dosing. Wallabies that recovered from the impaired coordination/lying down stage were generally deemed fully recovered within 24 hr.

Oral toxicity to Mallards

All ducks in the control groups survived, but there was mortality at all doses of PAPP (Table 3). The acute oral toxicity (LD_{50}) of PAPP in ducks was estimated from these data as 38 mg kg^{-1} (95% CI: 20–73).

Once released after dosing most ducks preened briefly before joining others sitting or standing in a sheltered corner of the enclosure. In comparison to control birds, within 10 min all ducks dosed with PAPP showed impaired coordination during walking and generally sat down in a group in a shaded corner of the enclosure within this time. In the first dose group (500 mg kg^{-1}) two of the six ducks vomited approximately 2 min after dosing, and by 15 min after dosing all six ducks showed labored breathing with beaks agape and head and neck stretched forward, in some cases almost touching the ground. One duck in this group displayed a distinctive "head swaying" movement, followed by an arching movement of the neck backwards over the body, which appeared spasmodic over the following 2 hr. This general progression of signs was evident in the other PAPP dose groups, although vomiting was observed in only one other duck in the 250 mg kg^{-1} group. Labored breathing with beak agape and neck stretched out was the most "universal" sign in PAPP-dosed ducks, which generally drank within 4 hr but did not eat offered food, compared with control ducks, which readily ate.

All PAPP-dosed treated ducks were either reluctant or apparently unable to move from a sitting position by 4 hr after dosing but were alert on close approach. The distinctive backwards or sideways neck-arching movement observed in one duck in the 500 mg kg^{-1} group also occurred in the 250 (1 duck), 125 (1 duck), and 62.5 mg kg^{-1} (2 ducks) groups, but was not observed in lower PAPP dose groups or in the control groups. Salivation was observed in two ducks in each of the 15.63 and 62.5 mg kg^{-1} groups. Three mortalities occurred within 3 hr of dosing with PAPP (two ducks in the 125 mg kg^{-1} group, one duck in the 500 mg kg^{-1} group), but most ducks died during the night following dosing (within 12 hr of dosing) and in nearly all cases appeared to have died in the same position in which they were last observed. In contrast, PAPP-dosed ducks that survived ate and were moving normally by the following morning and over consecutive days.

DISCUSSION

The toxicity values reported here are the first estimated for marsupials and are within the range for eutherian herbivores/omnivores. Some general differences in

the oral toxicity of PAPP to groups of species are evident when available LD_{50} values (Table 1) are compared. The median oral toxicity of PAPP in rodents (223 mg kg^{-1}) and birds (178 mg kg^{-1}) is much lower than in mammalian carnivores (canids, felids, and mustelids combined 8.4 mg kg^{-1} excluding the value for red fox in Table 1, which is not a formal LD_{50} estimate). Although the susceptibility of possums appears relatively low and comparable to those reported for guinea pigs and some strains of laboratory rodents, wallabies were more susceptible than possums, having an LD_{50} value most similar to those for raccoons (*Procyon lotor*) and North American badgers (*Taxidea taxus;* Table 1). The acute oral toxicity of PAPP estimated for ducks (LD_{50} 38 mg kg^{-1}) in this study indicates a considerably greater susceptibility than previously reported for bird species by Savarie et al. (1983).

Methemoglobin (MetHb) is physiologically inactive in that it does not carry oxygen (Coleman and Coleman, 1996). Toxicity of PAPP in eutherian mammals is thought to be mediated by a *p*-hydroxy metabolite with high oxidative capacity that is responsible for direct formation of MetHb in erythrocytes (Graffe et al., 1964; Marrs et al., 1991; Marino et al., 1997). In normal erythrocytes there is a slow and continuous production of MetHb (Board et al., 1977), and mammals have intrinsic enzymic systems that reduce MetHb back to hemoglobin, so that MetHb concentrations rarely exceed 1–2% of the total pigment in erythrocytes (Board et al., 1977). Elevated MetHb concentrations cause anemia (Smith, 1969) and result in anoxic effects if sufficiently high (Marrs and Bright, 1987). In humans MetHb concentrations greater than 70% are usually fatal (Coleman and Coleman, 1996).

Many variables contribute to the overall toxic effect of MetHb-forming compounds, including rates of absorption, metabolism, and excretion and the intrinsic capacity of erythrocytes to withstand oxidative insult to hemoglobin. Because the rate of oxidation of hemoglobin is also dependent on the localized concentration of the MetHb-forming compound in the erythrocyte (Marrs et al., 1987), interspecies difference in the pathways and rates of the metabolic activation of PAPP will influence the rate and extent of MetHb formation.

Wood et al. (1991) reported that in rats, PAPP was metabolized by N-acteylation, while in dogs, ring and aliphatic hydroxylation occurred; in monkeys, both N-acetylation and oxidation took place. However, the metabolic activation pathways of PAPP in possums, wallabies, and bird species appear undescribed. Although MetHb concentrations were not measured in this study, the signs observed in ducks dosed with PAPP were consistent with those previously associated with elevation of MetHb in birds. For example, Japanese Quail administered phenylhydroxylamine (another MetHb-forming compound) exhibited panting, opisthotonus (a spasm where the neck, head, and/or spine are arched backwards), and ruffling of feathers, and cramps in the upper legs, all of which are signs of metabolic oxygen shortage (Blaauboer et al., 1980).

A further factor influencing susceptibility of a species is the rate of detoxification and elimination of the MetHb-forming compound (Marrs et al., 1987). Tepperman and Bodansky (1946) demonstrated hepatic conjugation and extensive excretion in urine of PAPP in rats, and in humans up to 90% of PAPP was excreted in urine after 24 hr (Tepperman and Bodansky, 1946). However, distinct intraspecific differences in the urinary excretion of N-hydroxy derivatives of PAPP have been shown between dogs, guinea pigs, and rabbits (von Jagow et al., 1966). Assuming that glucuronic acid conjugation is an important detoxification mechanism for PAPP, interspecies variation in the capacity of this pathway will also contribute to susceptibility to PAPP. For exam-

ple, cats glucuronidate phenolic compounds poorly and are highly susceptible to the toxic side effects of many drugs (Court and Greenblatt, 1997), and ferrets also have relatively poor glucuronidation (Court, 2001), which may partially account for the relatively high toxicity of PAPP in these carnivores. Although no studies of the detoxification or excretion of PAPP by marsupials appear to have been published, brushtail possums are likely to have an active glucuronic acid pathway (Dash, 1988; McLean et al., 2003). The extent to which PAPP is metabolized and excreted by wallabies and possums is not known, but it is likely that the brushtail possum, at least, can metabolize and excrete PAPP relatively rapidly.

Birds also utilize glucuronidation. The activity of UDP-glucuronyl transferase was relatively high in liver slices from turkeys and rats in comparison to ducks (Bartlet and Kirinya, 1976), with some evidence of generally lower levels of conjugative and oxidative activity in duck liver than in chickens (Short et al., 1988). The higher susceptibility of ducks to PAPP in comparison to some other birds may be due to a relatively reduced capacity to detoxify the compound and its metabolites before toxic elevations of MetHb occur.

The rate of MetHb formation may be influenced by the sensitivity of species hemoglobin; for example, cat hemoglobin is relatively sensitive to oxidation because there are 8–10 reactive sulfhydryl groups per hemoglobin tetramer compared to four reactive groups per tetramer in other species (Harvey, 1989). In erythrocytes the continual reduction of MetHb back to functional hemoglobin is carried out by an array of oxidant-defence enzymic systems in the presence of suitable substrates (Board et al., 1977). Under normal conditions these MetHb reduction systems have been described as "more corrective than protective" (Harvey, 1989), so responses to a strong oxidative challenge will also depend on interspecies differences. Endogenous activity of the enzyme MHb reductase (MR) reflects this capacity (Rockwood et al., 2003). Marrs et al. (1987) suggest that interspecies difference in MR activity is the greatest source of variation in sensitivity to MetHb-forming compounds and reported that rodents, especially mice, have a high MR capacity, whereas humans, dogs, and cats have much lower capacities.

Whittington et al. (1995) reported MR activities in marsupials, including tammar wallabies, were similar to those reported for eutherian species. However, there are some indications that in comparison to other marsupial species (including wallabies), brushtail possums have relatively high activities of the enzymes associated with antioxidant defense systems in erythrocytes (e.g., Baker et al., 1995; Ogawa et al., 1998), which may partially account for their relatively low susceptibility to PAPP in comparison to wallabies.

Avian erythrocytes differ from mammalian erythrocytes in being nucleated and oval (El-Mekawi et al., 1993), possessing mitochondria and an intact tricarboxylic (TCA) cycle and having different glucose metabolism to mammalian cells (Blaauboer et al., 1979). Because the TCA cycle generates NADH used for reduction of MetHb, nucleated erythrocytes have a significant capacity to reduce MetHb (Board et al., 1977). Birds thus appear to have a relatively high MetHb-reduction capacity compared with most mammals (Blaauboer et al., 1980). However, birds also have a higher metabolic rate and body temperature than mammals, and when the rate of MetHb reduction is high, oxygen consumption is also increased (Blaauboer et al., 1980). The relatively low ambient temperatures in the outdoor housing of ducks in this study may have contributed to mortality during PAPP toxicosis.

The LD_{50} values calculated in this study for PAPP in possums and wallabies suggest a low risk of nontarget poisoning of these species if PAPP is used as a bait-delivered toxicant for pest predator control in Australia. PAPP is not sufficiently

toxic to warrant further consideration as a potential toxicant for controlling these wallabies or possums where they are pests. The reasons for the apparently greater susceptibility of ducks to the other bird species so far evaluated remains unclear, and further investigation of this would seem a priority to better gauge potential nontarget risks to birds. If PAPP is utilized as a bait-delivered toxicant for mustelid control in New Zealand, further consideration of the potential nontarget risks to avian wildlife will be an important consideration in developing appropriate field application methods.

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