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Fox control using a para-aminopropiophenone formulation with the M-44 ejector

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Abstract

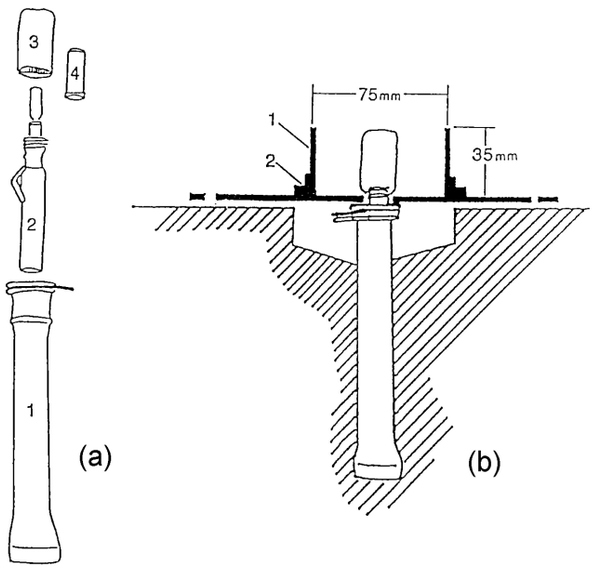
*The M-44 ejector ('ejector') has proven to be a highly target-specific means of delivering toxicants to the exotic European red fox (*Vulpes vulpes*) in south-eastern Australia. Para-aminopropiophenone (PAPP) is a potent methaemoglobin (MetHb) forming compound in canids. A formulation of PAPP, dimethylsulphoxide (DMSO) and condensed milk was investigated as a new toxicant formulation for delivery by the ejector. Dosage of eight foxes in the laboratory with a sequential dose demonstrated that the formulation caused a dose-dependent and rapid elevation of MetHb. A strong inverse correlation between MetHb and oxyhaemoglobin concentrations was detected in each case. The symptoms of the toxicosis in the laboratory included progressive cyanosis, lethargy and then collapse when MetHb levels reached 56–76%. A polynomial model was a good fit for describing the relationship between sub-lethal doses of PAPP and the resulting peak MetHb levels. In a pen trial, an ejector was fitted with a bait and loaded with a standard dose of 226 mg PAPP in the same formulation and set at one end of a pen. After voluntarily triggering the ejector, all five foxes in this trial became progressively more lethargic and either lay prostrate or collapsed after 14–25 min, and death was confirmed after a mean of 43 min. We compared some clinical features of PAPP toxicosis with 15 cases of lethal sodium fluoroacetate (1080) poisoning using 0.5 mg kg^{-1} 1080. PAPP produced a mean time to death that was 7.7 times faster than 1080, with the onset of first symptoms being 15 times faster. It was associated with much less activity prior to death and convulsions, spasms and paddling commonly associated with 1080 poisoning after collapse were not detected during PAPP toxicosis. We conclude that the PAPP formulation appears to be a rapidly acting and apparently humane lethal agent for fox control when used in conjunction with the ejector.*

Keywords: *1080, animal welfare, PAPP, para-aminopropiophenone, predator control, red fox*

Introduction

The European red fox (*Vulpes vulpes*) was introduced into Australia during the 1870s (Rolls 1984) and has been implicated in the extinction of a variety of vertebrate species, including six mammals in south-eastern (SE) Australia (Bennett *et al* 1989). The fox remains an on-going threat to the conservation of a range of terrestrial Australian species (Mansergh & Marks 1993; Anon 1994; Saunders *et al* 1995). The most common control measures involve the use of poison baits containing sodium fluoroacetate (1080) (Saunders *et al* 1995). During 1997, over one million commercially manufactured 1080 fox baits were sold in New South Wales, and between 1995 and 1998, 579 932 were sold in Victoria (File data: Department of Primary Industries, Victoria, Australia). As the caching of 1080 meat baits by foxes has been shown to be common (Saunders *et al* 1999; Van Polanen *et al* 2001), baiting within urban and urban–rural fringe areas is ill-advised given the possibility of domestic dog poisoning after baits have been translocated. Within Victoria there is a need for fox control within such habitats (Mansergh & Marks 1993; Marks & Short 1996). In foxes, 1080 toxicosis has a mean latent period of 4.05 h before the onset of identifiable behavioural symptoms, which last for a mean of 1.57 h before death (Marks *et al* 2000). The initial symptoms of running and retching occur when the animal is conscious, and therefore it is likely that some suffering occurs at this stage. However, as the convulsions and tetanic spasms that follow may occur when the animal is experiencing severe central nervous system disruption, pain or distress may not be perceived (Gregory 1996; Marks *et al* 2000). In herbivores, such as the European rabbit (*Oryctolagus cuniculus*), its action does not appear to produce significant amounts of distress prior to unconsciousness, which occurs after sudden cardiac fibrillation (Williams 1996). The humaneness of 1080 is controversial with respect to its use in the control of carnivores (Gregory 1996; Oogjes 1996; Marks *et al* 2000), but until recently the humaneness of techniques used for vertebrate pest control in Australia has received little attention (Fisher & Marks 1996; Jones 2003). It is

Figure 1



(a) The M-44 toxicant ejector with (1) metal stake; (2) spring-loaded piston; (3) capsule holder; and (4) capsule containing the PAPP formulation. **(b)** Method of deployment in the pen trial where the ejector was buried and surrounded by (1) a cylindrical plastic collar which (2) was attached to a metal plate.

increasingly accepted that no technique or strategy used to control pest species should cause unnecessary suffering (Scott 1976; Ross 1986; Marks 1999; Jones 2003). Improvements are sought to ensure the humaneness of vertebrate pest control techniques and our research has focused upon investigating additional lethal agents and target-specific delivery mechanisms.

Para-aminopropiophenone (PAPP) is a potent methaemoglobin (MetHb) forming compound (Eyer 1983; Marrs & Bright 1986). As MetHb cannot carry oxygen, sufficient concentrations will cause life-threatening anoxia (Kurata *et al* 1993). Canids appear much more susceptible to oral doses of PAPP than do rodents, mustelids and birds (Savarie *et al* 1983). We sought to assess PAPP as an alternative toxicant for fox control. In SE Australia, 35 endemic mammals are considered to be capable of consuming meat baits and being exposed to the toxicants they contain (Marks 2001a). However, the M-44 ejector ('ejector') (Connolly 1988) (Figure 1a) has shown good field performance for fox control in SE Australia (Marks *et al* 2004b) and is estimated to exclude most endemic mammals from exposure to toxicants used in it (Marks 2001b; Marks & Wilson in press). Accordingly, we investigated a formulation of PAPP that may be delivered by the ejector. This paper reports on a preliminary dose-response and pen trial to assess the practicability of delivering a lethal dose of the PAPP formulation to red foxes. We contrast the major clinical symptoms of PAPP toxicosis with those observed for 1080 reported in a previous trial (Marks *et al* 2000).

Materials and method

Foxes were captured on rural and bushland properties using Victor Soft-Catch® traps (Meek *et al* 1995) and were held in pens constructed from cyclone wire mesh measuring 12 × 6 × 2 m. Water was provided *ad libitum* and they were fed a ration of chicken meat, vegetables and canine vitamin/mineral supplement (Vet-a-mix: Iowa, USA). All foxes held in captivity were euthanased by an intra-cardiac injection of 3 ml sodium pentobarbitone (Lethabarb®: Virbac, Sydney, Australia) if they had not begun to feed by the fourth day.

Laboratory trial

Ejector capsules were loaded with a mixture of PAPP (Merck-Schuchard, Germany) dissolved in dimethylsulphoxide (DMSO [Merck, Melbourne, Australia]) and sweetened condensed milk (Carnation®: Nestlé, Melbourne, Australia). DMSO was found to greatly enhance the solubility of PAPP in the condensed milk formulation. In addition, it is known to assist in the penetration of biological membranes and provide some topical anaesthesia as well as having extremely low toxicity (Jacob & Herschler 1986). The capsules were sealed with a plastic disc and microcrystalline wax coating and then loaded into the ejector. Preparation of the capsules occurred 24 h before each trial and PAPP doses at selected concentrations were based upon the weight of the fox upon capture.

Eight foxes were used for this trial and they were sedated with a 4 mg kg^{-1} intra-muscular (IM) dose of Zoletil® (50:50 tiletamine:zolazepam mixture) (Virbac, Melbourne, Australia) and then brought in to the laboratory individually or in pairs, weighed and then placed into a 112 × 56 × 84 cm wooden recovery box. After the drug effect had abated and the fox attempted to stand upright, it was restrained by holding it by the scruff and the ejector contents were fired onto the back of its throat. The concentrations of PAPP used were 1.96, 3.04, 4.6, 6.5, 9.9, 25.2, 30.5 and 37 mg kg^{-1} PAPP. Diazepam (a benzodiazepine) has been used successfully to manage stress-induced hyperthermia in farmed silver foxes without necessitating paralytic sedation (Moe & Bakken 1998). After dosage, foxes were anaesthetised with a 15 mg kg^{-1} IM dose of Zoletil and held for a further 30 s, and then returned to the recovery box where behaviour was observed by infra-red-sensitive video cameras (Watec® WAT-902H: Hadland Photonics, Melbourne, Australia).

Immediately before dosing with the ejector a 0.2 ml baseline blood sample was taken from the cephalic vein and this was repeated every 10 min thereafter. Determination of MetHb and oxyhaemoglobin (HbO) were made with an oximeter (OSM™ 3 Hemoximeter™: Radiometer, Copenhagen, Denmark). Three consecutive determinations were made for each sample taken. Three foxes were given doses of PAPP that were intended to be potentially lethal, but without the administration of an additional dose of Zoletil so that symptoms during the full toxicosis could be observed. The end-point of the experiment was established

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as a MetHb concentration of >85% (death as an experimental end-point is discouraged in Victoria), after which the fox was euthanased by an intra-cardiac injection of 3 ml sodium pentobarbitone (Lethabarb®: Virbac, Sydney, Australia) while under deep anaesthesia produced by an IM dose of 15 mg kg^{-1} of Zoletil. The peak MetHb concentrations resulting from sub-lethal doses of PAPP were fitted to a polynomial model that best described the relationship and predicted a lethal end-point.

Pen trial

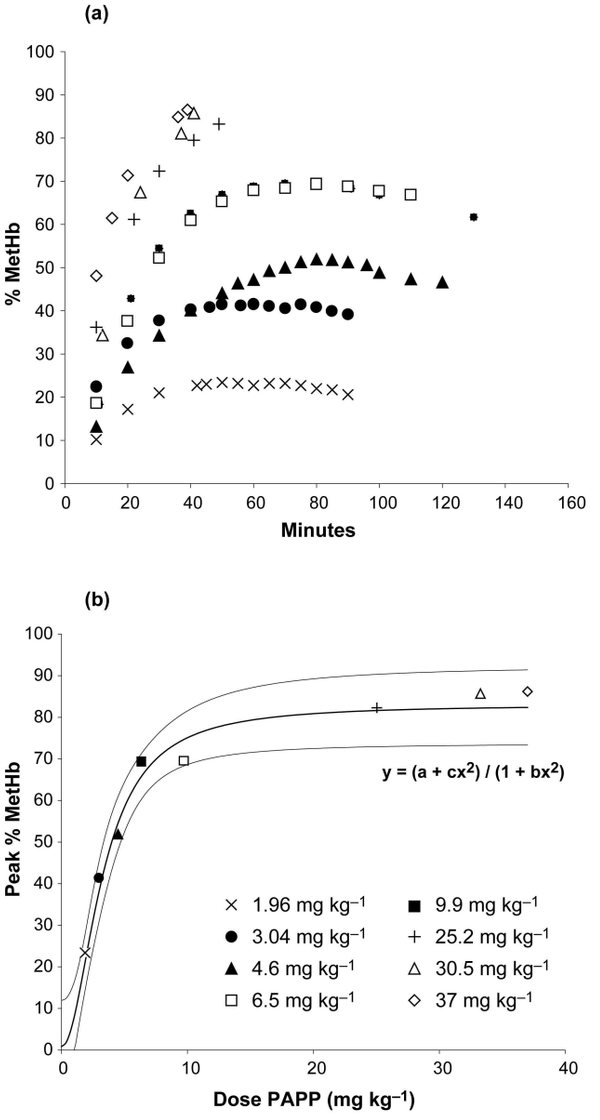
Benzodiazepines can have significant muscle-relaxant and anticonvulsant properties (Rehm & Schatzmann 1985). A pen trial was designed so that the behaviour of foxes could be observed without drug effects altering the symptoms of the toxicosis, and after the voluntary triggering of an ejector. A total of five foxes were used in the pen trial, and on the day before each trial, individually housed foxes were sedated with a 4 mg kg^{-1} IM dose of Zoletil and fitted with custom-built activity-monitoring radio-collars (Titley Electronics: Bellena, Australia) using the design and monitoring protocol described by Marks *et al* (2000). Capsules containing a standard dose of 226 mg of PAPP were prepared using the formulation and method employed in the laboratory trial. An ejector station was established on one side of the fox pen where an ejector was loaded with the capsule and the spring mechanism engaged. It was baited with deep-fried liver and deployed in the manner described by Busana *et al* (1998) (Figure 1b). Behaviour during the trials was filmed by three infra-red-sensitive video cameras (Watec® WAT-902: Hadland Photonics, Melbourne, Australia); one mounted 1 m from the ejector station at a height of 200 mm, and one at roof level at each end of the pen. The trial pen was lit with a 100 W infra-red floodlight mounted next to the roof camera and a 40 W infra-red floodlight which illuminated the ejector station (Marks *et al* 2004a). After foxes had triggered the ejector they were observed remotely until they were believed to be unconscious, after which their corneal reflex was monitored. The major clinical symptoms of PAPP toxicosis in foxes poisoned with PAPP were compared with those observed for 1080 reported in a previous trial (Marks *et al* 2000).

Results

Laboratory trial

At each dose, at 10 min post-dosage, MetHb concentrations were elevated and HbO concentrations had declined. When foxes achieved MetHb concentrations of between 36% and 56% the first visible clinical sign of methaemoglobemia was the pale appearance of the gums and tongue. As MetHb concentration increased the tongue darkened progressively from a chocolate brown to black as concentrations approached 80%. Strong and highly significant inverse correlations between MetHb and HbO measurements were found for each animal at each dose concentration ($r^2 > 0.9$; $P < 0.001$ for each fox). Peak MetHb levels were found to be significantly related to dose ($r^2 = 0.84$; $df = 8$; $P < 0.01$) (Figure 2a). No vocalisations, convulsions, tetanic spasms or retching were observed in the three foxes that were not anaesthetised by a second Zoletil dose (those receiving 25.2, 30.5 or 37.0 mg kg^{-1} PAPP). Of these three, the two individuals that received the highest doses exceeded the 85% MetHb end point and were euthanased, while the fox given 25.2 mg kg^{-1} PAPP died before the end point was reached. The relationship between dose and resulting peak MetHb levels in the five foxes given sub-lethal doses (Figure 2a) was found to be a good fit for the polynomial

Figure 2



(a) Methaemoglobin (MetHb) measurements for oral doses at various concentrations of PAPP formulation in the laboratory trial. **(b)** Polynomial model [$y=(a+cx^2)/(1+bx^2)$] describing the relationship between sub-lethal doses (1.96–9.9 mg kg^{-1}) and peak MetHb concentration ($P < 0.05$). Doses that resulted in death or where the end-point of >85% MetHb resulted in euthanasia (25.2, 30.5 and 37 mg kg^{-1}) were not included in the calculation of the model but are included for comparison.

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Table 1 Comparison of major events and symptoms of PAPP toxicosis in the pen trial compared to 1080 toxicosis described by Marks *et al* (2000)[1].

Description of group and symptoms	PAPP (pen)	1080[1]
n	5	16
Dose (mg kg^{-1})	41–63	0.5
Mean time (h) from dosage to death ($P < 0.05$)	0.71 ± 0.1*	5.45 ± 0.98
Mean time (h) from dosage to first behavioural symptoms ($P < 0.05$)	0.27 ± 0.08	4.05 ± 0.86
Mean time (h) from first behavioural symptoms to death ($P < 0.05$)	0.7 ± 0.1*	1.57 ± 0.46
Mean total activity from dosage to death ($P < 0.05$)	239.4 ± 52.9	1071.1 ± 382.7
Retching	0/5	13/16
Manic running	0/5	2/16
Paddling	0/5	16/16
Tetanic spasms	0/5	14/16
Clonospasms	0/5	3/16

* Based on n = 4 animals

relationship $y=(a+cx^2)/(1+bx^2)$ ($r^2 = 0.99$; $F = 140.1$; $df = 2$; $P < 0.001$). The peak MetHb levels for the three foxes given the highest lethal doses were found to fit within the 95% confidence interval calculated for the model, although these data were not included in its calculation (Figure 2b).

Pen trial

Immediately after triggering the ejector, foxes intermittently shook their heads vigorously for a period of 29–50 s with all foxes returning to examine the ejector. Within the following 1–9 min after triggering the ejector three out of five foxes resumed feeding from the bait. No spillage of the PAPP formulation was observed and foxes received an assumed dose of 41–62.7 mg kg^{-1} PAPP. No abnormal activity was observed until 10–24 min post-dosage, where staggering and lethargy preceded either collapse or the fox adopting a prostrate position before rolling onto its side. In four out of five cases the fox later attempted to stand but was unable to do so, as it appeared to become progressively more lethargic. In all foxes, no activity was detected after 30–43 min and death was confirmed by loss of corneal reflex after a mean of 43 min (0.71 h), although death probably occurred sooner as inspections were made only after 3 min of observing no obvious movement. The mean time from dosage to death for PAPP was 7.7 times faster than the corresponding 1080 trial data, and the time from dose to the first outward signs of toxicosis was 15 times faster. The mean time from the onset of the first behavioural symptoms of PAPP toxicosis until death was 2.2 times faster than for 1080, whilst mean total activity recorded between dosage and death for PAPP was significantly lower than for 1080 ($t = 4.73$; $df = 19$; $P < 0.001$). Although 1080 toxicosis was found to be commonly associated with retching prior to collapse, and with paddling and tetanic spasms after collapse, none of these symptoms were observed in foxes that succumbed to PAPP. Clonospasm and manic running were also not observed during PAPP toxicosis, although these were sometimes observed during 1080 toxicosis (Table 1).

Discussion

The formulation of PAPP delivered by the ejector was shown to cause a rapid elevation of MetHb, which closely corresponded to a reduction in red blood cell (RBC) HbO. PAPP has previously been recognised as a potent MetHb-forming compound (Eyer 1983; Marrs & Bright 1986) that may cause anoxia (Kurata *et al* 1993). Lethal anoxia produced by carbon monoxide (CO) intoxication and the formation of carboxyhaemoglobin is believed to be a humane method of euthanasia (Carding 1977; Kurata *et al* 1993; Marks 1999), and death through rapid methaemoglobinemia may likewise not be associated with significant suffering. In the pen trials, death occurred within 39–53 min with no obvious behavioural indicators of distress, apart from a brief period of head shaking immediately after the discharge of the ejector. The willingness of foxes to investigate the ejector after its discharge, and to resume feeding from it up until the onset of the first symptoms, implies a lack of significant distress at this stage of the toxicosis. The major symptoms associated with 1080 toxicosis were not observed during the progression of PAPP toxicosis. The duration of the PAPP toxicosis was much shorter and associated with less activity than 1080 poisoning, and therefore appears to be closer to the objectives of humane euthanasia in a clinical setting where rapid loss of consciousness until death is sought (Anon 2003).

The ejector capsule load of 226 mg PAPP used in the pen trials was based upon a concentration of 27.2 mg kg^{-1} to accommodate an 8.3 kg animal, which is considered the upper weight range for a free-ranging fox in SE Australia (Marks *et al* 2002). A deliberately high dose of PAPP was selected in the pen trials given the uncertain dosing success of the ejector, as some dosage loss has been implied in previous trials (Marks *et al* 2002). However, the rapid

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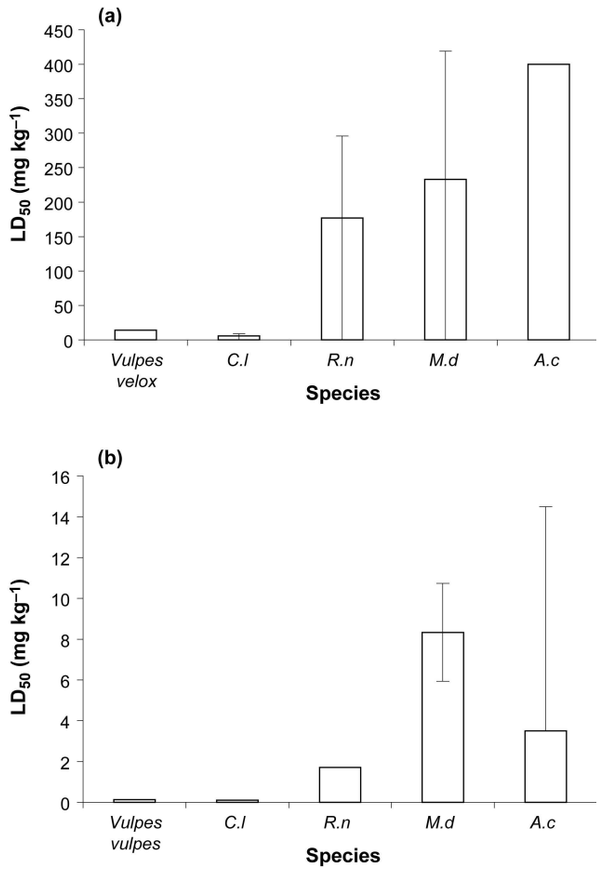
progression of the toxicosis in the pen trials suggests that capsule doses could be substantially reduced after a better estimate of PAPP LD_{100} for foxes is obtained.

Fatal methaemoglobinemia has been demonstrated to occur in rabbits when the measured value of HbO is lower than 20% (Ohshima *et al* 1992). Death in humans has been reported to occur when MetHb concentrations are 76% (Saito *et al* 1996) and 78% (Saito *et al* 2000), and levels between 70% and 83% are assumed to be lethal (Caudill *et al* 1990), although lethal concentrations of MetHb in red foxes have not been reported. Our model was selected so that beyond a critical dose of PAPP an asymptote occurs at approximately 80% MetHb; however, the appropriate concentration of MetHb that results in death is unknown. A single observation where the fox, given 25.2 mg kg^{-1} PAPP, died prior to the experimental end-point of 85% MetHb supports this model. It is unknown if the MetHb levels in the two foxes that exceeded the end-point and were euthanased would have continued to increase.

PAPP forms the active metabolite para-hydroxyaminopropiophenone (PHAPP) after *N*-hydroxylation, and alone will not form MetHb *in vitro* (Marrs & Bright 1986). PHAPP is thought to enter into inter-erythrocytic catalytic cycles that produce MetHb, which probably accounts for its high MetHb-forming potency (Eyer 1983; Marrs & Bright 1986). In contrast, 4-dimethylaminophenol (DMAP) is a para-aminophenol that appears to immediately form MetHb after oxidation by HbO to quinoneimine. Elimination of DMAP will occur subsequent to conjugation of DMAP with SH groups and glutathione, whilst PHAPP appears to be much less easily eliminated and will thus remain within the RBC for longer periods (Marrs & Bright 1986). Humans are generally regarded as being sensitive to MetHb-forming compounds, although dogs will form approximately three times the amount of MetHb from IM and intravenous (IV) doses of DMAP (Klimmek *et al* 1983). On a weight-for-weight basis, approximately five times as much DMAP in dogs is required to produce the same amount of MetHb compared to PAPP (Marrs & Bright 1986). A disparity in the relative rodent toxicity of a range of para-aminophenols was related to the number of carbon atoms in the alkyl chain and was believed to relate to the speed of *N*-hydroxylation of each (Pan *et al* 1983). It is unknown if the variations in alkyl chain length had a similar influence on the toxicity of these same compounds in canids.

In Australia, 1080 is used for the control of exotic carnivores primarily because of their relatively greater sensitivity to the compound compared to endemic wildlife species (McIlroy 1981, 1986). Some native fauna in Western Australia have evolved a greater tolerance to 1080, as it occurs naturally in many plant species (Twigg & King 1991; Twigg 1993). A substantial difference in the relative sensitivity of canids to oral doses of PAPP compared with other species has also been recognised. The coyote (*Canis latrans*) and swift fox (*Vulpes velox*) were found to have an oral LD_{50} for PAPP of 5.6 mg kg^{-1} and 14 mg kg^{-1} respectively. Other mammal species (rodents and mustelids) were

Figure 3



Oral doses estimated to be lethal to 50% of the population (LD_{50}) in selected species for **(a)** PAPP (Savarie *et al* 1983) and **(b)** 1080 (McIlroy 1982; Eisler 1995) (*C.l* = *Canis latrans*, *R.n* = *Rattus norvegicus*, *M.d* = *Mus domesticus*, *A.c* = *Aquila chrysaetos*) ($P < 0.05$).

estimated to be between 10 and 30 times less sensitive than the swift fox and coyote respectively. Birds, such as the golden eagle (*Aquila chrysaetos*), were estimated to have an LD_{50} value approximately 29 and 71 times higher than that of the swift fox and coyote (Savarie *et al* 1983). A comparison of relative sensitivity for species where a LD_{50} estimate exists for both PAPP (Figure 3a) and 1080 (Figure 3b) suggests that a similar species difference in sensitivity exists for both 1080 and PAPP in some species outside of Western Australia. Species differences in the metabolism of xenobiotic compounds have long been recognised. Various studies have reported profound species differences in both the therapeutic response to drugs and their relative toxicity (Williams 1973; Walker 1978; Gaunt *et al* 1981; Eason *et al* 1982, 1988). Exploitation of such species differences in xenobiotic metabolism has been proposed as a basis for the development of highly target-specific vertebrate pest control techniques in Australia (Marks 2001b). As yet, no accounts of the sensitivity of Australian marsupials to PAPP have been published. However, the specificity of the toxicant delivery technique will also determine the risk that

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lethal agents pose to non-target species. An assessment of the target-specificity of the ejector in SE Australia predicted that of 31 non-target mammals considered, only the spotted-tailed quoll (*Dasyurus maculatus*), Tasmanian devil (*Sarcophilus harrasii*), and large brushtail (*Trichosaurus vulpecula*) and mountain brushtail possums (*Trichosaurus canis*) may be able to trigger an ejector (Marks & Wilson in press). Current research aims to investigate whether these species are at risk. Thereafter, an assessment of the sensitivity of these four native species to the PAPP formulation may be required.

Animal welfare implications

The PAPP formulation shows promise as a humane lethal agent that is delivered by the ejector in a highly target-specific manner. As the ejector cannot be moved or cached it has the potential to be used strategically in areas where effective fox control is not currently possible. The combination of the new PAPP formulation and the ejector may allow for a target-specific and humane method of fox control where conventional baiting is inappropriate.

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