Literature search for mustelid-specific toxicants

M.L. Wickstrom¹ and C.T. Eason²

Landcare Research², P.O. Box 69, Lincoln, New Zealand

¹Present address: Toxicology Centre, 44 Campus Drive, University of Saskatchewan, Canada
²Contact and address for correspondence

ABSTRACT

Survival of some species of native birds in New Zealand requires long-term control of introduced mustelid predators. Control strategies using poisoned baits currently rely on the use of sodium monofluorooacetate (compound 1080), or anticoagulant rodenticides. While effective, the widespread use of 1080 is controversial due to its lack of target specificity, whereas anticoagulants are under increasing scrutiny as a result of persistent environmental residues. The Department of Conservation has indicated a need for a more target-specific toxicant for mustelid control that is effective, humane, and non-persistent. As an initial step Landcare Research reviewed the relevant literature on the toxicology and physiology of the Mustelidae to determine if mustelids exhibit unusual sensitivity to any particular class of foreign compound, which could be linked to a physiological anomaly in the absorption, metabolism, or excretion of that compound. Such an anomaly might be exploited in the design of a targeted toxicant. A thorough review of the international scientific literature was conducted by searching on-line databases in toxicology, physiology, and veterinary medicine. In addition, the clinical toxicology database at the National Animal Poison Control Center (University of Illinois, USA), was searched for all mustelid exposures. Experts at the mink environmental toxicology research group (Michigan State University, USA) and the Centre National d’Informations Toxicologiques Veterinaires (Lyon, France) were also consulted. Results indicated that mustelids appear to be unusually sensitive to planar organochlorine compounds, oestrogen analogues, pyrethrin / pyrethroid-type insecticides, methaemoglobin inducing agents, and possibly non-steroidal anti-inflammatory agents. Organochlorines and oestrogens are not appropriate for use as vertebrate pesticides, and humaneness may be a concern with the insecticides. Methaemoglobin-inducing agents appear to be sufficiently humane and non-persistent to warrant toxicity testing to verify efficacy / sensitivity and humaneness in captive ferrets and stoats.

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1. Introduction

The peer-reviewed scientific literature on the toxicology and physiology of the Mustelidae, and North American and European clinical veterinary toxicology databases were searched by Landcare Research for the Department of Conservation (DOC) in 1997/98. This review was intended to identify potential physiological idiosyncrasies, or trends in mortality data in the clinical toxicology databases that could be consistent with unusual sensitivity of members of this mammal family to a specific class of foreign compounds. Such information could be exploited in the effort to identify or develop a more target-specific toxicant for mustelid control in New Zealand.

The objective was to review the scientific literature and clinical veterinary toxicology databases to determine if specifically targeted poisons for mustelid control can be identified or developed.

1.1 BACKGROUND

Stoats (Mustela erminea), ferrets (Mustela furo), and weasels (Mustela nivalis) were introduced into New Zealand in the last century in an attempt to control rabbits (Oryctolagus cuniculus). They are now widely distributed in a variety of habitats throughout the country, and have become serious predators of native fauna. In particular, stoat predation is considered to be the primary factor contributing to the decline of mainland kiwi, Apteryx spp. (McLennan et al. 1996) and kaka, Nestor meridionalis (Wilson et al. 1998) populations, as well as affecting cavity-nesting birds (Elliott et al. 1996; O’Donnell et al. 1996). Survival of some species of native birds on the mainland of New Zealand will require effective, long-term control of these introduced mustelids. Control strategies using poisoned baits currently rely on the use of sodium monofluoroacetate (compound 1080), or to a lesser extent, on anticoagulant rodenticides (Ogilvie et al. 1996, Spurr 1996, Spurr and Hough 1997, Spurr et al. 1997a, 1997b, Ogilvie and Eason 1998). While effective, the widespread use of 1080 in New Zealand is increasingly controversial, due in part to its lack of target specificity (Eason 1997), while anticoagulants are under increasing scrutiny as a result of persistent environmental residues (Eason et al. 1996). Vertebrate pest control programmes must be proactive in addressing issues of environmental safety and humaneness, and in seeking to minimise non-target impacts, in order to remain socially acceptable and politically defensible. The need for humane, effective, and more target-specific toxicants for predator control in New Zealand was highlighted at a recent DOC workshop on predator control strategies (Sim and Saunders 1997), in DOC Science and Research’s Predator Research Strategy 1997–2002 document, and at a DOC workshop entitled ‘Priorities for predator research’ held in August 1998.

Environment Australia recently funded a review of specific toxic substances for feral cat control by researchers at the Victoria Institute in Melbourne, which has led to the identification of a promising toxicant. The mechanism of action of this toxicant targets a known idiosyncrasy in feline physiology, the unusual sensitivity of cat haemoglobin to oxidation. This mode of action makes the toxicant relatively cat-
specific and humane. The sensitivity of non-target Australian animals remains to be determined, but if trials prove successful, the new agent may eventually replace 1080 in cat baits, both in Australia and New Zealand. The current study takes a similar approach to the Australian effort, intending to assess the feasibility of developing a mustelid-specific toxicant.

2. Methods

Several members of the family Mustelidae, including mink and ermine (stoats), have been farmed for commercial fur production in North America, Europe, and Russia for many years. In addition, zoological parks and universities have extensive collections of mustelids in captivity for display and research purposes, and ferrets have recently become common pet animals. As a consequence, there is a relatively extensive scientific and clinical veterinary database on mustelid physiology, medicine, and toxicology. The initial step in the identification / development of a species-specific toxicant was a review of this literature. This review was intended to determine if mustelids exhibit unusual sensitivity to any particular class of pharmaceutical agent, environmental contaminant, or other foreign compound, which could be linked to a physiological anomaly in the absorption, metabolism, or excretion of that compound. Such an anomaly might be exploited in the design of a mustelid-specific toxicant. A thorough review of the international scientific literature was conducted by searching on-line databases in toxicology, physiology, and veterinary medicine. Databases searched included Medline, Toxline, Poisindex®, CAB Abstracts, Current Contents, Biological Abstracts, Agricultural On-line Abstracts, and Veterinary Information Services.

In addition to searching the peer-reviewed literature, the clinical toxicology database at the National Animal Poison Control Center (NAPCC) at the University of Illinois, USA, was searched for all mustelid exposures. The NAPCC is the only veterinary poison information centre in North America, and has been in continuous (24 h) operation since 1978. It has compiled the largest veterinary toxicology database in the world, containing information on >250 000 cases involving animal exposures, including species and number affected, toxic substance (if known), dose (if known, or estimated), route of exposure, clinical signs, other diagnostic data (e.g. clinical pathology, radiography, histopathology), treatment, and outcome. A total of 525 mustelid exposures were identified in the NAPCC database. Veterinary toxicology experts affiliated with the Centre National d’Informations Toxicologiques Veterinaires (Lyon, France), which is the European equivalent of the NAPCC, were also consulted concerning case histories of Mustelidae. Finally, scientists affiliated with the mink (Mustela vison) environmental toxicology research group at Michigan State University, USA, were consulted regarding the sensitivity of mustelids to various environmental contaminants.
3. Results

Ferrets and mink are highly sensitive to elevated levels of endogenous oestrogen or dietary oestrogen analogues (Hart 1987, 1988), or to naturally occurring phyto-oestrogens or oestrogenic mycotoxins (Yamini et al. 1997). Toxic effects include irreversible alteration of blood-forming elements in the bone marrow, leading to progressive aplastic anaemia, thrombocytopenia, and leucopenia, and liver damage. The bone marrow changes are characterised clinically by weakness, coagulopathy (failure of blood clotting mechanisms leading to fatal haemorrhaging) and increased susceptibility to infectious diseases.

Many studies demonstrated that mink, and to a lesser extent, ferrets (Bleavins et al. 1980) and otters, *Lutra canadensis* (Wren 1991) and *L. lutra* (Keymer et al. 1988, Mason and Madsen 1993), are highly sensitive to synthetic, planar organochlorine compounds such as polychlorinated biphenyls, PCBs (Bleavins et al. 1980, Hornshaw et al. 1983, Aulerich et al. 1985, 1986, Wren et al. 1987a, Kihlstrom et al. 1992), polychlorinated dibenzo-p-dioxins, PCDDs (Hochstein et al. 1988, Tillitt et al. 1996), and polychlorinated dibenzofurans, PCDFs (Tillitt et al. 1996). Toxic effects include reproductive failure (Patnode and Curtis 1994, Heaton et al. 1995a), decreased kit survival (Wren et al. 1987b, Heaton et al. 1995a), altered immune system function (Smits et al. 1996a, 1996b), haematological and histopathological changes (Heaton et al. 1995b) and death (Bleavins et al. 1980, Aulerich et al. 1987). These compounds are common environmental contaminants in many industrialised regions, and are bioaccumulative and highly persistent.

The mustelid exposures identified in the NAPCC database that were confirmed to have resulted in death are summarised in Table 1. Most of these fatal exposures were to pet ferrets, with the balance involving ranch mink. More than 50% of the fatal mustelid exposures identified in the clinical veterinary toxicology databases involved pyrethrin or pyrethroid insecticides applied dermally to pet ferrets or to the animals’ environment, for controlling fleas or other insect pests. Although doses could not be determined, in most cases the use of the agent was appropriate, indicating that ferrets may be highly sensitive to this class of insecticides. Clinical signs included diarrhoea, weakness, neurological signs ranging from ataxia and mild tremors to seizures, renal failure, and death.

Another class of compounds implicated in lethal exposures in pet ferrets was the non-steroidal anti-inflammatory agents, including ibuprofen and naproxen (Table 1). Signs associated with the accidental ingestion of these human pharmaceuticals included vomiting, ataxia, tremors, renal failure, coma, and death.

In at least one study, ferret erythrocytes (red blood cells) were reported to be relatively sensitive to oxidative stress, leading to the conversion of haemoglobin to methaemoglobin, which is incapable of binding oxygen (Davis et al. 1993). The findings of this study were reinforced by several cases from the clinical toxicology database (Table 1) in which pet ferrets exhibited unusual sensitivity to acetaminophen (paracetamol), a human analgesic that induces methaemoglobin in cats at low doses (< 40 mg/kg). This pharmaceutical causes liver failure in most other species at doses of ≥ 100 mg/kg, with methaemoglobin formation occurring in more severe cases, > 200 mg/kg (Beasley et al. 1997).
<table>
<thead>
<tr>
<th>SPECIES</th>
<th>TOXIC AGENT(S)</th>
<th>CASES</th>
<th>USE</th>
<th>CLINICAL SIGNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferret</td>
<td>pyrethrins and synergists “methoprene”</td>
<td>9</td>
<td>Applied dermally</td>
<td>disorientation, depression, weakness, anorexia, vomiting, melena, icterus, dyspnea, tachypnea, coma</td>
</tr>
<tr>
<td>Ferret</td>
<td>tetramethrin, resmethrin, phenothrin</td>
<td>1</td>
<td>Used in house</td>
<td>seizures, hyperthermia</td>
</tr>
<tr>
<td>Ferret</td>
<td>deltamethrin</td>
<td>1</td>
<td>Used in house</td>
<td>depression, pulmonary edema</td>
</tr>
<tr>
<td>Ferret</td>
<td>cypermethrin</td>
<td>2</td>
<td>Used in house</td>
<td>facial edema, erythema, tremors</td>
</tr>
<tr>
<td>Ferret</td>
<td>d-trans-allethrin, permethrin</td>
<td>1</td>
<td>NQ (used in house)</td>
<td>diarrhoea, depression, anorexia, adipse</td>
</tr>
<tr>
<td>Ferret</td>
<td>cyfluthrin</td>
<td>2</td>
<td>Applied dermally</td>
<td>diarrhoea, hematuria, dyspnea, tremors, seizures, renal failure</td>
</tr>
<tr>
<td>Ferret</td>
<td>tralomethrin</td>
<td>1</td>
<td>Applied dermally</td>
<td>ataxia, weakness</td>
</tr>
<tr>
<td>Ferret</td>
<td>chlorpyrifos</td>
<td>2</td>
<td>Used in house</td>
<td>depression, disorientation, ataxia, weakness, anorexia</td>
</tr>
<tr>
<td>Mink</td>
<td>chlorpyrifos</td>
<td>1</td>
<td>Mix in feed</td>
<td>salivation, seizures</td>
</tr>
<tr>
<td>Ferret</td>
<td>carbaryl</td>
<td>3</td>
<td>Applied dermally</td>
<td>salivation, vomiting, diarrhoea, GI haemorrhage, weakness, tenesmus, dysuria</td>
</tr>
<tr>
<td>Mink</td>
<td>glyphosate</td>
<td>1</td>
<td>Unknown source</td>
<td>vomiting, depression, weakness, crystalluria, renal failure</td>
</tr>
<tr>
<td>Mink</td>
<td>clomazone</td>
<td>1</td>
<td>Spray drift</td>
<td>diarrhoea</td>
</tr>
<tr>
<td>Ferret</td>
<td>bromethalin</td>
<td>1</td>
<td>Ingested rat bait</td>
<td>diarrhoea, depression, progressive paralysis</td>
</tr>
<tr>
<td>Mink</td>
<td>anticoagulant rodenticide (unidentified)</td>
<td>1</td>
<td>NQ (ingested rat bait)</td>
<td>depression, melena epistaxis, oral haemorrhage</td>
</tr>
<tr>
<td>Ferret</td>
<td>ivermectin</td>
<td>1</td>
<td>Used as anthel-mintic</td>
<td>ataxia, tachypnea, peripheral vasoconstriction, coma</td>
</tr>
<tr>
<td>Ferret</td>
<td>iron</td>
<td>1</td>
<td>NQ (sup-plement)</td>
<td>vomiting, anorexia, weight loss</td>
</tr>
<tr>
<td>Ferret</td>
<td>acetaminophen</td>
<td>7</td>
<td>Owner misuse (&lt;80B &lt;500 mg)</td>
<td>salivation, depression, ataxia, diarrhoea, icterus, tachypnea, cyanosis, methaemoglobinemia</td>
</tr>
<tr>
<td>Ferret</td>
<td>ibuprofen</td>
<td>2</td>
<td>Owner misuse</td>
<td>vomiting, ataxia, metabolic acidosis, renal failure, coma</td>
</tr>
<tr>
<td>Ferret</td>
<td>naproxen</td>
<td>1</td>
<td>Owner misuse</td>
<td>vomiting, tremors, renal failure, coma</td>
</tr>
<tr>
<td>Ferret</td>
<td>octyl decyl dimethyl ammonium chloride</td>
<td>1</td>
<td>Disinfect cages</td>
<td>vomiting, anorexia</td>
</tr>
<tr>
<td>Ferret</td>
<td>glycolic acid, butyl carbitol, sulfuric acid</td>
<td>2</td>
<td>Disinfect cages</td>
<td>vomiting, anorexia, dehydration, neurologic signs (chewing fits)</td>
</tr>
</tbody>
</table>

1 Number of animals per case ranged from 1 to 22,000
2 Clinical signs in some cases are as described by the animal owner to NAPCC toxicologists, and in other cases as described by the referring veterinarian. The quality of this type of data is therefore somewhat variable.
4. Conclusions and recommendations

Mustelids appear to be unusually sensitive to oestrogens and oestrogen analogues, planar organochlorine compounds, pyrethrin / pyrethroid-type insecticides, methaemoglobin inducing agents, and possibly non-steroidal anti-inflammatory agents. Use of synthetic oestrogen analogues (e.g. diethylstilboestrol) as a pest control agent would probably be cost-prohibitive, and would have significant human and environmental health implications. It can not be recommended at this time.

The synthetic planar organochlorine compounds (PCBs, PCDDs, and PCDFs) are serious environmental contaminants as a result of their persistence, potential to bioaccumulate in living organisms, reproductive toxicity, and carcinogenicity. Therefore, deliberate release of these compounds into the environment for any purpose is inappropriate.

Use of the pyrethrin / pyrethroid class of insecticides may deserve further investigation. However, these compounds have the potential to cause severe neurological signs, including seizures, in mammals at high doses. Therefore, the humaneness of these compounds would need to be confirmed in pen trials with a small number of captive ferrets and stoats before large-scale evaluation of their efficacy and palatability could be considered.

Lethal doses in ferrets accidentally exposed to non-steroidal anti-inflammatory agents were not quantifiable, but may have been high in at least some cases (>500 mg/kg). Therefore, sensitivity is difficult to determine from existing case-study data. Range-finding studies with captive ferrets and stoats would be required to confirm that mustelids are in fact unusually sensitive to these compounds.

Both controlled studies of haemoglobin sensitivity and case studies of exposed animals indicate that ferrets may be highly sensitive to agents that oxidise haemoglobin to methaemoglobin. This same effect is also seen in cats, and is the physiological basis for the cat-specific toxicant now under development in Australia. If mustelids are in fact similar to cats in their sensitivity to methaemoglobin inducers, this class of agents would be the most promising for further research in the effort to develop a targeted toxicant. There are many agents that induce methaemoglobin in sensitive species. These include nitrates (in ruminants and neonates of many species), nitrites, copper, chlorates, naphthalene, paracetamol (in cats), resorcinol (in cats), azo dyes (like phenazopyridine), local anaesthetics (like benzocaine) (Osweiller 1996, Beasley et al. 1997). Another group of compounds that oxidise haemoglobin, but are co-oxidised with oxyhaemoglobin, forming methaemoglobin and hydrogen peroxide, include N-hydroxy arylamine (like dapsone hydroxylamine), phenolic compounds (like 5-hydroxy primaquine) and hydrazines (like phenylhydrazine) (Fletcher et al. 1988, Coleman and Jacobus 1993).

While there is a range of compounds that could be used to induce methaemoglobin in sensitive species, the toxicant currently under development in Australia (C. Marks pers. comm.) is likely to be the most promising option as a first choice. A database on the toxicology of this compound has been developed since 1994, with the intent of using it as a vertebrate pesticide. Therefore, some of the preliminary issues that might
affect its suitability as a predacide, such as humaneness, have already been addressed, at least in cats.

Based on the above, the author recommends:

- The efficacy and humaneness of methaemoglobin-inducing agents should be evaluated in captive ferrets and stoats. If available, the first choice for this test compound would be the toxicant undergoing evaluation for feral cat control in Australia. Negotiation with Australian research groups to obtain samples of this compound should be conducted.

- Range-finding studies should be conducted to determine the relative sensitivity of captive ferrets and stoats to representative non-steroidal anti-inflammatory agents (e.g. ibuprofen, naprosyn).

- The relative humaneness of representative pyrethrin or pyrethroid insecticides should be evaluated in captive ferrets and stoats prior to efficacy and palatability studies. A compound should be chosen from the range of flea control products that have already been shown to be fatal to mustelids (e.g. tetramethrin, resmethrin, phenothrin, cypermethrin, permethrin, d-trans-allethrin, deltamethrin, or cyfluthrin). Most of the formulations used for flea control include piperonyl butoxide and / or MGK-264 as synergists to inhibit microsomal monooxygenase detoxification and thus enhance toxicity to the insects. Test compounds should include these ancillary formulation constituents in the event that they also contribute to mammalian toxicity.

- Developing a mustelid-specific toxicant should not proceed until evaluation of the toxicology of the Australian toxicant and its suitability for use in mustelids has been completed.

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6. References


