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# **Para-aminopropiophenone and its Registration and Use as a Vertebrate Pesticide in New Zealand**

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**ABSTRACT:** PAPP is short for *para*-aminopropiophenone and is a new vertebrate pesticide. It is a compound with the formula  $C_9H_{11}NO$ , it is comparative humane, has low secondary poisoning risk, and has an antidote. PAPP was originally trialed in the 1960s as an antidote for human radiation and cyanide poisoning. In the USA, it has been investigated as a tool for coyote control and was found to be specifically much more toxic to carnivores than to birds and humans. In Australia, it will be used for field control of foxes, wild dogs, and feral cats. In New Zealand, PAPP was registered in 2011 for the control of stoats and feral cats, following the completion of pen and field trials and submission of extensive dossiers covering its effectiveness as a pest control agent and on its ecotoxicology, toxicology, and metabolism.

**KEY WORDS:** cats, *Felis catus*, *Mustela erminea*, New Zealand, PAPP, *para*-aminopropiophenone, registration, stoats, vertebrate pesticides

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## **INTRODUCTION**

New Zealand wildlife evolved in the absence of mammalian predators, and birds have been particularly affected by the introduction of non-native predators. Over 40% of the pre-human land bird species are now extinct in New Zealand, and the proportion of birds classed as threatened is one of the highest in the world (Clout 1997). Introduced species including feral cats (*Felis catus*) and stoats (*Mustela erminea*) are targeted to protect native birds. For example, stoats are responsible for approximately half of kiwi (*Apteryx* spp.) chick deaths in many areas throughout New Zealand; cats also prey, to a lesser extent, on kiwi chicks. The combined effect of these predators results in only 10% of kiwi chicks surviving to the age of 6 months. Young kiwi chicks are vulnerable to stoat predation until they reach about 1-1.2 kg in weight, at which time they can usually defend themselves. Control methodologies for these predators currently rely largely on labour-intensive trapping. Hence the development of a safe, humane toxin for predator control is highly desirable.

PAPP is short for *para*-aminopropiophenone ( $C_9H_{11}NO$ ). PAPP is a new vertebrate pesticide that has now been developed in New Zealand as a new tool for the control of stoats and feral cats (Murphy et al. 2007, Eason et al. 2010a). PAPP was originally trialed in the 1960s as an antidote for human radiation and cyanide poisoning (Marrs and Bright 1987). In historical pharmaceutical trials, PAPP was found to be specifically much more toxic to carnivores than to birds and humans. In the USA, it has been investigated as a tool for coyote control (Savarie et al. 1983). In Australia, it will be used for field control of foxes, wild dogs, and feral cats. We have provided progress reports on the earlier research on new toxins including PAPP in the past (Eason et al. 2008, Shapiro et al. 2010). PAPP was registered in New Zealand in 2011 for the control of stoats and feral cats.

This short paper provides a brief overview of features of PAPP that have underpinned its registration.

## **MODE OF ACTION**

PAPP's primary mode of action is via a toxic effect on red blood cells, mediated by a toxic metabolite, *para*-hydroxylaminopropiophenone (PHAPP) (DeFeo et al. 1972). Following administration or ingestion in bait, PAPP is absorbed into the blood stream. It causes a condition called methaemoglobinaemia. It acts by rapidly forming methaemoglobin (the ferric state of haemoglobin), which is unable to release bound oxygen.

Methaemoglobinaemia is a disorder characterized by the presence of a higher than normal level of methaemoglobin in the blood. It is a form of haemoglobin in red blood cells that has a decreased affinity for oxygen. When methaemoglobin concentration is elevated in red blood cells, tissue hypoxia (lack of oxygen to tissue) can occur. Normally, methaemoglobin levels are <1%. Some drugs such as local anaesthetics can cause methaemoglobinemia and it can also be inherited, and these individuals will have levels higher than 1%. Symptoms are proportional to the methaemoglobin concentration in the blood and include skin colour changes (with blue or grayish pigmentation) and blood colour changes (brown or chocolate colour) at methaemoglobin levels up to 15%. Moderate methaemoglobinaemia (<30 % of total haemoglobin oxidised) causes discomfort (e.g., headache), with severe methaemoglobinaemia (>50 % being possibly life threatening. Levels of methaemoglobin above 70% in the blood are usually fatal (Coleman and Coleman 1996). This creates a lethal deficit of oxygen in cardiac muscle and the brain. Death in stoats and feral cats usually occurs within 1.5 h after eating a lethal dose. The animals appear lethargic and sleepy before they die (Eason et al. 2010a)

## TOXICOLOGY

### Acute Toxicity

An extensive database on the acute toxicity of PAPP in a diverse spectrum of species exists. LD<sub>50</sub> of PAPP in the two target pest species in New Zealand, namely stoats and feral cats, is <10 mg/kg. Cats and stoats are extremely susceptible (Eason et al. 2010a) and as noted above, most other mammalian carnivores are highly sensitive to poisoning, with lethal doses that are far lower in these species than in non-carnivorous mammalian species. There is no LD<sub>50</sub> value for humans. However, cynomolgus monkeys have been administered 150 mg/kg/day for 2 weeks without mortality (Lackenby 1987), hence the single dose oral LD<sub>50</sub> for this species is clearly well in excess of 150 mg/kg, and it is probable that this is also the case for humans.

PAPP has been shown to be generally less toxic to birds than to mammalian carnivores (Savarie et al. 1983, Eason et al. 2010b). Whilst birds are less susceptible to PAPP than stoats or feral cats, or mammalian carnivores in general, it appears some bird species are adversely affected and it will be important to limit their exposure when PAPP is used for predator control. The risk to any non-targets will be less with stoat bait than a cat bait, as only ~13 mg PAPP is needed for stoats compared with ~80 mg PAPP for cats (Murphy et al. 2007, Shapiro et al. 2010).

As a result of our understanding of PAPP's mode of action, variations in LD<sub>50</sub> values can be viewed as a function of the differences in the metabolism of PAPP between species, in the metabolism and excretion of the degradation products (Wood et al. 1991), and possibly also to differences between species in the rates of haemoglobin oxidation and to a lesser extent, in the relative capacity of species to reduce methaemoglobin to haemoglobin.

The two reptile species assessed in Australia (*Varanus* spp. or goanna) were more sensitive to PAPP than dogs (McLeod and Saunders 2013). This sensitivity of reptiles could have relevance to PAPP use in New Zealand, and care with baiting strategies will be advisable. In a practical sense, the risk from the use of PAPP needs to be evaluated in the context of the impacts of stoats and feral cats on threatened species populations, including reptiles.

### Chronic Toxicity

Multi-dose studies in animals have been conducted to shed light on additional potential sub-lethal effects and possible target organ toxicity, using periods of exposure of 14 and up to 30 days duration (Doull and Plzak 1963, Baskin and Fricke 1992). In a review paper, Baskin and Fricke (1992) report sub-acute oral toxicity of PAPP in laboratory rats and cynomolgus monkeys exposed to a 14-day treatment period, followed by a 14-day treatment-free period. Minor changes observed in PAPP-treated animals returned to control levels following cessation of treatment. Baskin and Fricke's (1992) review concludes that the pathological and histopathological effects seen with PAPP treatment were to be expected as consequences of high methaemoglobin concentrations, implying an indirect rather than a direct effect of PAPP.

PAPP toxicology has also been studied in humans.

Paulet et al. (1963) showed that sub-lethal doses (80 mg or 100 mg) administered orally to 51 human volunteers produced methaemoglobin concentrations ranging from 2% to 48%. There was no evidence of physical, intellectual, or psychological impairment, appetite was not suppressed, and renal systems were normal. Therefore, the available data appear to indicate that PAPP is less acutely toxic to humans than to canids.

The carcinogenic potential of PAPP has been evaluated by *in vitro* and *in vivo* testing. PAPP is not mutagenic (Baskin and Fricke 1992). Furthermore, exposure of individuals or communities to amounts of PAPP that would cause effects should be most unlikely when it is handled and used carefully for predator control.

### METABOLISM

Wood et al. (1991) investigated the metabolism and excretion of radio-labelled PAPP in Sprague-Dawley laboratory rats (*norvegicus*), dogs, and cynomolgus monkeys. PAPP was rapidly absorbed by all 3 species with peak plasma concentrations at 15 min (male rats), 1 h (female rats), 30 min-h (beagles), and 1-1.5 h (monkeys) after oral ingestion. As a result of metabolic and excretory processes (Wood et al. 1991), levels of plasma radioactivity decline rapidly, with plasma concentrations declining to very low levels by 72 hours. This indicates that PAPP is likely to be slightly more persistent than cyanide in live animals but as, or less persistent than 1080, and substantially less persistent than anticoagulants. It also means it will not bioaccumulate in the food chain, and secondary poisoning risks are low, particularly for the majority of bird species.

### WELFARE

One of the drivers for developing PAPP has been animal welfare. A humane death has been identified as a very important aspect and is a key to the effectiveness of PAPP for stoat and feral cat control. When delivered at a lethal dose, rapid induction of high levels of methaemoglobin quickly induces death with minimal symptoms of distress. Research has shown the symptoms of poisoning are similar in both feral cats and stoats. The onset of symptoms of poisoning and time to death are swift in comparison to the anticoagulant toxins or 1080 (Eason et al. 2010a). The sequence of behavioural changes in animals is consistent with our understanding of the toxicology of PAPP, namely that the compound is rapidly absorbed and quickly induces methaemoglobinaemia. In sub-lethally dosed stoats and feral cats, there was recovery from sub-lethal poisoning without any long term adverse effects being observed.

### EFFECTIVENESS

The currently registered product containing PAPP is a soft green paste that contains 410 mg/kg PAPP as the active ingredient. It comes in pre-loaded syringes, packed in a secure carry box with instructions. Baits are prepared by enclosing a small amount of paste in green-dyed raw minced meat to form a small meatball. These meatballs are placed in bait stations. Meat baits containing PAPP must be treated as potentially poisonous to non-target species and must be handled as carefully as any other

type of toxic bait. To date, field experience with PAPP is limited, but where it has been used it has been very successful. Trials undertaken in Waitutu Forest, Southland, achieved a reduction in stoat abundance of 83-87% over 5 nights. These results indicate that PAPP is an effective toxin for stoats in the field and has the potential to provide a significant new tool for conservation of native species (Dilks et al. 2011). Similar results have been obtained with radio-collared feral cats (Shapiro et al. 2010, Murphy et al. 2011). Long-life baits are being researched and a resetting toxin delivery system to achieve long-term suppression of stoat populations is showing promise in pen trials (Blackie et al. 2012). Stoats have been killed in enclosure trials by a paste containing PAPP sprayed onto the chest and stomach by a resetting systems triggered by the stoats passing through a tunnel (Blackie et al. 2012), and field trials with resetting devices are now showing promise (E. Murphy, pers. comm.).

## CONCLUSIONS

Over the last 3 decades, considerable effort has been put into improving and refining the use of 1080 in New Zealand. Complementing this new tools and traps are being developed. PAPP is just one example. Land managers, pest control professionals, and community groups can use it for stoat control to protect vulnerable native species from predation. The use of PAPP baits can complement traditional trapping and may enable better protection of native birds, such as kiwi, over larger areas. PAPP provides an additional control tool targeted specifically at stoats and feral cats, species that are notoriously difficult to control. PAPP is humane in action, is not persistent in the environment, and is unlikely to cause secondary poisoning, although care is needed to prevent dogs and pets from primary poisoning by eating baits directly. PAPP was approved by the New Zealand EPA and registered for use as a vertebrate toxic agent (VTA) by the Agricultural Chemical and Veterinary Medicines Group of the Ministry for Primary Industries in 2011. As an extension to research and development on PAPP, we have explored other methaemoglobinaemia-inducing chemicals as potential rodenticides or VTAs for mammalian pest control. After several years of research and development, conducted in parallel to our development of PAPP, we have successfully registered sodium nitrite for possum and feral pig control in 2013. Unfortunately, whilst sodium nitrite is effective for those two species, it could not be made to work as an effective rodenticide. Knowing that PAPP is not sufficiently toxic to rats to be a rodenticide, we also synthesized compounds related to PAPP as candidate rodenticides. Despite screening many compounds related to PAPP with the same mode of action, none were sufficiently effective in baits to warrant further development (Rennison et al. 2013). At this time, we conclude that PAPP will be effective for the control of a number of predator pest species, and sodium nitrite for feral pigs and possums; however, we do not believe compounds with this mode of action will be effective rodenticides unless a substance with an LD<sub>50</sub> of <40 mg/kg can be identified.

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