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PAPP

(Para amino propiophenone)

A NEW VERTEBRATE PESTICIDE

Briefing note to practicing Veterinarians and Veterinary Lecturers

PREPARED MARCH 2016 BY
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Briefing note to Veterinarians

Para Amino Propiophenone (PAPP): A new vertebrate pesticide

This technical briefing provides more detailed information to Veterinarians than is provided in ACTA product booklets and industry fact sheets, which are for a general audience.

The objectives of this briefing are to provide:

- Background to the use of PAPP as a pesticide
- Summary information regarding PAPP
- Toxicity facts on PAPP in canids & non-target species
- Features of approved FOXECUTE® and DOGABAIT baits
- An overview of methylene blue as an antidote for accidental poisonings (a clinical guidance sheet on methylene blue will be provided shortly)
- Links to labels for FOXECUTE® and DOGABAIT baits
- Links to draft product booklets as further background
- A short bibliography of relevant published literature
- Refresher information on 1080 poisoning.

The registration approval and launch of PAPP baits as an additional tool for canid pest management has taken 11 years research by the Invasive Animals Cooperative Research Centre (IA-CRC) and Animal Control Technologies (Australia) Pty Ltd (ACTA), with support from many agencies together with substantial financial support from Australian Wool Innovation (AWI).

The new products have strengths and weaknesses that will compliment sodium fluoroacetate (1080) based vertebrate baits. It is essential for Australian agriculture, biodiversity and environment that both PAPP and 1080 baits are available as tools to manage wild canids.

We hope that this briefing will assist all Veterinarians to diagnose or treat any unexpected poisonings and that veterinary lecturers will include this information into training for all new veterinary students into the future.

We would also appreciate if veterinarians would contact ACTA (enquiries@animalcontrol.com.au) if they encounter unexpected outcomes from the early adoption of PAPP based products that are not easily resolved during normal clinical practice so ACTA has an adverse effect database for the new products.

OVERALL SUMMARY

Foxes and wild dogs have been implicated in the extinction of native species, cause millions of dollars of stock losses every year, and also pose significant human and animal biosecurity risks. PAPP baits provide an additional proven effective tool for the control of these important pest species. The development and registration work by IA-CRC and ACTA has taken 11 years and has been supported by Australian Wool Innovation (AWI).

Para amino propiophenone (PAPP) is an amine substituted propiophenone that can be administered orally to induce methaemoglobinaemia. To oxidise haemoglobin, PAPP must first undergo hydroxylation in the liver. Due to different metabolic pathways in different species the effects of PAPP vary between species. Foxes and dogs amongst the most sensitive due to their rapid hydroxylation of PAPP. These species also have a relative lack of *methemoglobin reductase* that normally protects against methaemobglobinaemia.

Methaemoglobin levels <50% are well tolerated, but once above about 80% the reduction in oxygen-carrying capacity can result in painless unconsciousness and death by hypoxia. The effect is similar to that of carboxy-heamoglobinaemia, arising from exposure to carbon monoxide and is equally as humane.

The use of PAPP as a toxin for controlling wild canids was first investigated by researchers in the United States (Savarie et al., 1983) following discoveries that equivalent PAPP doses caused much higher methaemoglobinaemia in dogs than in other animals. Any compound that reduces methaemoglobin, such as methylene blue, is antidotal.

Australia, has built on this foundation work and registered two new products for the management of foxes (**FOXECUTE® PAPP Fox Bait**) and wild dogs (**DOGABAIT PAPP Wild Dog Bait**) that include marker beads to aid Veterinary diagnosis.

WHAT IS PAPP?

PAPP is a simple molecule consisting of a benzene ring structure with an amide group at the para position, relative to a propionic acid substitution. PAPP is more expensive than 1080 and much higher quantities are required for an effective bait. While PAPP does not occur naturally, PAPP is subject to degradation in different ways by mammals and microorganisms. PAPP does not persist in the environment and is rapidly cleared from all tissues and blood within hours in vivo.

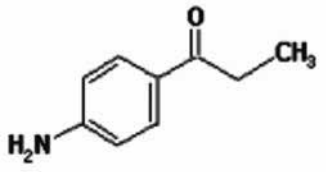


FIGURE 1

Structure of para-aminopropiophenone (PAPP)

CLINICAL SIGNS

PAPP toxicosis is rapid and relatively free of symptoms. Animals consuming lethal doses become lethargic, lose limb coordination, show a progressive cyanosis of extremities and mucous membranes and eventually lose consciousness and die. Clinical trials with the present bait formulation have shown that mild vomiting can occur prior to losing consciousness in some dogs, but vomiting has not been seen in foxes. In late stages of toxicosis dogs may paddle and vocalize whilst otherwise unresponsive.

MECHANISM OF TOXICITY AND OF SPECIES SPECIFICITY

The toxic effects of PAPP are due primarily to the rapid formation of methaemoglobin in red blood cells, leading to a rapid and lethal deficit of oxygen in cardiac muscle and the brain.

Methaemoglobin is the oxidised form of haemoglobin, where the iron is in the ferric (3+) state, rather than ferrous (2+) state. The ferric form of iron within methaemoglobin has a much lower affinity for oxygen than the normal ferrous state.

PAPP is not a direct oxidiser of haemoglobin. Following absorption, PAPP must first undergo transformation in the liver to an active metabolite. The active metabolite in canids is N-hydroxylamino-propiophenone (PHAPP; De Feo et al., 1972, Marrs et al. 1991).

It is the PHAPP metabolite which oxidises haemoglobin to methaemoglobin in an NADPH-dependent catalytic process within the red blood cell. The transformation of PAPP to metabolites for excretion occurs via different pathways in different species and this forms the basis of a degree of species specificity. Animals that do not hydroxylate at the meta position are much less affected than those species that can perform this transformation.

During studies of the toxicity of PAPP it was found canids were more susceptible than rats and primates due to their capability to hydroxylate PAPP to PHAPP. Canids also have lower methaemoglobin reductase compared to several other species (Robin and Harley, 1966, Smith and Beutler, 1966, Stolk and Smith, 1966). Thus, canids not only convert more PAPP to PHAPP but are less efficient at converting methaemoglobin back to heamoglobin.

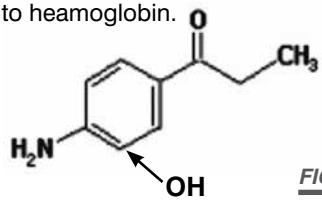


FIGURE 2

Meta position hydroxylation of PAPP for form PHAPP

In canids the hydroxylation occurs in the liver and within 30 minutes after oral absorption. Once formed, PHAPP is rapidly absorbed by red blood cells where it catalyses the oxidation of haemoglobin to methaemoglobin. *In vitro*, about 600 molecules of haemoglobin can be oxidised by each molecule of PHAPP. PHAPP does this via a redox cycle in circulating erythrocytes termed the "Kreisprozess" (see figure 3 below). The PHAPP metabolite has a half-life of only minutes *in vivo*

Methaemoglobinaemia is exacerbated in the Kriesprozess by intra-erythrocytic NADPH, generated from glucose-6-phosphate dehydrogenase, which reduces a secondary PAPP metabolite p-nitrosopropiophenone (PNPP) back to the highly potent methaemoglobin inducer PHAPP (Baskin and Fricke, 1992).

While PHAPP induces methaemoglobin formation, the amount of methemoglobin achieved will also depend on the rate of reduction of methaemobglobin back to normal hemoglobin by *methaemoglobin reductase* enzyme (Smith and Beutler, 1966). The end lethal result occurs when the oxidation process exceeds the rate of the reduction for sufficient time to allow high levels (typically >80%) of methaemoglobin to be induced.

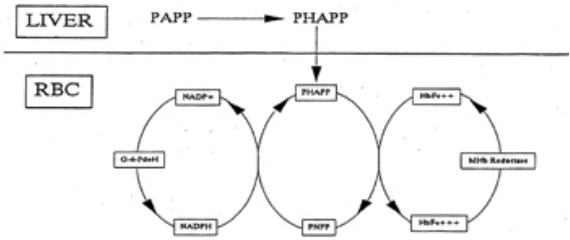


FIGURE 3

The Kreisprozess. Intraerythrocytic recycling of PHAPP and p-nitrosopropiophenone (PNPP) to bring about the simultaneous oxidation of haeme Fe2+ to Fe3+. Reaction is dependent on glucose-6-phosphate dehydrogenase (G-6-PdeH) for the generation of reducing equivalents necessary to convert PNPP to PHAPP (Baskin and Fricke, 1992).

CLEARANCE OF PAPP

Baskin and Fricke (1992) summarised the different metabolic pathways in rats, dogs and primates. In rats, PAPP is metabolised by N-acetylation to N-acetyl-PAPP and ultimately to N-acetyl-p-aminophenol sulphate. In contrast, the majority of degradation of PAPP in dogs was by ring and aliphatic oxidation to 4-amino-3-hydroxypropiophenone and 1-(4-amino-3-hydroxy)-2-hydroxypropiophenone and ultimately conversion to their sulphated conjugates for excretion predominantly in urine. In primates, a combination of both pathways exist that result in N-acetylation and oxidation of PAPP to N-acetyl PAPP and p-aminobenzoic acid and ultimately glucuronide and sulphated conjugates of N-acetyl-p-aminobenzoic acid and N-acetyl-p-aminophenol respectively.

The metabolism of PAPP itself is rapid ($t_{1/2}$ of about 1 hour). The *in vivo* half-life of PHAPP is minutes, so if effects are sub-lethal, recovery is quick.

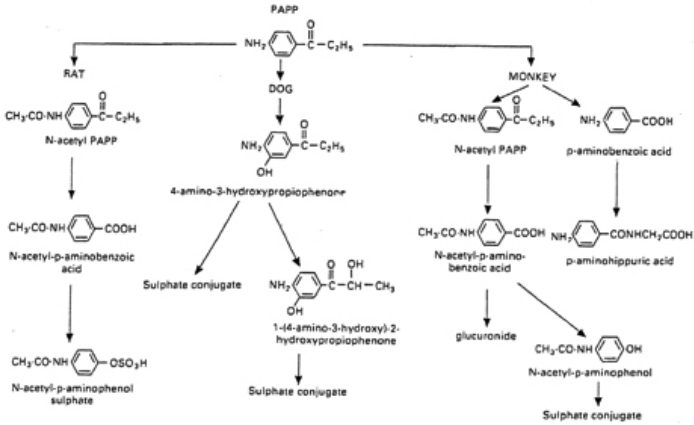


FIGURE 4

Differential metabolic pathways for the detoxification and excretion of PAPP in the rat, dog, and monkey (from Baskin & Frick 1992)

PHARMACOKINETICS OF PAPP TOXICOSIS

The typical clinical outcome from methaemoglobinaemia depends on the factors which simultaneously act to promote or depress methaemoglobin concentrations in red blood cells.

Typically, during the first 30 minutes following ingestion significant quantities of PAPP have been absorbed. During passage through the liver a proportion of the absorbed PAPP is converted to the active metabolite PHAPP, while some is also degraded to in-active amino acid or sulphur conjugates for excretion (Wood et al 1991).

Peak methaemoglobin concentrations in all species lag peak plasma PAPP levels by approximately 30 - 60 minutes (Marrs et al 1991; Paulet et al., 1963, Bright and Marrs, 1982, Marrs and Bright, 1986, Marino et al., 1997). This lag is a function of the rate of PAPP absorption, the metabolism of PAPP to the active metabolite (PHAPP), and thirdly the accumulation of PHAPP in red blood cells, where the PHAPP oxidises the haem group (Marino et al., 1997).

The duration of the lag phase as expressed by clinical symptoms is dose-dependent at low doses but less so once an overdose is reached.

Therefore, by the end of the second hour from exposure to a bolus dose of PAPP methaemoglobinaemia will have either reached acutely toxic levels (lethal), or begun to subside, due to the enzymatic reduction of methaemoglobin to haemoglobin at a greater rate than methaemoglobin formation.

CLINICAL SIGNS

The effect of PAPP in test species appears to be rapid and free of clinical signs, other than those resulting directly from methaemoglobin formation. Observations of treated foxes and dogs indicates a slight tendency to salivate and to drink water but these effects are minor.

There is no tissue damage or other biochemical impact. The primary clinical outcome from lethal toxicosis with PAPP in susceptible species is metabolic anoxia, in the brain, myocardium and other tissues.

Sublethal exposures to PAPP are cleared quickly and cause no long-term impact. There is no bioaccumulation, so repeated small exposures are also well tolerated.

The lethal sequelae arise only if a large dose of PAPP is absorbed acutely to enable the conversion of more than about 80% of haemoglobin to methaemoglobin. FOXECUTE® and DOGABAIT baits are designed to maximize rapid bioavailability of PAPP in the stomach resulting in a lethal dose to wild canids.

Clinical symptoms from PAPP toxicosis in susceptible animals are characterised as lethargy, ataxia, unresponsiveness, unconsciousness and death. PAPP induced methaemoglobinaemia is accepted as a very humane method of killing canid pest animals, such as wild dogs and foxes.

Unconsciousness occurs between 30-60 minutes and death between 45-90 minutes, but these timeframes are dose dependent (mg/kg bodyweight). PAPP works more quickly than 1080. For comparison, a fox exposed to a standard dose of 3mg of 1080, has an average lag phase of 4.1 hrs to first clinical effect and a 30 minute clinical phase.

The fast action of PAPP will result in more carcasses being found than would be expected for 1080 poisoned animals. This does not mean that PAPP is “more effective” than 1080. Both PAPP and 1080 baits are highly effective control tools.

Due to early clinical trials of PAPP as a potential cyanide prophylactic in a military context, there is good knowledge of the lack of clinical symptoms in sub lethally dosed humans. There was no induction of pain or discomfort, and no treatment effects on blood pressure or electrocardiograms in human trials in subjects receiving a fixed oral dose of 100mg (subjects weighed between 55.6 to 90kg) or on respiration rate when an oral dose of 80mg was administered to subjects weighing from 51-96kg. No neurological, gastrointestinal effects or mucous membrane inflammations were noted. Nausea was noted in some individuals.

SUB-LETHAL ACUTE EXPOSURES OR EXPOSURE TO A LETHAL DOSE OVER AN EXTENDED PERIOD

Oral absorption of sub lethal quantities of PAPP induces some methemoglobin formation, but studies in humans have shown that levels of up to 50% are generally tolerated without discomfort or clinical symptoms under normal exercise. Recovery is quick (1 to 4 hours), even without clinical intervention, due to the rapid metabolism and clearance of PAPP and PHAPP and also because most species possess *methaemoglobin reductase* enzyme, that provides a protective reduction mechanism for reduction of methaemolglobin to normal haemoglobin.

ANTIDOTE TO PAPP TOXICOSIS

Clinical effects of PAPP can also be reversed by the administration of agents that reduce methaemoglobin to haemoglobin. This can be achieved even when a PAPP affected animal is close to death. Chief amongst these agents is **methylene blue** (Bodansky and Guttman 1947, Coleman & Coleman 1996). Thus, accidentally poisoned animals can be effectively treated.
However, there are several important points regarding the use of this antidote:

- In the early stages of toxicosis (prior to recumbency) induce emesis using 2-5 washing soda crystals (per os) or apomorphine.
- In the late stages of toxicosis (post recumbency) administer methylene blue antidote prior to inducing emesis using 2-5 washing soda crystals (per os) or apomorphine.
- The methylene blue treatment must be administered intravenously by a veterinarian.
- PAPP can kill an animal within 45-90 minutes after consumption so it's imperative to administer the antidote treatment promptly. PAPP will induce lethargy and unconsciousness before death, so dog owners need to be watchful for signs of cyanosis to distinguish a PAPP affected dog from one that is resting normally.
- Formulations of methylene blue are not isotonic, so it is important to administer the 5-10mL dose of 10g/L solution slowly over 2-5 minutes to avoid excessive lysis of red blood cells.
- An over dose of methylene blue is contraindicated (do not exceed 10mg/kg liveweight over 24hrs), so treatment needs to be monitored and top-up doses administered carefully until clinical effects of the PAPP decline.

A separate fact sheet is being prepared by IACRC with AVA on clinical practice using methylene blue.

DOSING OF FOXECUTE® AND DOGABAIT BAITS

The bait products contain the following amounts of the active constituent:

- FOXECUTE®® fox baits weigh approximately 35 grams and contain **400mg PAPP**/bait
- DOGABAIT wild dog baits weigh 60 grams and contain **1000mg PAPP**/bait

Wild captured foxes fed PAPP dispersed in the FOXECUTE® bait matrix to achieve doses between 10 and 45mg/kg showed that baits containing >40mg/kg were 100% effective at inducing a rapid progression to unconsciousness and death after a short period of lethargy and ataxia.

A large dog may survive a 400mg fox bait dose but a conservative approach to treatment is recommended and all dogs suspected of eating a fox bait should be taken to a vet for treatment. A dog bait containing 1000mg of PAPP will pose an immediate threat to any dog.

The lower dose used in fox baits does not provide an absolute safety factor for dogs exposed to a fox dosed bait, but may allow some safety to working dogs during fox control programs. **Regardless, it is a strong label recommendation that muzzles or restraints be used to prevent access to bait by working dogs during any PAPP based baiting program.** The approved use patterns for the baits are:

1 Fox baits - ground placement (buried/covered) at a density of not more than 20 baits/ km^2, and not less than 200m apart.

2 Dog baits - ground placement at not less than 500m between baits.

Aerial deployment of PAPP baits has not been approved as PAPP is toxic to goannas and to three native carnivores. Despite this, the Environment Protection Agency (EPA) has independently assessed that use of PAPP baits provides a net benefit to native carnivores on a population basis, due to lower risks of predation and competition after predator removal.

SAFETY TO OPERATORS

Manufacturing and use controls are adequate to prevent exposure of operators to PAPP during product use. PAPP is not readily absorbed through skin but instructions conservatively recommend use of rubber gloves while handling baits. There is no risk of bioaccumulation from infrequent small exposures. Contamination of skin or clothing is easily removed by washing using soapy water.

Other possible toxicological effects of PAPP have been assessed.

PAPP has weak mutagenic potential so mitigating exposure is recommended. The use of PAPP as a canid bait toxicant with acute effects is not expected to result in residues or accumulation of PAPP or its metabolites in crops or the animal or human food chains.

FIRST AID & SAFETY DIRECTIONS

First aid and safety directions are included on the APVMA approved FOXECUTE® and DOGABAIT labels in accordance with Office of Chemical Safety assessment:

FIRST AID: Speed in treatment is essential. If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 13 11 26. Remove from the contaminated area. Apply artificial respiration if not breathing.

SAFETY DIRECTIONS: Wear disposable gloves when handling the baits. After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. Product may be harmful if swallowed. Exposed persons should be immediately moved into fresh air, and a physician called. PAPP induces methaemoglobinaemia and reduces oxygen transport in blood. PAPP has been used at low doses experimentally in humans without adverse consequences. Substances that reduce methaemoglobin are antidotal.

EVIDENCE FOR LOW TOXICITY TO MOST NON-TARGET SPECIES

Apart from the requirement for hydroxylation of PAPP to PHAPP that is limited in many non-target species, there are differing levels of methaemoglobin reductase, between species.

Swain et al (1984) characterised the toxicity of PAPP (LD50) via the oral route in different species into three general groups;

1 LD_{50} <50mg/kg
dogs most sensitive, then cats>bobcats>kit foxes and coyotes;

2 LD_{50} 100-500mg/kg
encompassing the majority of species tested; and

3 LD_{50} >1000mg/kg
female mice and guinea pigs.

ORAL LETHAL DOSE
ADAPTED FROM

SPECIES	METHOD OF ADMINISTRATION
Dog (Canis familiaris)	Not reported
Coyote (Canis latrans)	Cod liver oil
Kit fox (Vulpes velox)	0.05% Carbopol 914
Red fox (Vulpes vulpes)	DMSO* and sweetened condensed milk
Cat (Felis libyca domestica)	0.05% Carbopol 914
Bobcat (Lynx rufus)	0.05% Carbopol 914
North American badger (Taxidea taxus)	0.05% Carbopol 914
Raccoon (Procyon lotor)	0.05% Carbopol 914
Striped skunk (Mephitis mephitis)	0.05% Carbopol 914
Stoat (Mustela erminea)	PAPP-HCl monopropylene glycol
Ferret (Mustela furo)	PAPP-HCl monopropylene glycol
Guinea pig (female) (Cavellio porcinus)	DMSO solvent
Mouse (albino)	Propylene glycol
Mouse (female)	DMSO solvent
Mouse (male) (Swiss Webster strain)	Propylene glycol
Rat (female) (Porton Wistar strain)	DMSO solvent
Rat (male)	DMSO solvent
Rat	Propylene glycol
Rat (male) (Sprague-Dawley)	Propylene glycol
Golden eagle (Aquila chrysaetos)	Propylene glycol
Coturnix quail (Coturnix coturnix)	Propylene glycol
Starling (Sturnus vulgaris)	Propylene glycol
Red-winged Blackbird (Agelaius phoenicus)	Propylene glycol
Black-billed Magpie (Pica pica)	Propylene glycol
Common Crow (Corvus brachyrhynchos)	Propylene glycol

Fisher et al. (2008) reviewed oral lethal dose (LD50) values for PAPP. The table above is adapted from this citation to demonstrate relative species sensitivities.

(LD50) VALUES OF PAPP

FISHER ET AL. (2008)

LD50 MG/KG	REFERENCE
7.5	Coleman et al., 1960 reported from handbook of toxicology
5.6	Savarie et al., 1983
14.1	Savarie et al., 1983
25.2 (estimate from non-lethal model)	Marks et al., 2004
5.6	Savarie et al., 1983
10	Savarie et al., 1983
100	Savarie et al., 1983
142	Savarie et al., 1983
400	Savarie et al., 1983
9.3	Fisher et al., 2005
15.52	Fisher and O'Connor, 2007
1,020	Scawin et al., 1984
223	Savarie et al., 1983
5,000	Scawin et al., 1984
168	Pan et al., 1983
223.7	Scawin et al., 1984
475	Scawin et al., 1984
177	Savarie et al., 1983
221	Pan et al., 1983
50	Savarie et al., 1983
316	Savarie et al., 1983
316	Savarie et al., 1983
133	Savarie et al., 1983
178	Savarie et al., 1983
178	Savarie et al., 1983

***DMSO – Dimethylsulphoxide.**

(LD_{50}) VALUES DETERMINED BY FISHER ET AL., (2008)

Acute toxicity of the hydrochloride salt of PAPP was tested by oral gavage in possums, wallabies and mallard ducks by Fisher et al. (2008) to determine possible application of PAPP for possum control in NZ and also to assess possible non target risks.

SPECIES	METHOD OF ADMINISTRATION	LD_{50} MG/KG	REFERENCE
Brushtail possums (Trichosurus vulpecula)	PAPP-HCl monopropylene glycol	≥500	Fisher et al 2008
Dama wallabies (Macropus eugenii)	PAPP-HCl monopropylene glycol	89	Fisher et al 2008
Mallards (Anas platyrhynchos)	PAPP-HCl monopropylene glycol	38	Fisher et al 2008

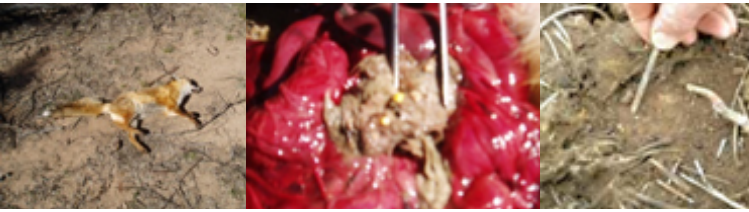
NOTE: differences in method of administraton (solvent, bait, oral or gavage etc) mean these comparisons are approximate only.

SUMMARY OF FOXECUTE® AND DOGABAIT PAPP BAITS

- PAPP is absorbed quickly from specially designed ACTA baits which have been proven to be highly effective.
- Once absorbed, PAPP is metabolised to a substance that changes normal haemoglobin to a form that does not carry oxygen. An affected animal becomes inactive, loses consciousness and dies quickly with few clinical signs.
- PAPP products have an effective antidote. However, it must be administered promptly by a veterinarian. Therefore normal precautions to protect pets and working dogs in rural areas are still recommended.
- Accidentally poisoned animals given antidote can recover with no long-term effect.
- PAPP degrades in the environment and poses low risk to most native species.
- The baits are targeted to wild dogs and foxes with no interest from herbivores.
- There is no risk of secondary poisoning of scavengers eating carcasses.
- ACTA has added small coloured marker beads (yellow for PAPP products and red for 1080 products) to assist veterinarians to know what type of bait has been eaten.

Orange scat marker beads are incorporated into PAPP baits

Red scat marker beads are incorporated into 1080 baits



PAPP poisoned carcasses can be found in the open as there is less time to seek refuge compared to 1080 poisoning. Scat marker beads can be detected in stomach contents and even in the area of decayed carcasses.

- FOXECUTE® PAPP baits and DOGABAIT PAPP baits were approved by the APVMA in January 2016, after extensive review by all relevant government agencies.
- PAPP products generate a royalty to assist research by AWI & IA-CRC.
- PAPP products will shortly become available to landholders via normal bait distribution channels under strict controls.
- PAPP products are schedule **RESTRICTED S7** and are subject to the same restrictions on access, storage and use as current 1080 baits.

FOXECUTE® and **DOGABAIT** baits will initially be available in packs of 10 and 40 (fox baits) or 10 or 50 (dog baits) and are packaged in sturdy polyethylene pails with re-sealable tamper-evident lids. Instructions caution about the dangers if stored where pets have access.

Sources of additional information & labels
www.animalcontrol.com.au
www.pestsmart.org.au

COMPARISON OF 1080 WITH PAPP

In the fox, 1080 has a latent period of several hours, before the onset of identifiable behavioral signs which then last for approximately 0.1 to 1 hr. The lag phase includes time for absorption of the fluoroacetate and its conversion to fluoro-acetyle Co-A, which then enters the mitochondria where it substitutes for normal acetyl Co-A in the TCA cycle. Further metabolic transformation to fluoro-succinate occurs, at which point the fluoro-succinate is unable to be processed or released by *aconitase*. This effectively blocks the TCA cycle by enzyme inhibition and so stops production of energy in the form of ATP and NADPH. Ultimately all energy-dependent metabolic processes are blocked in all cells, though the first affected tissues are the brain and heart, due to their high metabolic energy needs.

The initial symptoms, after the latent period occur when the animal is conscious but it is possible that some awareness of metabolic disorder may occur during this stage. Later convulsions and spasms result from disruption of muscle coordination. This effect is thought to result from citrate accumulation from progressive pyruvate pathway metabolism of sugars without the ability to further process metabolites in the TCA cycle. Citrate is a known chelator of extracellular calcium, so the terminal spasms are not a response to pain, but result from the hypocalcaemia.

While the evidence suggests that the 1080 poisoned animal is unaware of its demise and therefore not suffering (there is knowledge of citrate overdose in humans and the impacts have been also likened to painless hypoglycemic fits), to the untrained observer the vocalisation (barking and howling) and tetanic spasms are interpreted as a response to pain. Much controversy and much misinformation therefore surrounds the use of 1080 as a pesticide.

In 1992, when ACTA first released the FOXOFF® 1080 bait, a briefing regarding 1080 treatment was prepared for the Victorian Branch of the AVA. This advisory is reproduced below (with company name updates) in the event that the earlier document is no longer available.

AVA NEWSLETTER 1992

NEW 1080 BAIT RELEASED IN VICTORIA

A new shelf stable 1080 fox bait called FOXOFF has recently been released. The manufacturers claim that the size of each bait and the concentration of 1080 within the bait have been designed to minimise the risk of toxicity to small, native carnivores and to birds. The following information has been provided by the manufacturers in consultation with the Department of Conservation and Natural Resources with particular reference to the clinical signs and treatment of domestic dogs and cats accidentally poisoned with 1080.

Fox numbers in Victoria vary with season and location and peak densities have been estimated at 4/km2 on agricultural land. Densities vary between 1 and l0/km2 in other areas, being highest in outer suburban Melbourne. It has been conservatively estimated that just 1 million foxes in Victoria would eat more than $9 million worth of sheep meat per year even if only 50% is from fresh kills and sheep meat is valued at just $0.50/kg! The problems for individual farmers may be more acute with fox damage concentrated around lambing time. Foxes also pose a serious threat to native wildlife with many species being vulnerable to predation. Foxes are implicated in the decline of fairy penguins, little terns, Eastern barred bandicoots, lyrebirds, Murray tortoises, long-footed potoroos, Mallee fowl and brush tailed rock wallabies and probably reduce numbers of many other forms of native wildlife. Foxes are also vectors for several serious diseases.

Compound 1080 (sodium fluoroacetate), as part of an integrated fox management program, is considered to be the most suitable poison for fox control. Compound 1080 was traditionally injected into meat or offal baits for the control of foxes and wild dogs. ACTA has recently released a shelf-stable 1080 fox bait called FOXOFF. The size of each bait and the amount of 1080 within the bait (3mg) are designed to minimise the risk of toxicity to small, native carnivores and to birds. Also, the technique of buried placement further minimises the risk to non-target animals and permits eventual degradation of the 1080 by the action of ground bacteria and fungi.

Baiting for foxes is done at the time of lambing (spring and autumn) and also about the time of cub emergence in December and January. Herbivores are not attracted to the

FOXOFF baits. Baiting may be conducted at any time of the year to protect native animals but usually occurs at around the breeding time for the species being protected.

"Free feeding" using unpoisoned baits initially is used in some locations, particularly near urban areas, to ensure that baits are being taken by foxes where there is a perceived risk to non-target animals. Poisoned baits should then be placed only at confirmed sites of fox activity.

Unfortunately, baits intended for fox control may also be attractive to domestic carnivores, especially dogs. The clinical signs of 1080 toxicity in dogs progresses in the following phases:

(i) During the first hours after ingesting 1080, there are few clinical signs. The dog may be restless and irritable and may wander aimlessly, or it may whimper, whine and lie in corners.

(ii) This phase is followed by a period of barking and running with vomiting, urination in some cases and repeated defecation. Dyspnoea may develop with an increase in rate and depth of respiration.

(iii) The third phase consists of frenzied running, barking and wild circling. During this phase, the dog may be very difficult to catch. Eventually the dog collapses, presumably from exhaustion and impaired energy production in mitochondria. Several authors have suggested that this phase is not painful but is due to disorientation or an hallucinations state (Chenoweth 1949, Peters 1973, Batchelor 1978). It has been demonstrated that the electroencephalographs of dogs dosed with 1080 are similar to the cerebral dysrhythmias found in both grand and petit ma! epileptic seizures in man. The former are associated with unconsciousness and the latter with "lack of awareness" but in neither case is pain perceived. The disorientation, agitation and loss of consciousness of this phase of 1080 poisoning has also been likened to the effects of hyperinsulinism (Tortora and Anagnostakos, 1984). No pain has been reported in three published reports of humans who have experienced accidental poisoning with 1080.

(iv) Collapse is followed by a semicomatose state. Convulsions may occur, dyspnoea is evident and the dog is not conscious at this stage. Death due to respiratory failure occurs 2-12 hours after the onset of clinical signs. Cats intoxicated with 1080 usually do not exhibit the pronounced excitement seen in dogs, although convulsions and ventricular arrhythmias (including fibrillation) are common. Ventricular fibrillation is not usually seen in dogs exposed to 1080.

Ingestion of 0.05mg/kg bodyweight of sodium fluoroacetate can cause death in dogs. The sodium flouroacetate is converted in the body to fluoroacetyl coenzyme A (Co A) which replaces acetyl Co A in the tricarboxylic acid (TCA) cycle. This results in accumulation of citrate within the cell and interference with cellular respiration. This process takes between 30 minutes and 2 hours. Clinical pathology is not helpful in the diagnosis of 1080 toxicity ante mortem. Treatment of animals believed to have ingested 1080 and presented prior to the development of clinical signs is worth attempting. Absorption of the toxin from the gastrointestinal tract must be minimised using gastric lavage (under general anaesthesia and with endotracheal intubation) and the administration of a generous quantity of activated charcoal. Administration of glycerol monoacetate (Monacetin, Acetin, Acetin) may be useful if administered prior to, or during, the onset of clinical signs. The objective is to deluge the body with acetate ions and competitively overwhelm the toxin. A suggested regimen is O.l-0.5mg/kg

BW intramuscularly at 60 minute intervals for several doses. Sub lethal doses of 1080 are eventually metabolised and excreted in the urine.

Following the development of clinical signs, symptomatic treatment may be attempted but is usually unrewarding and a grave prognosis should be given. Convulsions may be controlled using short-acting barbiturates or general anaesthesia. Oxygen may be administered as required. Lignocaine, procainarnide hydrochloride or quinidine may be useful in controlling cardiac arrhythmias.

Following death, rigor mortis sets in rapidly with the limbs fixed in extensor rigidity. Post mortem findings are usually non-specific. The stomach, colon and urinary bladder are usually empty and the carcass may be cyanotic. The liver and kidneys are dark and congested and the heart is usually in diastole with sub-pericardial haemorrhages. Vomitus, stomach contents, liver, kidney and suspect bait material may be submitted for laboratory analysis, but there are few sites for 1080 analysis in Australia and many laboratories rely on a method based on fluoride detection.

The supply of FOXOFF baits is strictly controlled with exclusive supply only from authorised Land Protection Officers of the Victorian Department of Conservation and Natural Resources or authorised officers of Pasture Protection Boards in other states. These officers have an excellent track record of conservative and cautious supply, often involving interviews and site visits with follow-ups on farms.

The regulations governing the use of FOXOFF baits are strictly enforced and require that neighbouring farmers be advised of their use, that the baits be buried 8-lOcm deep and that minimum distances to boundaries and habitable dwellings be observed. Even more stringent requirements apply to use of the baits adjacent to suburban areas.

Working dogs in rural areas should be carefully confined to prevent access to the baits. Consideration should be given to confining cats indoors or removing them from the rural area during the baiting period. Urban dog owners contemplating a visit to the country should also be advised to keep the dogs under strict control and to avoid allowing the dogs to run unleashed on rural property until discussions with the property owner have confirmed the absence of baits, but in any case these precautions should form part of responsible handling of pets in farming areas.

For further information on the availability and use of FOXOFF baits, contact the Department of Conservation and Natural Resources.

REFERENCES TO 1080 EFFECTS AND TREATMENTS

Batcheler, CL (1978) Compound 1080; Its Properties, Effectiveness, Dangers and Use. Report to the Ministry of Forests and of Agriculture and Fisheries. NZ Forest Research Institute.

Chenoweth, MB (1949) Monofluroetic acid and related compounds. J Pharmacology and Exp. Therapeutics 97; 383-424.

Cranna GR (1987) In Veterinary Clinical Toxicology, University of Sydney Post-Graduate Committee in Veterinary Science. Proceedings 103, 1987. pp 70-1. Humphreys DJ (1988) In Veterinary Toxicology 3rd Ed. Bailliere Tindal England. pp 179-81.

Oehme FW (1987) In Veterinary Clinical Toxicology, University of Sydney Post Graduate Committee in Veterinary Science. Proceedings 103, 1987. pp 435-6, 455-6, 485-6.

Peters, JA (1973) Toxicology of Wildlife Control: Facts and Fancies. NZ Forest Service Reprint #868.

Tortora, GJ and Anagnostakos, NP (1984) Principles of Anatomy and Physiology 4th Ed. (Harper & Row NY)

SELECTED PAPP REFERENCES FOR FURTHER READING

BASKIN, S. I. & FRICKE, R. F. 1992. The Pharmacology of p-Aminopropiophenone in the Detoxification of Cyanide. Cardiovascular Drug Review, 10, 358-375.

BODANSKY, O. & GUTTMAN, H. 1947. Treatment of PAPP-induced methemoglobinemia in dogs using intravenous methylene blue.

BRIGHT, J. E. & MARRS, T. C. 1982. A comparison of the methemoglobin-inducing activity of moderate oral doses of 4-dimethylaminophernol an p-aminopropiophenone. Toxicology Letters, 13, 81-86.

BRIGHT, J. E. & MARRS, T. C. 1987. Effect of p-amino propiophenone (PAPP), a cyanide antidote, on cyanide given by intravenous infusion. Human Toxicology, 6, 133-137.

COLEMAN, M. & COLEMAN, N. 1996. Drug-induced methaemoglobinaemia treatment issues. Drug Safety, 14, 394-405.

DeFEO, F. G., FITZGERALD, T. J. & DOULL, J. 1972. Synthesis and Biologic Activity of p-Hydroxylaminopropiophenone. Journal of Medical Chemistry, Vol. 15, No. 11 , 1185-1187.

FISHER, P. & O'CONNOR, C. 2007. Oral toxicity of p-aminopropiophenone to ferrets. Wildlife Research, 34, 19-24.

FISHER, P., O'CONNOR, C. E. & MORRISS, G. 2008. Oral toxicity of p-aminopropiophenone to brushtail possums (Trichosurus vulpecula), dama wallabies (Macropus eugeni), and mallards (Anas playtrhynchos). Journal of Wildlife Diseases, 44, 655-663.

FISHER, P., O'CONNOR, C. E. & MURPHY, E. C. 2005. Acute oral toxicity of p-aminopropiophenone to stoats (Mustela erminea). New Zealand Journal of Zoology, 32, 163-169.

MARINO, M. T., URQUHART, M. R., SPERRY, M. L., VON BREDOW, J., BROWN, L. D., LIN, E. & BREWER, T. G. 1997. Pharmacokinetics and kinetic-dynamic modeling of aminophenones as methaemoglobin formers. Journal of Pharmacy and Pharmacology, 49, 282-287.

MARKS, C. A., GIGLIOTTI, F., BUSANA, F., JOHNSTON, M. & LINDERMAN, M. 2004. Fox control using para-aminopropiophenone formulation with the M-44 ejector. Animal Welfare, 13, 1-7.

MARRS, T. C. & BRIGHT, J. E. 1986. Kinetics of methaemoglobin production (1). Kinetics of methaemoglobinaemia induced by the cyanide antidotes p-aminopropiophenone, p-hydroxyaminopropiophenone or p-dimethylaminophenol after intravenous administration. Human Toxicology, 5, 295-301.

MARRS, T. C., INNS, R. H., BRIGHT, J. E. & WOOD, S. G. 1991. The formation of methaemoglobin by 4-aminopropiophenone (PAPP) and 4-(N-hydroxy) aminopropiophenone. Human Toxicology, 10, 183-188.

PAULET, G., AUBERTIN, X., LAURENS, L. & BOURRELIER, J. 1963. On the methemoglobnizing effect of paraaminopropiophenone in man – with an experimental compliment in the dog. Archives Internationales de Pharmacodynamine et de Therapie, 142, 35-61.

PING PAN, H., SAVARIE, P. J., ELIAS, D. J. & FELTON, R. R. 1983. Alkyl chain length and acute oral toxicity of p-aminophenones. General Pharmacology, Vol. 14, No. 4, 465-467.

ROBIN, H. & HARLEY, J. D. 1966. Factors influencing response of mammalian species to the methaemoglobin reduction test. Australian Journal of Experimental Medical Science, 44, 519-526.

SAVARIE, P. J., PING PAN, H., HAYES, D. J., ROBERTS, J. D., DASCH, G. J., FELTON, R. & E.W., S. J. 1983. Comparative acute oral toxicity of para-aminopropiophenone (PAPP) in mammals and birds. Bulletin of Environmental Contamination and Toxicology, 30, 122-126.

SCAWIN, J. W., SWANSTON, D. W. & MARRS, T. C. 1984. The acute oral and intravenous toxicity of p-aminopropiophenone (PAPP) to laboratory rodents. Toxicology Letters, 23, 359-365.

SMITH, R. P. & BEUTLER, E. 1966. Methemoglobin formation and reduction in man and various animal species. American Journal of Physiology, 210, 347-350.

STOLK, J. M. & SMITH, R. P. 1966. Species differences in methemoglobin reductase activity. Biochemical Pharmacology, 15, 343-351.

WOOD, S. G., FITZPATRICK, K., BRIGHT, J. E., INNS, R. H. & MARRS, T. C. 1991. Studies of the pharmacokinetics and metabolism of 4-aminopropiophenone (PAPP) in rats, dogs and cynomolgus monkeys. Human and Experimental Toxicology, 10, 365-374.

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