Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the New Active 4-aminopropiophenone (also known as para-aminopropiophenone(PAPP)) in the Products Foxecute Fox Bait & PAPP Wild Dog Bait

APVMA Product Numbers 65095 and 65094

OCTOBER 2015

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This publication is available from the APVMA website: www.apvma.gov.au.

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PREFACE

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health, Office of Chemical Safety (OCS), Department of Environment (DE), and State Departments of Primary Industries.

The APVMA has a policy of encouraging openness and transparency in its activities and of seeking community involvement in decision making. Part of that process is the publication of Public Release Summaries for products containing new active constituents.

The information and technical data required by the APVMA to assess the safety of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes. Details are outlined in the APVMA's application requirements and data guidelines.

This Public Release Summary is intended as a brief overview of the assessment that has been conducted by the APVMA and of the specialist advice received from its advisory agencies. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience thereby encouraging public comment.

About this document

This is a Public Release Summary.

It indicates that the Australian Pesticides and Veterinary Medicines Authority (APVMA) is considering an application for registration of an agricultural or veterinary chemical. It provides a summary of the APVMA's assessment, which may include details of:

- the toxicology of both the active constituent and product
- the residues and trade assessment
- occupational exposure aspects
- environmental fate, toxicity, potential exposure and hazard
- efficacy and target crop or animal safety.

Comment is sought from interested stakeholders on the information contained within this document.

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether FOXECUTE FOX BAIT and PAPP WILD DOG BAIT should be registered. Submissions should relate only to matters that are required by the APVMA to be taken into

consideration in determining whether the safety, efficacy or trade criteria have been met. Submissions should state the grounds on which they are based.

Submissions must be received by the APVMA by close of business on 1 December 2015 and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

Relevant comments will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- contact name
- company or group name (if relevant)
- email or postal address (if available)
- the date you made the submission.

All personal information, and confidential information judged by the APVMA to be *confidential commercial information (CCI)*[1] contained in submissions will be treated confidentially.

Written submissions on the APVMA's proposal to grant the application for registration that relate to the grounds for registration should be addressed in writing to:

Case Management and Administration Unit
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604

Phone: +61 2 6210 4701
Fax: +61 2 6210 4721
Email: enquiries@apvma.gov.au

Further information

Further information can be obtained via the contact details provided above.

Copies of full technical evaluation reports covering toxicology, occupational health and safety aspects, residues in food and environmental aspects are available from the APVMA on request.

Further information on public release summaries can be found on the APVMA website: www.apvma.gov.au

[1] A full definition of "confidential commercial information" is contained in the Agvet Code.

1 INTRODUCTION

1.1 Purpose of application

Animal Control Technologies (Australia) Pty Ltd has applied to the APVMA for registration of the new products Foxecute Fox Bait and PAPP Wild Dog Bait containing the new active constituent 4- aminopropiophenone (also known as para-aminopropiophenone (PAPP)). Foxecute Fox Bait contains 11.4 g/kg para-aminopropiophenone (PAPP) [Each 35 g fox bait containing 400 mg para-aminopropiophenone (PAPP)] and PAPP Wild Dog Bait contains 16.8 g/kg para-aminopropiophenone (PAPP) [Each 60g wild dog bait containing 1000 mg para-aminopropiophenone (PAPP)]. These applications have been assessed in conjunction with the application for approval of the new active constituent 4- aminopropiophenone (also known as para-aminopropiophenone (PAPP)) received from Invasive Animals Ltd. The products are encompassed in a solid bait matrix and used solely as a vertebrate pesticide for the control of foxes and wild dogs respectively.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registrations of Foxecute Fox Bait and PAPP Wild Dog Bait and approval of the new active constituent, para-aminopropiophenone (PAPP).

1.2 Mode of action

The mechanism of action for PAPP as a vertebrate pesticide involves the biotransformation of PAPP to the metabolite N-hydroxylaminopropiophenone (PHAPP), which causes oxidation of haemoglobin to methaemoglobin (MetHb). The high methaemoglobin level (methaemoglobinaemia) reduces the oxygen-carrying capacity of blood, resulting in death by metabolic hypoxia at elevated methaemoglobin levels.

1.3 Product claims and use pattern

Foxecute Fox Bait and PAPP Wild Dog Bait products are intended for reduction of fox and wild dog numbers respectively, in non-crop and bushland areas including national parks, nature reserves, state forests and on private property. Both products are proposed for use at a rate of one bait station per 5–10 ha (up to 20 bait stations per km^2).

The APVMA has certified that it is in the public interest for Foxecute Fox Bait and PAPP Wild Dog Bait to be declared Restricted Chemical Products (RCPs) under section 93 of the Agvet Code (inclusion in Schedule 4 (Regulation 45) of the Agvet Code Regulations). The products will only be available to users appropriately authorised in the State and territory jurisdictions.

1.4 Overseas registrations

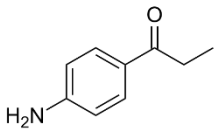
The products Foxecute Fox Bait and PAPP Wild Dog Bait are not registered in any overseas jurisdiction. Para-aminopropiophenone (PAPP) is registered for use to manufacture meat baits for control of stoats and feral cats in New Zealand.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

4-Aminopropiophenone (also known as para-Aminopropiophenone (PAPP)) is a new active constituent to be used as a vertebrate pest control agent. 4-Aminopropiophenone is a primary aromatic amine compound.

Chemical Characteristics of the Active Constituent

COMMON NAME:	4-Aminopropiophenone (PAPP)
IUPAC NAME:	1-(4-Aminophenyl)-1-propanone
CAS NAME:	4-Aminopropiophenone (also known as para-Aminopropiophenone)
CAS REGISTRY NUMBER:	70-69-9
MANUFACTURER'S CODES	PAPP
MINIMUM PURITY:	980 g/kg
MOLECULAR FORMULA:	C9H11NO
MOLECULAR WEIGHT:	149.19
STRUCTURE:	
CHEMICAL FAMILY	Primary aromatic amine
MODE OF ACTION	Death by metabolic hypoxia at elevated methaemoglobin levels

APVMA Active Constituent Standard for 4-Aminopropiophenone (PAPP)

CONSTITUENT	SPECIFICATION	LEVEL
4-Aminopropiophenone (PAPP)	4-Aminopropiophenone (PAPP)	Not less than 980 g/kg

Physical and Chemical Characteristics of Pure Active Constituent

PHYSICAL STATE:	Yellow crystalline powder
MELTING POINT:	140°C
BOILING POINT	305.8°C
PH	5.15 in a saturated aqueous solution (0.352 g/L)
SOLUBILITY IN WATER	352 mg/L at 37°C
SOLUBILITY IN SOLVENTS	Soluble in DMSO; Soluble in alcohol
VAPOUR PRESSURE (20OC):	5.02x10-4 mm Hg at 25°C
HENRY'S LAW CONSTANT	4.6×10-9 atm-cu m/mole (using fragment constant estimation method)
N-OCTANOL/WATER PARTITION COEFFICIENT	Log Kow = 1.25 (est)
HYDROLYSIS	Is not expected to undergo hydrolysis in the environment due to the lack of functional groups
DISSOCIATION CONSTANT (PKA)	pKa = 2.64 (est)
UV/VIS ABSORPTION	Reference states that the maximum UV absorption peak is at 310.3 nm
FLASH POINT	138.7°C
FLAMMABILITY:	Not combustible
EXPLOSIVE PROPERTIES:	Not explosive under normal conditions
OXIDISING PROPERTIES:	No oxidizing properties

2.2 Formulated products

The products Foxecute Fox Bait and PAPP Wild Dog Bait will be formulated in Australia and supplied in lots of 10 to 200 baits in (350 g to 7 kg) and (600 g to 12 kg) pack sizes respectively, in tamper-evident polypropylene (PP) pails.

Physical and Chemical Properties of Formulated Product Foxecute Fox Bait

FORMULATION TYPE:	Bait
APPEARANCE:	A 35 g cylindrical shaped bait with uniform brown colour and firm rubbery consistency
ACTIVE CONSTITUENT CONCENTRATION:	11.4 g/kg 4-aminopropiophenone (para-aminopropiophenone (PAPP)) [400 mg para-aminopropiophenone (PAPP) per 35 g bait]
PH VALUE:	5-6
SPECIFIC GRAVITY:	~1.03 g/cm3
SAFETY PROPERTIES:	Not corrosive, flammable, oxidising or explosive
PRODUCT STABILITY	The product should remain within specification for at least 2 years under normal conditions in PP packaging

Physical and Chemical Properties of Formulated Product PAPP Wild Dog Bait

FORMULATION TYPE:	Bait
APPEARANCE:	A 60g cylindrical shaped bait with uniform brown colour and firm rubbery consistency
ACTIVE CONSTITUENT CONCENTRATION:	16.67 g/kg 4-aminopropiophenone (para-aminopropiophenone (PAPP)) [1000 mg para-aminopropiophenone (PAPP) per 60g bait]
PH VALUE:	5–6
SPECIFIC GRAVITY:	~1.03 g/cm3
SAFETY PROPERTIES:	Not corrosive, flammable, oxidising or explosive
PRODUCT STABILITY	The product should remain within specification for at least 2 years under normal conditions in PP packaging

2.3 Conclusion

The APVMA is satisfied that the chemistry and manufacture data requirements necessary for the registration of the products Foxecute Fox Bait and PAPP Wild Dog Bait and approval of their active constituent 4 aminopropiophenone (para-aminopropiophenone (PAPP)), have been met.

3 TOXICOLOGICAL ASSESSMENT

3.1 Summary

PAPP (4-aminopropiophenone) is an aminophenone / phenol derivative. Foxecute Fox Bait contains 11.4 g/kg para-aminopropiophenone (PAPP) [Each 35 g fox bait containing 400 mg para-aminopropiophenone (PAPP)] and PAPP Wild Dog Bait contains 16.8g/kg para-aminopropiophenone (PAPP) [Each 60 g wild dog bait containing 1000 mg para-aminopropiophenone (PAPP)]. The products are encompassed in a solid bait matrix and used solely as a vertebrate pesticide for the control of foxes and wild dogs respectively. The bait products are not intended for use in domestic or urban areas. The products will only be available to appropriately authorised users in tamper-evident polypropylene pails. Foxecute Fox Bait will be supplied in 10 (350 g) to 200 (7 kg) bait pack sizes and PAPP Wild Dog bait will be supplied in 10 (600 g) to 200 (12 kg) bait pack sizes.

The mechanism of action for PAPP as a vertebrate pesticide involves the biotransformation of PAPP to the metabolite N-hydroxylaminopropiophenone (PHAPP), which causes oxidation of haemoglobin to methaemoglobin (MetHb). The high methaemoglobin level (methaemoglobinaemia) reduces the oxygen-carrying capacity of blood, resulting in death by metabolic hypoxia at elevated methaemoglobin levels. This mechanism is also the basis of the observable relevant clinical signs of toxicity in humans.

The data package provided in the present submission comprise a limited number of unpublished toxicity studies, including two 14–day studies in rats and monkeys; three in vitro and in vivo genotoxicity studies and one dermal pharmacokinetics study. The majority of the submission comprised published articles discussing the mechanism of action of PAPP and related MetHb-forming compounds, general discussion on methaemoglobinaema, and published information from human studies.

Based on the information included in the submission, PAPP is of high acute oral toxicity in dogs (LD50 30– 50 mg/kg bw); moderate acute oral toxicity in rats (LD50 177–221 mg/kg bw) and mice (LD50 168–233 mg/kg bw) and low acute oral toxicity in the guinea pig (1020 mg/kg bw). There were no acute dermal or acute inhalation studies available, and no irritancy or sensitisation studies.

In the two 14–day oral toxicity studies in rats or monkeys, a dose-dependent and time-related increase in MetHb levels was observed in all dose levels (from 20 mg/kg bw/d in rats, and from 17 mg/kg bw/d in monkeys), along with other haematological changes suggestive of changes in erythropoiesis, oxidative damage and haemolysis. No reproductive or developmental toxicity studies were available, while secondary carcinogenicity information suggested that chronic PAPP administration in Wistar rats resulted in an increased incidence of tumours. Genotoxicity studies (in vitro and in vivo) suggested that PAPP was an in vitro and in vivo genotoxicant.

There were no standard toxicity studies available on the products, though administration of the product PAPP Wild Dog Bait at 2000 mg/kg bw to mice in a non-Guideline dermal pharmacokinetics study did not result in clinical signs of toxicity or mortality in the very short observation period (24 hours) after dosing. Based on the toxicity and concentrations of the active and non-active constituents, Foxecute Fox Bait and PAPP Wild Dog Bait are likely to have low acute oral toxicity. While there are no data on the acute dermal and acute inhalational toxicity of the products, and no information on the irritancy and sensitisation potential,

due to the presentation of the products as solid bait formulations, the acute inhalational toxicity concern is expected to be low. Additionally, the dermal toxicity, skin and eye irritation and sensitisation risks may be managed by appropriate safety directions (noting that there are genotoxicity concerns for PAPP for which the OCS has recommended the use of personal protective equipment).

After consideration of the hazards associated with the active constituent and the proposed products, along with the exposure and risks expected with use of the proposed products, it was considered that the approval of the active constituent PAPP, and the proposed use of Foxecute Fox Bait and PAPP Wild Dog Bait for the control of foxes and wild dogs respectively will not be an undue health hazard to humans and will satisfy the safety criteria stipulated in Section 5A of the Agvet Code Act (1994), when used in accordance with the label directions.

3.2 Evaluation of toxicology

The toxicology data provided in the application contains limited conventional unpublished toxicology studies on PAPP: available studies included toxicokinetic studies, genotoxicity studies and short-term oral toxicity studies in rat and monkey. The majority of the submitted data were publications reporting results from old studies which were not conducted in accordance with contemporary test guidelines or with good laboratory practice requirements.

The OCS notes the lack of toxicity studies on specific endpoints, including acute dermal and inhalational toxicity studies, eye and dermal irritation and skin sensitisation studies, long-term toxicity studies, carcinogenicity studies, and reproduction and developmental studies. Overall, the toxicology profile for PAPP is considered incomplete, but in this case sufficient to inform key aspects of PAPP toxicology relevant to active constituent approval and scheduling considerations.

Chemical class

PAPP (4-aminopropiophenone) is an aminophenone / phenol derivative.

Toxicokinetics and metabolism

In experimental animals including dogs, rats and monkeys, PAPP is absorbed by the gastrointestinal tract more rapidly in rats and dogs (Tmax up to 60 min) than in monkeys (Tmax 1–1.5 hour). Urine is the major pathway of excretion (> 70% administered radiolabel), and faeces is the minor elimination route in these species.

The oral bioavailability of PAPP in dogs was reported as 32%–52%, while another study reported information that 65–90% of an orally administered 1.25 mg/kg bw dose of PAPP in humans was accounted for in urine samples.

It has been generally accepted that PAPP is biotransformed by the liver enzymes in vivo into a bioactive form, as the hydroxylamine derivative PHAPP. However, a submitted study reported a failure to detect PHAPP following dosing in rats, dogs and monkeys. This was interpreted as PHAPP having low stability in these species, which was supported by in vitro monkey data noting that PHAPP had a half- life of 1 min. In contrast, PHAPP was readily detected in the plasma of rabbits and guinea pigs following administration of

PAPP, and the kinetic and dynamic characteristics of PHAPP were consistent with those of PAPP in rabbits and mice, including dose-related increases in MetHb level. It was further demonstrated in another study that only PHAPP, but not PAPP, exerted a MetHb-forming effect under in vitro incubation conditions with mouse blood, suggesting that it is essential for PAPP to convert to PHAPP to exert its effect as a MetHb former, and the transformation only happens in vivo, likely by metabolism with liver enzymes.

As described above, PAPP is not a direct oxidant of haemoglobin and requires biotransformation to the active metabolite, PHAPP. Once formed, PHAPP is taken up by circulating erythrocytes where a redox cycle, known as kreisprozess, taken place, where PHAPP is converted to p-nitrosopropiophenone (PNPP), which brings about the simultaneous oxidation of heme Fe2+ to Fe3+. Intra-erythrocytic NADPH, generated from glucose-6-phosphate dehydrogenase, participates in the reduction of p-nitrosopropiophenone (PNPP) back to PHAPP, which again can oxidize a heme portion of the molecule (Hb) to MetHb.

The differences or deficiency in one or more of the key enzymes in the methaemoglobin-forming process (G6PDH or MetHb reductase) form the basis of inter-species differences, species selectivity and intra-species (individual) variations. For example, the lower toxicity of PAPP in rabbits and guinea pigs is attributed to a higher level of NADH-MetHb reductase and NADPH-MetHb reductase in these species, which reduce MetHb back to Hb more rapidly compared to dogs and humans.

High MetHb levels (methaemoglobinaemia) reduce the oxygen-carrying capacity of the blood, and can result in death by metabolic hypoxia. Noting the presence of the various MetHb reductases in mammalian species, gradual natural recovery from high MetHb levels occurs after cessation of PAPP treatment. The process of methaemoglobinaemia can also be reversed with appropriate MetHb reduction substances, such as methylene blue.

Overall, the MetHb response induced by PAPP is considered a toxicodynamic effect. This effect forms the basis of the mode of action of PAPP as a pesticide, its toxicity observed in animal and human studies, and its mechanism as an antidote against cyanides.

Percutaneous absorption

There were no standard data available for dermal absorption. In an unpublished mouse study examining blood PAPP concentrations and pharmacokinetics following dermal administration of PAPP (33 mg/kg bw) or PAPP Wild Dog Bait (a product formulation containing 1.67% PAPP), blood PAPP levels were below the LOQ identified in the study. The OCS notes that no mass balance of administered material was conducted, and the study design was not considered a standard pharmacokinetic or dermal absorption study protocol, and therefore is of limited relevance to these endpoints.

Acute toxicity

The data for the acute oral toxicity of PAPP were collected from research publications and review papers, and show large differences in various species. Based on the available information, PAPP is of high acute oral toxicity in dogs (LD50 30–50 mg/kg bw); moderate acute oral toxicity in rats (LD50 177–221 mg/kg bw) and mice (LD50 168–233 mg/kg bw) and low acute oral toxicity in the guinea pig (LD50 = 1020 mg/kg bw).

In the descriptive material from one study, clinical signs associated with oral toxicity included cyanosis, loss of muscle tone, piloerection and dyspnoea immediately after treatment, with cyanosis and piloerection persisting up to two days post-treatment in guinea pigs and four days in mice. Heinz body formation was noted in blood from rodents, but not guinea pigs. Additionally, some evidence of anaemia (up to 30% decreased erythrocyte counts) was present in rats only after PAPP administration.

Across the toxicity studies, PAPP-induced mortality and clinical signs were related to the blood level of MetHb; from the available data, the species differences in acute toxicity appear to be attributable to the enzyme activities in biotransforming PAPP to PHAPP, and the enzyme activities involved in oxidation of Hb to MetHb and the reduction of MetHb back to Hb.

There are no acute dermal or inhalational toxicity studies available for PAPP or the products. No data was available regarding skin or eye irritation, or skin sensitisation on either the active constituent or the product formulations. In what was described as a dermal pharmacokinetics study, single doses of PAPP (at 33 mg/kg bw) or the product formulation PAPP Wild Dog Bait (at 2000 mg/kg bw product, equivalent to ~33 mg/kg bw PAPP) were applied to mice, and no mortalities or clinical signs of toxicity were observed in the abbreviated observation period of 24 hours, and no PAPP was detected in blood samples drawn during the study.

Repeat-dose toxicity

Two short term toxicology studies for PAPP were evaluated: a 14–day oral study in rats, and a 14–day oral study in monkeys. No NOEL was established in either of these studies.

In the 14–day rat study, PAPP was administered at 0, 35/20, 90/50 or 140/130 mg/kg bw/d (for males/females (M/F) respectively). Enlarged spleens associated with erythroid hyperplasia, sinusoidal enlargement and pigment, and raised MetHb were observed in all dose levels, which led to a LOEL of 35 mg/kg bw/d in males and 20 mg/kg bw/d in females. In addition, reduced RBC count along with increased PCV and haemoglobin were evident at ≥90/50 mg/kg bw/d; pigment was also present in Kupffer cells of the liver and renal proximal tubular epithelial cells at the high dose level.

In the 14–day monkey study, PAPP was administered at 0, 17, 50 and 150 mg/kg bw/d, and a LOEL was established at 17 mg/kg bw/d on the basis of raised MetHb concentrations detected before dosing each day, RBC morphology and bone marrow changes and Heinz body formation in all test groups during the dosing period. These changes were not fully reversed after a 2–week recovery period. In both studies, the haematology data indicated the effects of PAPP on erythropoiesis, along with oxidative damage and haemolysis.

Genotoxicity and carcinogenicity

In a series of genotoxicity studies, PAPP was positive for mutagenic potential in the Ames test. Summary data from published literature suggested that PAPP was mutagenic in the presence of S9 metabolic activation in the forward gene mutation assay.

Two in vivo mouse micronucleus tests were provided in the submission. In the first study, PAPP (unpurified; unknown purity/concentration) elicited a negative clastogenicity response (Asquith, 1988), while in the second study, PAPP (>100% purity from the certificate of analysis) was considered to induce micronuclei in

bone marrow (i.e. elicited clastogenic potential), as the definition of a negative clastogenic response was not met.

The OCS notes that no primary Guideline-compliant in vitro genotoxicity data was provided in the submission, and the available in vivo micronucleus test data raises concerns regarding the in vivo clastogenic potential of the test (supported by the Ames test data). On this basis, the OCS considers that PAPP is likely to be genotoxic.

There are no relevant long term toxicity/carcinogenicity studies in the submission. Secondary data in a study suggested that chronic administration (4 mg/d, 18 months) of PAPP to rats resulted in an increased incidence of tumours (not defined) and carcinomas, though the reporting of the study was limited and findings could not be verified from the abstract provided. While there are data from a study where PAPP administered at up to 20 mg/kg bw twice weekly by i.p. injection for 72 days did not alter the frequency of neoplastic observations in the methylcholanthrene model of epidermal tumourigenesis, the OCS is unable to infer the carcinogenic potential of PAPP alone from this data.

Overall, from the information available, it is unknown whether PAPP is carcinogenic.

Reproductive and developmental toxicity

No data on reproduction and developmental toxicity were available.

Neurotoxicity

Some PAPP treatment related findings suggestive of a potential neurotoxic effect were identified in the evaluation of submitted data, such as decreased locomotor activity in mice and a lengthening of response-times of the conditioned reflex of avoidance of a noxious stimulus. However, the OCS notes that observed effects may also be related to induced hypoxia associated with in vivo MetHb formation after PAPP administration. Guinea pigs subcutaneously injected with PAPP at 12.5, 25, 37.5 or 50 mg/kg bw did not present with altered swim time or swim latency (as behavioural markers) in a swimming performance test. Overall, there is insufficient data to determine whether PAPP has neurotoxic potential.

Other toxicology data

A number of single low-dose oral toxicity studies in humans were evaluated.

In one study, PAPP was well absorbed in the human following ingestion of 1.25 mg/kg bw, and 65–90% of the administered dose was accounted for in the urine. The oral bioavailability of PAPP in humans is somewhat higher than that seen in dogs, where bioavailability was reported as 32–52%, depending on the publication cited.

An informative human study included 51 human volunteer subjects (aged 23–52 years, factory workers). In the study, PAPP was given orally to the volunteers at 50, 80 or 100 mg (equivalent to 0.8–1.8 mg/kg bw PAPP), and led to an average maximum MetHb level of 7% (n = 1), 13.1% (range 0–43%, n = 37) and 22% (range 2–48%, n = 13) respectively. MetHb formation began 15–30 minutes after PAPP treatment, and peak levels were reached at 1–2 hours after PAPP treatment. The high variability in the maximum MetHb level

within a dose group was likely related to differences in body weights and the contents of the gastric compartments, noting that fasting resulted in higher peak MetHb formation upon PAPP dosing. Other than bluish lips, the study did not note any clinical signs or other adverse effects associated with PAPP-induced methaemoglobinemia. There were no physical, intellectual or psychological abnormalities during the study, and no renal problems, no changes in ventilation rate, arterial pressure, or electrocardiogram findings (except 2 subjects showing slight changes in P, QRS and T wave values). These observations were generally supported by other human studies at similar dose levels.

In a separate human study, single oral doses of PAPP caused increases of MetHb levels in a dose-related manner in one normal female human subject, i.e. 3.5% and 15% MetHb after 1.14 and 3.4 mg/kg bw PAPP doses respectively (n = 1 only). In addition, two males showed higher responses to PAPP, with 24% and 32% MetHb formation after 1.45 and 1.39 mg/kg bw PAPP doses respectively. In a subject with sickle cell disease, repeat oral dosing of 100 mg PAPP at 4–hour interval for 37 doses caused sustained high level of MetHb, with a steady-state of 20–28% (no clinical observations were reported in the paper).

A number of general clinical review papers discussing methaemoglobinaemia in humans indicated that high MetHb levels resulted in a range of clinical symptoms/signs with scaling MetHb levels, including headache, dyspnoea, nausea and tachycardia occurring at ≥20% MetHb; lethargy, stupor and deteriorating consciousness occurring at up to 55% MetHb; cardiac arrhythmias, circulatory failure, coma and neurological depression at ≥ 55% MetHb, and death/mortality occurring at ≥70% MetHb.

Due to large species variation in the response to PAPP, the human studies provide valuable information regarding the effects of human response to PAPP. However, the information derived was mostly limited to single dose exposures at low dose levels (0.8–1.8 mg/kg bw). Even at this low dose range, PAPP caused a clear dose-related increase in MetHb levels in human subjects (up to 48%), suggesting that humans are sensitive to PAPP-mediated MetHb formation.

The available data suggests that the potency of PAPP to induce MetHb formation in humans after oral administration is broadly comparable to that observed in dogs, rather than in rats and mice. This is based on comparison of results from studies where 1 mg/kg bw single oral doses administered to dogs led to peak MetHb formation of 26% and 16% MetHb.

Public health standards

Poisons Scheduling

PAPP was referred to the Delegate of the Secretary of the Department of Health for scheduling consideration. Subsequently, the Delegate referred the application to the Advisory Committee for Chemicals Scheduling (ACCS) for advice in March 2015.

In their discussions, the ACCS recommended inclusion of 4-aminopropiophenone in Schedule 7 with cross-referencing in the index to para-aminopropiophenone. The ACCS also recommended the following Appendix J, condition 3, Part 1 entry:

4-Aminopropiophenone—Not to be used except by or in accordance with the directions of accredited government vermin control officers

The reasons for the recommendation were that the toxicity of PAPP was consistent with Schedule 7 factors, and that PAPP would be presented in a way that poses clear risks. On 23 July 2015 the Delegate to the Secretary of the Department of Health accepted the advice from the ACCS and published a final scheduling decision to create a new Schedule 7 listing of 4-aminopropiophenone with a cross-reference in the Poisons Standard index to the common name, para-aminopropiophenone (PAPP), and inclusion in Appendix J of the SUSMP with the condition *'Not to be used except by or in accordance with the directions of accredited government vermin control officers'*. The delegate confirmed the proposed implementation date of 1 October 2015.

The statement of reasons drawn from the interim and final decision of the Delegate is replicated below:

The toxicity profile of the active ingredient is consistent with SPF criteria for listing in Schedule 7, including an LD50 estimate in dogs at 30–50 mg/kg, positive evidence of genotoxicity potential, and indeterminate evidence relating to its potential carcinogenicity. The delegate noted the submissions that argued for creating an exception to Schedule 6 for the formulated bait products, but accepted ACCS advice that such an exception is not warranted on grounds of toxicity and the potential for a toddler to be seriously poisoned through consumption of complete bait. The delegate noted that repeated dose studies with PAPP failed to demonstrate a no observed adverse effect level (NOAEL) at the lowest doses tested (17–20 mg/kg/d) and that humans may be even more susceptible to methaemoglobinaemia formation, possibly at doses as low as 0.1–1.8 mg/kg.

The delegate also noted advice from ACCS members that access controls available through listing in Schedule 7 and Appendix J are required for use in jurisdictions where the products are likely to be used. The delegate noted that such controls would also complement the stated intention of the APVMA to regulate the products as Restricted Chemical Products.

ADI

The acceptable daily intake (ADI) for humans is the level of intake of an agricultural or veterinary chemical which can be ingested daily over an entire lifetime without appreciable risk to health. It is calculated by dividing the overall NOEL for the most sensitive toxicological endpoint from a suitable study (typically an animal study) by an appropriate safety factor. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to humans, intra-species variation, and the completeness of the toxicological database and the nature of the potential toxicologically significant effects.

Since PAPP and the formulated products Foxecute Fox Bait and PAPP Wild Dog Bait are proposed for use in non-food producing species that will not result in residues in food or livestock feed, establishing an ADI is not considered necessary.

ARfD

The acute reference dose (ARfD) is the estimate of the amount of a substance in food or drinking water, expressed on a milligram per kilogram body weight basis, that can be ingested over a short period of time, usually in one meal or during one day, without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation.

Since PAPP and the formulated products Foxecute Fox Bait and PAPP Wild Dog Bait are proposed for use in non-food producing species that will not result in residues in food or livestock feed, establishing an ARfD is not considered necessary.

3.3 Conclusion

After consideration of the hazards associated with the active constituent and the proposed products, along with the exposure and risks expected with use of the proposed products, the APVMA is satisfied that the approval of the active constituent PAPP, and the proposed use of Foxecute Fox Bait and PAPP Wild Dog Bait for the control of foxes and wild dogs respectively will not be an undue health hazard to humans and will satisfy the safety criteria stipulated in Section 5A of the Agvet Code Act (1994), when used in accordance with the label directions.

4 RESIDUES ASSESSMENT

The APVMA is satisfied that the proposed use of Foxecute Fox Bait and PAPP Wild Dog Bait will not be an undue hazard to the safety of people using anything containing their residues as the products are not proposed for use in food-producing areas or in food-producing animals.

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

The APVMA is satisfied that the proposed use of Foxecute Fox Bait and PAPP Wild Dog Bait would not adversely affect trade between Australia and places outside Australia as the products are not for use in animals producing any major Australian export commodities.

6 WORK HEALTH AND SAFETY ASSESSMENT

6.1 Summary

The products Foxecute Fox Bait and PAPP Wild Dog Bait will be used as vertebrate pesticides. The baits will be applied predominantly into pastoral farming areas to target wild dogs and foxes preying on livestock, and also in national parks and other crown land where wild dogs and foxes require management. The products will only be available to users appropriately authorised in the State and territory jurisdictions.

The baits will be applied by hand directly to the ground by burial in a shallow hole (8 cm deep) and covered with soil.

Aerial (above ground) baiting may be required by government authorities under limited circumstances such as for use in inaccessible areas where wild dog numbers are a threat to wildlife, and ground application is not feasible. Aerial application will not be generally available to other authorised users as it is prohibited on the product labels and will only be available via permit authorisation for such use.

Based on the formulation (a solid bait matrix) and product use pattern, dermal contact with the products baits will be the main route of exposure for users, with oral, ocular and inhalational exposure to the product expected to be minimal.

As no product-specific exposure data were provided, the OCS has used surrogate/modelling data related to bait usage along with the provided draft product label indications and applicant information for risk assessment. Based on the outcomes of the risk assessment, First Aid Instructions and Safety Directions have been recommended for inclusion on the product labels, along with language regarding public notification, poison notices and distance restrictions.

6.2 Health hazards

4-aminopropiophenone (also known as para-aminopropiophenone, or PAPP) (CAS: 70–69–9) is currently not listed on the Safe Work Australia Hazardous Substances Information System (HSIS) Database (SWA, 2015).

With the available toxicology information included in the present assessment report (OCS 2015), OCS recommends classification of the active constituent 4-aminopropiophenone as a hazardous substance according to NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004), with the following risk phrases:

T; R25	TOXIC IF SWALLOWED
Xn; R68/22 (Muta. Cat 3)	Possible risk of irreversible effects if swallowed

THE FOLLOWING DEFAULT CONCENTRATION CUT-OFFS APPLY:

Conc. ≥ 25%	T; R25, R68/22
10% ≤ Conc. < 25%	Xn; R22, R68/22
3% ≤ Conc. < 10%	Xn; R22

Based on the concentrations of active constituent and other constituents in the product, the products Foxecute Fox Bait (400 mg PAPP per 35 g bait, or 1.14% w/w) and PAPP Wild Dog Bait (1000 mg PAPP per 60 g bait, or 1.68% w/w) are not classified as hazardous substances in accordance with NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004).

6.3 Formulation, packaging, transport, storage and retailing

The products Foxecute Fox Bait and PAPP Wild Dog Bait will be formulated in Australia using the active constituent para-aminopropiophenone (PAPP) imported from overseas. The baits are packaged into packs of 10 to 200 baits, in a ready-to-use form.

6.4 Use pattern

The use pattern is similar to existing registered fox or wild dog baits, such as 1080 (sodium fluoroacetate) baits. Both Foxecute Fox Bait and PAPP Wild Dog Bait are applied at a rate of one bait per 5–10 ha (i.e. only one bait per site), up to 20 baits per km^2 depending on dog and fox densities. Baits are typically applied along transects, e.g., road sides or fence lines at intervals of 200–500 m in pastoral farming areas to target wild dogs and foxes preying on livestock, and also in national parks and other crown land where wild dogs and foxes require management.

The baits will be applied by hand directly to the ground by burial in a shallow hole (8 cm deep) and covered with soil. In a ground baiting program, a single worker can lay a maximum of 40 baits per day due to the need to find appropriate bait sites, careful site selection and use and removal of gloves, packaging, etc. at each site.

PAPP Wild Dog Bait may also be aerially applied by release from fixed wing aircraft or helicopter via placing baits into a chute, at a typical deployment rate of one bait per 500 metre distance, with no more than one bait per 5 ha. Aerial application is only used in remote areas where ground application is impractical and will only be available under permit authorisation.

6.5 Exposure during use

Based on the product use pattern, workers are likely to use the product as required during baiting periods, though the expected use frequency at any stage is likely to be intermittent. Based on the formulation (a solid bait matrix) and product use pattern, dermal contact with the products baits will be the main route of exposure for users, with oral, ocular and inhalational exposure to the product expected to be minimal.

As no product-specific exposure data were available for the proposed mode of application, the OCS has considered available surrogate/modelling data related to bait usage. In this instance, the OCS has used guidance from the European Union HEEG opinion on a harmonised approach for the assessment of rodenticides, along with the provided draft product label indications and applicant information in the absence of product specific data. Based on a concentration of 1.68% PAPP in the product PAPP Wild Dog Bait and an average weight of an adult of 70 kg, this would result in a systemic exposure of 0.053 mg PAPP/kg bw/d without gloves, and a systemic exposure of 0.0053 mg PAPP/kg bw/d with gloves.

The relevant endpoint identified for risk assessment was methaemoglobin formation observed across studies (noted as a toxicodynamic effect of PAPP administration). The LOEL of 0.8 mg/kg bw was selected for the risk assessment, and the margin of exposure (MOE) applicable to this risk assessment was identified as 100, consisting of a 10–fold intra-species variation, a two-fold safety factor for use of a LOEL, and a 5–fold safety factor for deficiencies in the PAPP database in this case. Comparison of the risk assessment endpoint LOEL with the expected daily exposure to the product indicates that the MOE for use of the product when wearing a single layer of clothing is 15 without gloves and 151 with gloves. This indicates that there is an adequate MOE for the product to be used according to the described use pattern with the use of appropriate PPE (use of single-layer of clothing and chemical-resistant gloves).

6.6 Exposure during re-entry/re-handling

Workers may be exposed to the baits during checking and bait replacement activities and collection of un-eaten bait after expiration of the baiting period. The following re-entry/rehandling statement has been included on the product label:

Do not re-handle product unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

6.7 Recommendations for safe use

Based on the estimated exposure and the risk assessment conducted, specific first aid instructions and safety directions have been recommended for use of the product, and for rehandling of the product after baiting is complete.

While the product is not intended for domestic use, a consideration of a reasonable worst case accidental exposure scenario was considered relevant and appropriate to inform the need for specific storage/handling considerations for the products in this instance. In the reasonable worst case accidental ingestion situation, if a whole bait is ingested by a toddler with body weight of 10 kg, this would result in a systemic exposure equivalent to 40–100 mg/kg bw PAPP.

In considering the toxicology of PAPP and PAPP-induced methaemoglobin formation, the available toxicity data indicates that relatively low doses of PAPP (approximately 0.8 mg/kg bw) would produce methaemoglobin in humans, albeit at relatively low levels, with no clinical signs of toxicity observed. The data also shows a steep dose response curve for methaemoglobin formation. In addition, reported acute oral LD_{50} values after ingestion of PAPP were 30–50 mg/kg bw in dogs, and 177–221 mg/kg bw in rats (though rats are not regarded as adequately predicting the acute oral toxicity potential of PAPP in humans).

Based on the reported acute oral toxicity information, it is noted that the resulting oral exposure to PAPP after accidental ingestion of a bait (40–100 mg/kg bw for a toddler) would not result in a sufficient margin of safety. However, noting that the product is not intended for domestic use, this risk of accidental ingestion of a bait by a toddler may be further mitigated by the addition of label warning statements and restraints limiting access to the products, and warning the general public when baiting operations are taking place, in a similar manner to that for other bait products such as 1080–based products (noting that uneaten bait will also be collected by workers after expiration of the baiting period). As Restricted Chemical Products the baits will only be available to users appropriately authorised in the State and territory jurisdictions and specific label restraints/statements and language regarding public notification, poison notices and distance restrictions have been recommended.

In summary, users should follow the First Aid Instructions, Safety Directions and note the risk management measures (notifications, re-handling statements and label restraints) recommended on the product label.

6.8 Conclusion

The approval of the active constituent PAPP and registration of the products Foxecute Fox Bait and PAPP Wild Dog Bait as vertebrate pesticides are supported.

Foxecute Fox Bait and PAPP Wild Dog Bait can be used safely if handled in accordance with the instructions on the product label and any other control measures described above. Additional information is available on the product Material Safety Data Sheet.

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

Animal Control Technologies Australia Pty Ltd (ACTA) has applied for registration of two end-use products containing the new active constituent para-Aminopropiophenone (PAPP). Foxecute Fox Bait contains the active constituent at a formulation concentration of 11.4 g/kg, sufficient to give a concentration of 400 mg PAPP per 35 g bait. In the second product, PAPP Wild Dog Bait, PAPP is present in the formulation at 16.8 g/kg, sufficient to give 1000 mg PAPP per 60 g bait. As restricted chemical products (RCPs) the bait products will only be available to users appropriately authorised in the State and territory jurisdictions.

In addition to data provided in the submission, additional information has been obtained from publicly available sources. Limited fate data are available for PAPP, and the environmental effects data available are focussed on toxicity to mammals, birds and reptiles, with little or no information available on other species. However, this is considered acceptable due to the very low per hectare application rate of the active constituent at discrete, widely dispersed points where the bait is placed, with no significant exposure of aquatic organisms, plants or terrestrial invertebrates and soil-dwelling organisms.

7.2 Environmental fate

Physicochemical properties

Studies indicate that PAPP is moderately soluble in water (230 mg/L at 22ºC), while its hydrochloride salt (PAPP-HCl) is much more water soluble (6,400 mg/L at 22ºC). The measured n-octanol/water partition coefficient indicates that PAPP is likely to be mobile in soil and is unlikely to bioconcentrate (log Pow = 1.7 at 22ºC). Modelling of the vapour pressure and Henry's Law Constant using the EPISuite program predicts that PAPP is slightly volatile and very slightly volatile from water.

Hydrolysis

A standard OECD guideline test indicates that PAPP is hydrolytically stable at pH 4, 7 and 9, and it is therefore considered to be hydrolytically stable within the environmental pH range. The same result was obtained in a similar test with PAPP-HCl.

Biodegradation

Ready biodegradation of PAPP and PAPP-HCl was tested following standard OECD test guidelines. Based on these results, PAPP can be concluded as being readily biodegradable. Greater than 90% degradation of PAPP-HCl was reached during the 28 day incubation period, providing evidence for inherent ultimate biodegradability.

Mobility

The potential for PAPP to leach through soil was investigated using four different soil columns. In sand, the whole applied amount was recovered in the water phase at the first elution. In the sandy loam and loam soils, 53–81% of applied was found in eluate, with the remainder presumably sorbed to the soil. The majority of PAPP appeared to sorb to the clay soil, with 14% of applied found in the eluate. A similar study conducted with PAPP-HCl indicated slightly less mobility in sand, but greater mobility in the other soils.

Bioaccumulation

Modelling using the EPISuite program predicts that PAPP is slightly bioconcentrating (BCF < 100).

Conclusions

Given its water solubility, baits falling out of bait stations, or dropped from the air may allow PAPP to leach out of baits and into the soil. PAPP is mobile in the soil. Results reported in this submission indicate the substance is unlikely to persist in the environment. PAPP is not expected to bioaccumulate.

7.3 Environmental effects

Mode of action

The mode of action of PAPP in vertebrate species occurs through the oxidation of haemoglobin to methaemoglobin, raising methaemoglobin from the low levels (<1%) normally present in blood. Methaemoglobin is unable to effectively transport oxygen. If sufficiently high levels are formed in blood, a lack of oxygen to the brain and heart results, leading to loss of consciousness and death due to respiratory failure. Species differ widely in their susceptibility, and with sub-lethal doses PAPP and its metabolites are metabolised and excreted. Less susceptible animals that are exposed to PAPP suffer partial 'methaemoglobinaemia' that is transitory and generally causes no clinical symptoms. Thus PAPP is an acute vertebrate poison and does not exhibit bioaccumulation once metabolised in the affected animal. Methylene blue is considered an antidote to PAPP exposure, with demonstrated effectiveness in dogs.

Avian

Studies indicating the acute oral toxicity of PAPP were available for 12 bird species. With an LD50 of 32– 38 mg/kg bodyweight (highly toxic), mallard duck (*Anas platyrhynchos*) were clearly more sensitive than other bird species. The acute LD50 of PAPP to the New Zealand weka (a flightless bird) was ~568 mg/kg, but this value was considered an underestimate of susceptibility of this species, due to slow recovery from sublethal effects, even at the lowest dose of 62 mg/kg. The next most sensitive species were little Australian raven (*Corvus coronoides*) and red-winged blackbird (*Agelatus phoenicus*), with LD50 = 130–133 mg/kg (moderately toxic). The Australian magpie (*Gymnorhina tibicen*) was one of the least sensitive bird species (LD50 = 1387 mg/kg—slightly toxic).

Aquatic organisms

A study indicated the 96–h acute toxicity of PAPP to fathead minnow was 146 mg/L (practically non-toxic to fish).

Terrestrial Invertebrates

An acute earthworm toxicity study with PAPP-HCl and earthworms (*Eisenia fetida*) indicated a 14–d LC50 of 61.3 mg/kg dry soil (moderately toxic to earthworms).

Mammals

Studies indicating the acute oral toxicity of PAPP were available for 24 mammal species, ranging from very highly toxic (LD50 < 10 mg/kg) to slightly toxic (LD50 in the range 500–2000 mg/kg). The most sensitive species, with LD50s in the range 5–10 mg/kg, were cat (*Felis catus*), coyote (*Canis latrans*), brown bandicoot (*Isodon obesulus*), dingo (*Canis familiaris* dingo hybrid), stoat (*Mustela erminea*) and bobcat (*Lynx rufus*). Spotted-tail quoll (*Dasyurus maculatus*) was the next most sensitive Australian native species tested, with LD50 = 24.8 mg/kg, similar to that for red fox (*Vulpes vulpes*). The toxicity to other native species tested ranged from 89–120 mg/kg for Dama wallaby (*Macropus eugenii*), fat-tailed dunnart (*Sminthopsis crassicaudata*) and Tasmanian devil (*Sarcophilus harrisii*), and > 500 mg/kg for brushtail possum (*Trichosurus vulpecula*), brown antechinus (*Antechinus stuartii*) and bush rat (*Rattus fuscipes*). The least sensitive species for which a reliable endpoint was available was the guinea pig (*Cavia porcellus*) (LD50 = 1020 mg/kg).

Reptiles

A study with Rosenberg's goanna (*Varanus rosenbergi*) indicated an LD50 of 12 mg/kg, and a similar level of toxicity was evident with Lace monitor (*Varanus varius*).

Conclusions

Acute toxicity data are available for a wide range of mammalian and avian species and for two reptile species (goannas). This indicates that there is a wide range in toxicity of PAPP to mammals, birds and reptiles, from ~5 to >1000 mg PAPP/kg bodywt. The most susceptible mammals are carnivores, which includes predators such as dogs and foxes that are the target for these products, but also some marsupial species that are carnivorous and goannas. The most susceptible bird was the mallard duck. Chronic toxicity data or additional data for other species are not required due to the mode of action of the substance and lack of exposure.

7.4 Risk assessment

These products are applied as baits and therefore present a very low exposure to the environment, with wide dispersal of baits at discrete points over the baited area (a maximum of 1 bait per 5 ha for both products, with repeat application up to 2–3 times per week over the 4–6 week duration of a baiting program). Use as proposed presents a minimal risk to aquatic or soil organisms, terrestrial invertebrates or plants.

Observations in field studies indicated that use of Foxecute Fox Baits had resulted in the death of several goannas, feral cats and a single southern brown bandicoot. With PAPP Wild Dog Bait, there were no known deaths attributed directly to bait ingestion, though there was camera evidence of cattle taking baits as well as goannas, foxes and several magpies. The applicant noted that extensive studies with camera monitored sites and carcase examinations with use of Foxecute Fox Baits and PAPP Wild Dog Baits and 1080 baits generally have shown that non-target take of baits is low.

Risk assessment therefore focussed on the potential for non-target animal exposure and toxicity through direct or incidental consumption of bait, or through secondary poisoning from consumption of the carcases of affected animals.

Species which may be affected through dietary behaviour

In order to estimate whether an animal might consume a lethal dose of PAPP through consumption of Foxecute Fox Bait or PAPP Wild Dog Bait, it is first necessary to use the available LD50 and typical body weight data to calculate the lethal dose of PAPP and then to convert this into a lethal bait dose for each bait type.

It is then necessary to relate this to daily dietary intake and consider whether an animal may consume this quantity of bait. Factors which affect this include the total daily food intake and the proportion of the food item in the diet. For PAPP, it is also necessary that the lethal dose be obtained over a relatively short period of time to achieve rapid induction to the 80% methaemoglobin level: detoxification and elimination mechanisms would limit the rise in methaemoglobin level and protect the animal with gradual nibbling at a bait over several hours.

Daily food intake for various animal species can be estimated based on their bodyweight using allometric equations which have been derived for different species groups, as follows:

Idf = 0.235W0.822 Eutherian mammals

Idf = 0.621W0.564 Rodents

Idf = 0.492W0.673 Marsupial mammals

Idf = 0.648W0.651 All birds

Idf = 0.013W0.773 Insectivorous iguanid lizards (no equation is listed for varanid lizards)

where Idf = food ingestion rate (dry weight) in g/d, and W = body weight (g live weight).

Calculated lethal doses of bait and daily food intakes as dry weight and adjusted to a moisture content of 85% (compared with the baits) are shown in Table 1.

As noted above, exposure to PAPP results in methaemoglobin formation, which is responsible for the toxic effects of PAPP. Providing levels of methaemoglobin remain below a critical threshold, exposure is not likely to have any adverse effects other than those described for sub-lethal toxicosis. The LD50 values have all been obtained with very acute exposure, such as oral gavage or force feeding. The extent to which this

represents exposure in practice depends on the feeding behaviour of the animal, e.g. consumption at intervals over the day or night, or gorge feeding, and consumption of alternative food sources.

Results where the percentage of the diet giving a lethal dose is <10% have been highlighted, assuming this may be a reasonable value to address the need for rapid intake of the lethal dose from a single food source (the bait). As might be expected, the lethal dose of the bait for target predators is low and represents a low proportion of their daily food intake (<5%). This is also the case for southern brown bandicoot, spotted-tail quolls and fat-tailed dunnarts (consistent with the observation of a dead bandicoot in the field studies). Potential for lethal effects to ducks is indicated by the results for the mallard duck with both products, with the little Australian raven the next most susceptible bird species of those evaluated in Table 1 below and only just above the 10% of diet level. Based on the acute LD50 values for PAPP, ducks are the most sensitive bird species tested, and there is considerable interspecies variation in response to PAPP by birds.

Table 1 – The calculated lethal dose of PAPP to various animals based on the LD50 value related to the estimated daily food intake for those species.

SPECIES	LD50 (MG PAPP /KG)	AVERAGE BWT (G)	ESTIMATED DAILY FOOD INTAKE (G)		LETHAL DOSE OF BAIT (G)		% OF DIET GIVING LETHAL DOSE	
			DWT	FWT	FOXECUTE FOX BAIT	PAPP WILD DOG BAIT	FOXECUTE FOX BAIT	PAPP WILD DOG BAIT
Cat	5.6	5000	258	304	2.45	1.68	1	1
Brown bandicoot	6.4	850	46.1	54.2	0.48	0.33	1	1
Dingo	8.5	16000	671	790	11.9	8.16	2	1
Spotted-tail quoll	24.8	5000	152	179	10.9	7.44	6	4
Red fox	25.2	6500	320	377	14.3	9.83	4	3
Dama wallaby	89	5000	152	179	38.9[1]	26.7	22	15
Fat-tailed dunnart	105	15	3.04	3.58	0.14	0.09	4	3
Tasmanian devil	120	8000	208	245	84.0[1]	57.6	34	23
Rat	177	320	16.1	18.9	4.96	3.40	26	18
Brown antechinus	571	35	5.38	6.33	1.75	1.20	28	19
Bush rat	697	125	9.46	11.1	7.62	5.23	69	47

SPECIES	LD50 (mg PAPP /kg)	AVERAGE BWT (g)	ESTIMATED DAILY FOOD INTAKE (g)		LETHAL DOSE OF BAIT (g)		% OF DIET GIVING LETHAL DOSE	
Brushtail Possum	500	3500	119	141	153[1]	105[1]	109	75
Mallard duck	32	1200	65.5	77.0	3.36	2.30	4	3
Little Australian raven	130	610	42.2	49.6	6.94	4.76	14	10
Silver gull	1000	290	26.0	30.6	25.4	17.4	83	57
Australian magpie	1387	320	27.7	32.6	38.8[1]	26.6	119	82
Lace monitor	3	4300	8.37	9.84	1.13	0.77	11	8
Rosenberg's goanna	12	1100	2.92	3.43	1.15	0.79	34	23

[1] Equivalent to more than one bait, but exposure to more than one bait at a time is not expected due to the distance between bait stations.

The approach used does not indicate a clear impact on goannas, though it is clear from field observations that goannas may be harmed. A likely explanation is the eating behaviour of goannas, which are evidently gorge feeders (in regard to assessment of the possibility of secondary poisoning of scavengers, the applicant indicates that goannas will, where they can, consume an entire carcass in a single mouthful). Assuming that goannas may consume an entire day's food intake in a very short period, they may readily consume a lethal dose.

Secondary poisoning

A possible route of exposure of non-target animals is consumption of carcases of dead animals containing residues of PAPP. The total PAPP residues in a dead animal will be less than the dose initially contained in a bait as some loss of the ingested poison must occur for toxicity to be induced. Rapid metabolism and clearance of the active hydroxylated metabolite PHAPP and PAPP have been shown to occur with sub-lethal dosing, thus some continuing loss may also be anticipated as an animal receiving a lethal dose succumbs.

The submission noted that residue data are available from necropsy samples of foxes taken during pen studies and discussed the implications of these for secondary poisoning of scavengers, as follows.

The results for the stomach contents and entrails indicate quite high concentrations of PAPP remained post humorously, which predatory and scavenging species may ingest. The high concentrations in the stomach presumably reflect the residues of the original dosing pill and may be highly localised. Of the native animals likely to scavenge a fox carcase, only the dingo and goanna could be expected to be impacted by PAPP baiting of foxes and wild dogs. Dingos will largely consume the muscle tissue, whilst goannas will, where

they can, consume the entire carcase in a single mouthful. The rate of biodegradation of PAPP is unknown, but expected to be quite quick, based on the ready biodegradation study. The Tasmanian devil will also scavenge, but their expected 80% MetHb threshold exceeds 120 mg/kg of PAPP. Table 1 indicates primary toxicity is not a concern for Tasmanian devils.

It is concluded that while it is possible that species such as goannas that are susceptible to primary poisoning may also be susceptible to secondary poisoning if they scavenge from the stomachs of fresh carcases, but PAPP is not expected to persist in the environment or bioaccumulate and any impacts would be limited to individual animals and are not likely to have a significant impact on non-target populations.

Conclusions

In addition to submission data provided for environmental fate and effects, additional information was obtained from publicly available sources. Limited fate data are available for assessment, and the effects data available are focussed on toxicity to mammals, birds and reptiles, with little or no information available on other species. However, this is considered acceptable due to the very low per hectare application rate of the active constituent at discrete, widely dispersed points where the bait is placed, with no significant exposure of aquatic organisms, plants or terrestrial invertebrates and soil-dwelling organisms.

In considering the submitted data, particular attention has been given to the potential for non-target animal exposure and toxicity through direct or incidental consumption of baits and through secondary exposure of scavengers to residues in carcases. Based on the submitted data, it is concluded that lethal effects may possibly occur to marsupial carnivores and goannas with use as proposed, deaths of individual non-target animals (goannas, marsupial carnivores, bandicoots and some sensitive bird species) may occur. However, such deaths are not likely to have a significant impact on non-target populations and suitable steps can be undertaken to mitigate the potential for non-target deaths, such as burial of baits at bait stations with ground application. In addition to bait burial, suitable steps can be undertaken to mitigate the potential for non-target deaths, such as controlling the timing and location of baiting.

Aerial (above ground) baiting may be required by government authorities under limited circumstances such as for use in inaccessible areas where wild dog numbers are a threat to wildlife, and ground application is not feasible. Aerial application will not be generally available to other authorised users as it is prohibited on the product labels and will only be available via permit authorisation for such use.

The following protection statements are included on the product labels for Foxecute Fox Bait and PAPP Wild Dog Bait:

DO NOT contaminate dams, rivers, streams, waterways or drains with the product or used containers.

DO NOT feed baits to non-target animals including birds.

PAPP is highly toxic for wild dogs, dogs, foxes and cats but is less toxic for most native species. However, PAPP is toxic to marsupial carnivores and unlike traditional baits containing 1080 poison, PAPP baits can pose a risk to goannas and bandicoots. While uptake of buried wild dog baits by these species is low, additional care should be taken in application of baits in areas where these native species are present. Baits should not be laid at times when, or in locations where, non-target wildlife are likely to be harmed by them.

Where appropriate, risks should be reduced by correct bait placement, selection of the minimum effective rate and avoidance of baiting during the main breeding season. Use of PAPP baits in winter months (when goannas are less active) is preferred in areas of high goanna abundance. PAPP can pose a risk to some bird species (including ducks) if they access baits. Burial of baits should minimise this risk.

In order to assess the risk posed by baiting programs, consult local government agency, the ACTA web site (www.animalcontrol.com.au) or Feral.org web site for information on non-target animal distribution, conservation status, habitat preference, diet, tolerance to PAPP, body weight and size of home range. Most non-target animals are not readily susceptible to the dose of PAPP used for wild dog or dog management. A sub-lethal exposure to PAPP is rapidly metabolised, excreted and an affected animal recovers quickly.

To the extent possible, recover untaken baits at the end of a baiting campaign. Untaken baits and animal carcasses should be destroyed by burning or burial according to the requirements of the State/Territory in which use has occurred.

7.5 Conclusion

The APVMA is satisfied that the proposed use of para-aminopropiophenone (PAPP) in Foxecute Fox bait and PAPP Wild Dog Bait, when used according to the product label instructions and appropriate controls on use, would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed use pattern

Animal Control Technologies (Australia) Pty Ltd has applied to the APVMA for registration of the new products Foxecute Fox Bait and PAPP Wild Dog Bait containing the new active constituent 4- aminopropiophenone (also known as para-aminopropiophenone (PAPP)). Foxecute Fox Bait contains 11.4 g/kg para-aminopropiophenone (PAPP) [Each 35 g fox bait containing 400 mg para-aminopropiophenone (PAPP)] and PAPP Wild Dog Bait contains 16.8 g/kg para-aminopropiophenone (PAPP) [Each 60 g wild dog bait containing 1000 mg para-aminopropiophenone (PAPP)]. The products are encompassed in a solid bait matrix and used solely as a vertebrate pesticide for the control of foxes and wild dogs respectively.

The mechanism (mode) of action (MoA) for PAPP as a vertebrate pesticide involves the biotransformation of PAPP to the metabolite N-hydroxylaminopropiophenone (PHAPP), which causes oxidation of haemoglobin to methaemoglobin (MetHb). The high methaemoglobin level (methaemoglobinaemia) reduces the oxygen-carrying capacity of blood, resulting in death by metabolic hypoxia at elevated methaemoglobin levels.

Foxecute Fox Bait and PAPP Wild Dog Bait products are intended for reduction of fox and wild dog numbers respectively, in non-crop and bushland areas including national parks, nature reserves, state forests and on private property. Where both pest species are present then use of PAPP Wild Dog Bait is recommended.

The use pattern is similar to existing registered fox and wild dog baits, such as 1080 (sodium fluoroacetate) baits. Both Foxecute Fox Bait and PAPP Wild Dog Bait are applied at bait stations at a rate of one bait per 5–10 ha (i.e. only one bait per site), up to 20 baits per km^2 depending on fox and dog densities. Baits are typically applied along transects, e.g., road sides or fence lines at intervals of 200–500 m in pastoral farming areas to target wild dogs and foxes preying on livestock, and also in national parks and other crown land where wild dogs and foxes require management for the protection of native wildlife.

The baits will be applied by hand directly to the ground by burial in a shallow hole (8 cm deep) and covered with soil. In a ground baiting program, repeat application may be required up to 2–3 times per week over the 4–6 week duration of a baiting program.

Aerial (above ground) bait application will not be generally available to authorised users as it is prohibited on the product labels. However this may be required by government authorities under limited circumstances such as under an off-label use permit for use in inaccessible areas where wild dog numbers are a threat to wildlife, and ground application is not feasible.

The APVMA has determined that it is in the public interest for Foxecute Fox Bait and PAPP Wild Dog Bait to be declared Restricted Chemical Products (RCPs) under section 93 of the Agvet Code (inclusion in Schedule 4 (Regulation 45) of the Agvet Code Regulations). The products will only be available for both supply and use to persons appropriately authorised in the State and territory jurisdictions.

8.2 Assessment of study/trial data

Efficacy

A variety of scientific argument, published papers and the results of many research trials were presented to support each of the two registration packages.

Several published papers were presented that documented that PAPP has had a long history of toxicological research, including in dogs. They indicated that the mechanism of action of PAPP and effects in dogs are well known.

A valid scientific argument was made, that additional research on use patterns for the new baits was not required as PAPP has been substituted for 1080 in existing bait substrates. Since those baits have undergone extensive field testing and have been registered for many years, further use pattern research is unwarranted. Subsequently, new research to support Foxecute Fox Baits and PAPP Wild Dog Baits focussed on demonstrating that PAPP can kill foxes and dogs with existing use patterns.

The trial data provided in support of Foxecute Fox Bait comprised 7 pen trials and 3 field trials. The trial data provided in support of PAPP Wild Dog Bait comprised 3 pen trials and 3 field trials.

The pen trials were used to develop the baits, including determining an appropriate dose of PAPP to kill foxes and dogs and an appropriate means of dispersing PAPP within the baits. Due to intra-species variability the minimum effective dose (in terms of mg/kg bw) could not be definitively determined. Optimal doses of 400 mg per 35 g bait for Foxecute Fox Bait and 1000 mg per 60 g bait for PAPP Wild Dog Bait were selected. Proof of concept that these were sufficient doses was achieved where all test foxes were killed at 400 mg of PAPP and all test dogs were killed at 1000 mg of PAPP.

Three field trials demonstrated efficacy of Foxecute Fox Bait, generally by measuring declines in multiple activity indices (which are correlated with population size) and also by locating dead foxes that had been poisoned by Foxecute Fox Bait. One trial conducted near Phillip Island in Victoria demonstrated a decline of greater than 80% in fox activity after baiting. In addition, a dead fox was identified that had consumed bait as ascertained by the presence of bait marker beads in the fox stomach. A second trial at Werribee demonstrated up to 65% decline in a large fox population. A third trial near Dubbo across a large study site demonstrated a decline of greater than 70% as measured with several activity indices. Dozens of dead foxes were observed which were correlated with bait uptake.

Three field trials were implemented to support the efficacy of PAPP Wild Dog Bait. A trial in southern Queensland demonstrated approximately a 79% reduction in wild dog numbers (with reductions sustained for many months). An additional trial in the Strzelecki desert was well conducted, but subject to adverse weather conditions (high rainfall before the trial leading to abundant alternative food and dispersal of dogs away from water points). This trial demonstrated that wild dogs can be definitely killed by PAPP Wild Dog Baits and also demonstrated a modest population level reduction which was comparable with previous 1080 baiting campaigns. A third trial provided a small amount of support to claims of PAPP Wild Dog Bait efficacy. That trial occurred in Hat Head National Park, where the canid population was predominantly foxes and the results showed a large decline in canid numbers. Observations of off-target effects on native species in the

wild dog trials revealed that non-target impacts are possible in some species, for example in goanna populations. This is discussed in detail in the assessment of environmental effects.

Safety/Tolerance

Based on the use pattern there is potential for unintended effects on other animals such as non-target lethal effects from accidental poisoning of domestic and working dogs and other domestic animals. In the event of poisoning, immediate veterinary assistance is required and the compound methylene blue is antidotal to methaemoglobinaemia induced by PAPP. The labels provide advice of the potential for the PAPP doses in Foxecute Fox Bait and PAPP Wild Dog bait to kill dogs, and details of the measures needed to be taken by users of the products for protection of domestic animals and working dogs. As Schedule 7 Poisons, these products are not allowed to be used in domestic situations, and the label controls require appropriate setbacks from dwellings, permanent and flowing waterways, boundary fences and public roadways. As restricted chemical products the baits will only be available to, or for use by, authorised persons as allowed by State jurisdictions. Requirements for notification of neighbours and signage to alert the public when baiting is in progress, are stated on the labels. These and other controls such as appropriate training, as required for use of vertebrate poisons in the State jurisdictions, will provide suitable mitigation to the risks posed from use as proposed.

8.3 General conclusions

The label claims and instructions proposed in the Claims for use statement and the Directions for use and other label instructions are consistent with the results of the trials and other information presented.

The APVMA is satisfied, based on the trial data submitted and the advice provided, that Foxecute Fox Bait and PAPP Wild Dog Bait are expected to be effective, and that adequate margins of safety are provided when the products are used according to Good Agricultural Practice (GAP) and Restricted Chemical Product (RCP) controls to be implemented under the Agvet Code and complementary States and Territories legislation.

9 LABELLING REQUIREMENTS

DANGEROUS POISON

KEEP OUT OF REACH OF CHILDREN
READ SAFEY DIRECTIONS BEFORE OPENING

FOXECUTE Fox Bait

ACTIVE CONSTITUENT: 11.4 g/kg PARA-AMINOPROPIOPHENONE (PAPP)
Each 35 g bait contains 400 mg PARA-AMINOPROPIOPHENONE (PAPP)

For reduction in fox numbers

RESTRICTED CHEMICAL PRODUCT - ONLY TO BE SUPPLIED TO OR USED BY AN AUTHORISED PERSON.

THIS PRODUCT MUST BE USED IN ACCORDANCE WITH THE LABEL INSTRUCTIONS AND ANY RELEVANT DOCUMENTATION ISSUED WITH STATE/TERRITORY AUTHORISATION TO USE PAPP PRODUCTS.

Important: Read the attached leaflet before use.

Individual baits are not for separate sale or distribution

Contents: 10 (350 g) - 200 (7 kg) baits

Animal Control Technologies (Australia) Pty Ltd
46–50 Freight Drive, Somerton VIC 3062
www.animalcontrol.com.au

Emergency Telephone Contact 03 9308 9688

AUTHORISED PERSONS:
Only authorised persons may possess, store, transport, handle or use FOXECUTE FOX BAIT.

STORAGE AND DISPOSAL: Do not store FOXECUTE Fox Bait in a position accessible to children, livestock or domestic pets. This pesticide is only to be kept, stored or transported in a container bearing this APVMA-approved label, as supplied by the manufacturer. Store in a secure locked facility. Store in the closed, original container in a dry, cool, and well-ventilated area out of direct sunlight. DO NOT allow baits to contaminate foodstuffs, or feed, for human or non-target animal consumption. DO NOT reuse containers for any other purpose.

Triple or pressure rinse empty containers before disposal. Break, crush or puncture and dispose of empty containers in an approved waste management facility. Deliver remaining baits in the original and labeled container to an approved waste management facility. If an approved waste management facility is not available, bury the FOXECUTE Fox Bait any PAPP contaminated rinsate and empty packaging 0.5 m below the surface in a disposal pit at the site of use specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots in compliance with relevant Local, State or Territory government regulations. DO NOT burn empty container or product unless authorised by relevant Local, State or Territory Government Authority and as per the relevant Local, State or Territory Government Authority instructions.

SAFETY DIRECTIONS:
Harmful if swallowed. Do not touch or rub eyes, nose or mouth with hand. Avoid contact with eyes and skin. If on skin and after each baiting, wash thoroughly with soap and water. When opening container and using the product wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. After each days use, wash gloves and contaminated clothing.

FIRST AID: If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126, New Zealand 0800 764766. Remove from contaminated area. Apply artificial respiration if not breathing. If poisoning occurs get to a doctor or hospital quickly.

MATERIAL SAFETY DATA SHEET.
Additional information is listed in the Material Safety Data Sheet (MSDS) and the enclosed leaflet that forms part of this label.

Batch: Date of Manufacture:

APVMA Approval No: 65095/50137

DANGEROUS POISON

KEEP OUT OF REACH OF CHILDREN
READ SAFEY DIRECTIONS BEFORE OPENING

FOXECUTE Fox Bait

ACTIVE CONSTITUENT: 11.4 g/kg PARA-AMINOPROPIOPHENONE (PAPP)
Each 35 g bait contains 400 mg PARA-AMINOPROPIOPHENONE (PAPP)

For reduction in fox numbers

RESTRICTED CHEMICAL PRODUCT - ONLY TO BE SUPPLIED TO OR USED BY AN AUTHORISED PERSON.

THIS PRODUCT MUST BE USED IN ACCORDANCE WITH THE LABEL INSTRUCTIONS AND ANY RELEVANT DOCUMENTATION ISSUED WITH STATE/TERRITORY AUTHORISATION TO USE PAPP PRODUCTS.

Important: Read this leaflet before use.

Individual baits are not for separate sale or distribution

Animal Control Technologies (Australia) Pty Ltd
46–50 Freight Drive, Somerton VIC 3062
www.animalcontrol.com.au
Emergency Telephone Contact 03 9308 9688

APVMA Approval No. 65095/50137

DIRECTIONS FOR USE

Only for use by persons authorised by the relevant government authority.

Note: Relevant Government Authority means the State or Territory Government Authority responsible for authorising people to possess and use products containing para-aminopropiophenone (PAPP).

Restraints

DO NOT apply more than one bait per bait station.

DO NOT apply by air.

Situation	Pest	Rate
Non-crop and bushland areas including: National parks, Nature reserves, State forests and Private property	Fox (*Vulpes vulpes)*	One bait station per 5–10 ha (up to 20 bait stations per km^2). One bait is sufficient to kill a fox.

Critical Use Comments:

Bait density and placement

A bait station is a location where baits are placed. Usually these are shallow holes (<8 cm deep) where baits can be placed then covered over with dirt to reduce access by non-target animals. Approximately one bait station per 5–10 ha (up to 20 bait stations per km2) is needed for effective fox control. For ground application, individual baits must be buried in holes of approximately 8 cm depth at intervals of 200–500 metres, at marked sites, usually along fence lines, vehicle tracks or in locations known to be frequented by foxes. Foxes readily dig up buried baits, and this technique reduces uptake by non-target animals.

Number of baits per bait station

Since only one bait is needed to kill a fox, uptake of several baits by the same animal should be avoided. PAPP is rapidly effective so the risk of multiple bait take by a single animal is reduced compared to traditional fox baits. Place only one bait at each bait station and do not place bait stations too close together.

Bait replacement

Foxes often mark sites of baits by urinating and defecating at the bait station. For effective control, it is necessary to replace taken baits several times, as other foxes may visit the same station. Check bait stations 2 or 3 times per week during the baiting program and place new baits at sites where baits are taken.

Length of baiting program

A single round of bait placement will generally not control all foxes in an area. For effective control, it is necessary to conduct a 4 to 6 week program. Replacement of baits should continue until bait take stops. Initially, bait take will remain high until fox numbers are depleted. Wild dogs will also take baits and so foxes may have reduced access to bait in areas where wild dog numbers are high. Use PAPP Wild Dog Bait where wild dogs are present as a 400 mg PAPP fox bait may not be sufficient to kill a dog.

NOT TO BE USED FOR ANY PURPOSE OR IN ANY MANNER, CONTRARY TO THIS LABEL UNLESS AUTHORISED BY APPROPRIATE LEGISLATION

DO NOT USE THIS PRODUCT IN THE HOME GARDEN.
(see also DISTANCE RESTRICTIONS below)

PUBLIC NOTIFICATION:
The PAPP dose in FOXECUTE Fox Baits (400 mg PAPP) may kill small domestic and working dogs. Neighbours must be notified to allow them to take appropriate action. The notification should advise that steps (e.g. restraint, muzzling) need to be taken to ensure that domestic dogs do not gain access to PAPP baits. The notification must specify the dates between which baiting will occur. This notification must be given to all adjoining landholders at least 72 hours in advance. A record of the notifications must be kept. If baiting is not undertaken within the dates specified an additional notification must be made.

POISON NOTICES:
Signage is compulsory for all lands where baiting occurs. Do not lay baits until signage is in place. Signage must include—date baits laid, contact numbers, toxin name (PAPP), target animal and a warning that domestic animals and pets can be affected. Users must ensure that signs are put up before baiting with this product commences on the property and are placed according to requirements specified by the relevant State/Territory authority. These notices must remain up for at least 4 weeks after the authorised period of bait lay has expired or after all untaken baits have been collected.

DISTANCE RESTRICTIONS
It is important to reduce risks of accidental poisoning of working and pet dogs. Baits must be placed at least 150 m from a dwelling; 20 m from permanent or flowing water bodies; 5 m from boundary fences; and 5 m from the edge of formed public roadways.

PRECAUTIONS

Not for domestic use.
Keep out of reach of children.
DO NOT handle baits when there is a risk of contaminating food, drinking water or animal feed.

Re-entry / Re-handling: Do not re-handle product unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

PROTECTION OF DOMESTIC/WORKING DOGS

The PAPP dose in FOXECUTE Fox Bait (400 mg/bait) may kill domestic and working dogs of a smaller size. If the baited area is in close proximity to locations of pets or working dogs, the person using the baits should advise neighbours to tie up working or pet dogs and ensure they do not enter the control area during fox control operations. Alternatively working dogs can be muzzled prior to entering paddocks to safeguard against accidental poisoning. In the event of accidental poisoning seek immediate veterinary assistance
DO NOT place the FOXECUTE Fox Baits in a position accessible to domestic dogs.

PROTECTION OF WILDLIFE, FISH, CRUSTACEA AND ENVIRONMENT
DO NOT contaminate dams, rivers, streams, waterways or drains with the product or used containers

DO NOT feed baits to non-target animals including birds.

PAPP is highly toxic for wild dogs, dogs, foxes and cats but is less toxic for most native species. However, PAPP is toxic to marsupial carnivores and unlike traditional baits containing 1080 poison, PAPP baits can pose a risk to goannas and bandicoots. While uptake of buried baits by these species is low, additional care should be taken in application of baits in areas where these native species are present. Baits should not be laid at times when, or in locations where, non-target wildlife are

likely to be harmed by them. Where appropriate, risks should be reduced by correct bait placement, selection of the minimum effective rate and avoidance of baiting during the main breeding season. Use of PAPP baits in winter months (when goannas are less active) is preferred in areas of high goanna abundance. PAPP can pose a risk to some birds (including ducks) if they access baits. Burial of baits should minimise this risk.

In order to assess the risk posed by baiting programs, consult local government agency, the ACTA web site (www.animalcontrol.com.au) or Feral.org web site for information on non-target animal distribution, conservation status, habitat preference, diet, tolerance to PAPP, body weight and size of home range. Most non-target animals are not readily susceptible to the dose of PAPP used for wild dog or dog management. A sub-lethal exposure to PAPP is rapidly metabolised, excreted and an affected animal recovers quickly.

To the extent possible, recover untaken baits at the end of a baiting campaign. Untaken baits and animal carcasses should be destroyed by burning or burial according to the requirements of the State/Territory in which use has occurred.

STORAGE AND DISPOSAL: Do not store FOXECUTE Fox Bait in a position accessible to children, livestock or domestic pets. This pesticide is only to be kept, stored or transported in a container bearing this APVMA-approved label, as supplied by the manufacturer. Store in a secure locked facility. Store in the closed, original container in a dry, cool, and well-ventilated area out of direct sunlight. DO NOT allow baits to contaminate foodstuffs, or feed, for human or non-target animal consumption. DO NOT reuse containers for any other purpose.

Triple or pressure rinse empty containers before disposal. Break, crush or puncture and dispose of empty containers in an approved waste management facility. Deliver remaining baits in the original and labeled container to an approved waste management facility. If an approved waste management facility is not available, bury the FOXECUTE Fox Bait any PAPP contaminated rinsate and empty packaging 0.5 m below the surface in a disposal pit at the site of use specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots in compliance with relevant Local, State or Territory government regulations. DO NOT burn empty container or product unless authorised by relevant Local, State or Territory Government Authority and as per the relevant Local, State or Territory Government Authority instructions.

SAFETY DIRECTIONS:
Harmful if swallowed. Do not touch or rub eyes, nose or mouth with hand. Avoid contact with eyes and skin. If on skin and after each baiting, wash thoroughly with soap and water. When opening container and using the product wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. After each days use, wash gloves and contaminated clothing.

FIRST AID: If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126, New Zealand 0800 764766. Remove from contaminated area. Apply artificial respiration if not breathing. If poisoning occurs get to a doctor or hospital quickly.

MATERIAL SAFETY DATA SHEET.
Additional information is listed in the Material Safety Data Sheet (MSDS).

CONDITIONS OF SALE and DISCLAIMER:
Animal Control Technologies (AUST) Pty Ltd (ACTA) will not accept responsibility for losses or damage arising for the supply or use of these goods other than the responsibility for the

merchantable quality of the goods. To the extent allowed by the relevant laws in each State/Territory, the liability of ACTA is limited for the replacement of goods in the event that a valid claim of deficiencies in merchantable quality is proven.

DANGEROUS POISON

KEEP OUT OF REACH OF CHILDREN
READ SAFEY DIRECTIONS BEFORE OPENING

PAPP Wild Dog Bait

ACTIVE CONSTITUENT: 16.8 g/kg PARA-AMINOPROPIOPHENONE (PAPP)
Each 60 g bait contains 1000 mg PARA-AMINOPROPIOPHENONE (PAPP)

For reduction in wild dog numbers

RESTRICTED CHEMICAL PRODUCT—ONLY TO BE SUPPLIED TO OR USED BY AN AUTHORISED PERSON.

THIS PRODUCT MUST BE USED IN ACCORDANCE WITH THE LABEL INSTRUCTIONS AND ANY RELEVANT DOCUMENTATION ISSUED WITH STATE/TERRITORY AUTHORISATION TO USE PAPP PRODUCTS.

Important: Read the attached leaflet before use.

Individual baits are not for separate sale or distribution

Contents: 10 (600 g) - 200 (12 kg) baits

Animal Control Technologies (Australia) Pty Ltd
46–50 Freight Drive, Somerton VIC 3062
www.animalcontrol.com.au
Emergency Telephone Contact 03 9308 9688

AUTHORISED PERSONS:
Only authorised persons may possess, store, transport, handle or use PAPP WILD DOG BAIT.

STORAGE AND DISPOSAL: Do not store PAPP WILD DOG BAIT in a position accessible to children, livestock or domestic pets. This pesticide is only to be kept, stored or transported in a container bearing this APVMA approved label, as supplied by the manufacturer. Store in a secure locked facility. Store in the closed, original container in a dry, cool, and well-ventilated area out of direct sunlight. DO NOT allow baits to contaminate foodstuffs, or feed, for human or non-target animal consumption. DO NOT reuse containers for any other purpose.

Triple or pressure rinse empty containers before disposal. Break, crush or puncture and dispose of empty containers in an approved waste management facility. Deliver remaining baits in the original and labeled container to an approved waste management facility. If an approved waste management facility is not available, bury the PAPP WILD DOG BAIT any PAPP contaminated rinsate and empty packaging 0.5 m below the surface in a disposal pit at the site of use specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots in compliance with relevant Local, State or Territory government regulations. DO NOT burn empty container or product unless authorised by relevant Local, State or Territory Government Authority and as per the relevant Local, State or Territory Government Authority instructions.

SAFETY DIRECTIONS:
Harmful if swallowed. Do not touch or rub eyes, nose or mouth with hand. Avoid contact with eyes and skin. If on skin and after each baiting, wash thoroughly with soap and water. When opening container and using the product wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. After each days use, wash gloves and contaminated clothing.

FIRST AID: If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126, New Zealand 0800 764766. Remove from contaminated area. Apply artificial respiration if not breathing. If poisoning occurs get to a doctor or hospital quickly.

MATERIAL SAFETY DATA SHEET.
Additional information is listed in the Material Safety Data Sheet (MSDS) and the enclosed leaflet that forms part of this label.

Batch: Date of Manufacture:

APVMA Approval No: 65094/50136

DANGEROUS POISON

KEEP OUT OF REACH OF CHILDREN
READ SAFEY DIRECTIONS BEFORE OPENING

PAPP WILD DOG BAIT

ACTIVE CONSTITUENT: 16.8 g/kg PARA-AMINOPROPIOPHENONE (PAPP)
Each 60 g bait contains 1000 mg PARA-AMINOPROPIOPHENONE (PAPP)

For reduction in wild dog numbers

RESTRICTED CHEMICAL PRODUCT - ONLY TO BE SUPPLIED TO OR USED BY AN AUTHORISED PERSON.

THIS PRODUCT MUST BE USED IN ACCORDANCE WITH THE LABEL INSTRUCTIONS AND ANY RELEVANT DOCUMENTATION ISSUED WITH STATE/TERRITORY AUTHORISATION TO USE PAPP PRODUCTS.

Important: Read this leaflet before use.

Individual baits are not for separate sale or distribution

Animal Control Technologies (Australia) Pty Ltd
46–50 Freight Drive, Somerton VIC 3062
www.animalcontrol.com.au
Emergency Telephone Contact 03 9308 9688

APVMA Approval No. 65094/50136

DIRECTIONS FOR USE

Only for use by persons authorised by the relevant government authority.

Note: Relevant Government Authority means the State or Territory Government Authority responsible for authorising people to possess and use products containing para-aminopropiophenone (PAPP).

Restraints

DO NOT apply more than one bait per bait station.

DO NOT apply by air.

Situation	Pest	Rate
Non-crop and bushland areas including: National parks, Nature reserves, State forests and Private property	Wild dogs	One bait station per 5–10 ha (up to 20 bait stations per km^2). One bait is sufficient to kill a wild dog.

Critical Use Comments:

Bait density and placement

A bait station is a location where baits are placed. Usually these are shallow holes (<8 cm deep) where baits can be placed then covered over with dirt to reduce access by non-target animals. Approximately one bait station per 5–10 ha (up to 20 bait stations per km2) is needed for effective wild dog control. For ground application, individual baits must be buried in holes of approximately 8 cm depth at intervals of 200–500 metres, at marked sites, usually along fence lines, vehicle tracks or in locations known to be frequented by wild dogs. Wild dogs readily dig up buried baits, and this technique reduces uptake by non-target animals.

Number of baits per bait station

Since only one bait is needed to kill a wild dog, uptake of several baits by the same animal should be avoided. PAPP is rapidly effective so the risk of multiple bait take by a single animal is reduced compared to traditional wild dog baits. Place only one bait at each bait station and do not place bait stations too close together.

Bait replacement

For effective control, it is necessary to replace taken baits several times, as other wild dogs may visit the same station. Check bait stations 2 or 3 times per week during the baiting program and place new baits at sites where baits are taken.

Length of baiting program

A single round of bait placement will generally not control all wild dogs in an area. For effective control, it is necessary to conduct a 4 to 6 week program. Replacement of baits should continue until bait take stops. Initially, bait take will remain high until wild dog numbers are depleted. Foxes will take baits and so wild dogs may have reduced access to bait in areas where fox numbers are high.

NOT TO BE USED FOR ANY PURPOSE OR IN ANY MANNER, CONTRARY TO THIS LABEL UNLESS AUTHORISED BY APPROPRIATE LEGISLATION

DO NOT USE THIS PRODUCT IN THE HOME GARDEN.
(see also DISTANCE RESTRICTIONS below)

PUBLIC NOTIFICATION:
The PAPP dose in PAPP WILD DOG BAIT (1000 mg/bait) will kill domestic and working dogs of any size. Neighbours must be notified to allow them to take appropriate action. The notification should advise that steps (e.g. restraint, muzzling) need to be taken to ensure that domestic dogs do not gain access to PAPP baits. The notification must specify the dates between which baiting will occur. This notification must be given to all adjoining landholders at least 72 hours in advance. A record of the notifications must be kept. If baiting is not undertaken within the dates specified an additional notification must be made.

POISON NOTICES:
Signage is compulsory for all lands where baiting occurs. Do not lay baits until signage is in place. Signage must include – date baits laid, contact numbers, toxin name (PAPP), target animal and a warning that domestic animals and pets can be affected. Users must ensure that signs are put up before baiting with this product commences on the property and are placed according to requirements specified by the relevant State/Territory authority. These notices must remain up for at least 4 weeks after the authorised period of bait lay has expired or after all untaken baits have been collected.

DISTANCE RESTRICTIONS
It is important to reduce risks of accidental poisoning of working and pet dogs. Baits must be placed at least 150 m from a dwelling; 20 m from permanent or flowing water bodies; 5 m from boundary fences; and 5 m from the edge of formed public roadways.

PRECAUTIONS

Not for domestic use.
Keep out of reach of children.
DO NOT handle baits when there is a risk of contaminating food, drinking water or animal feed.

Re-entry / Re-handling: Do not re-handle product unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.

PROTECTION OF DOMESTIC/WORKING DOGS
The PAPP dose in PAPP WILD DOG BAIT (1000 mg/bait) will kill domestic and working dogs of any size. If the baited area is in close proximity to locations of pets or working dogs, the person using the baits should advise neighbours to tie up working or pet dogs and ensure they do not enter the control area during wild dog control operations. Alternatively working dogs can be muzzled prior to entering paddocks to safeguard against accidental poisoning. In the event of accidental poisoning seek immediate veterinary assistance.
DO NOT place the PAPP WILD DOG BAITS in a position accessible to domestic dogs.

PROTECTION OF WILDLIFE, FISH, CRUSTACEA AND ENVIRONMENT
DO NOT contaminate dams, rivers, streams, waterways or drains with the product or used containers

DO NOT feed baits to non-target animals including birds.

PAPP is highly toxic for wild dogs, dogs, foxes and cats but is less toxic for most native species. However, PAPP is toxic to marsupial carnivores and unlike traditional baits containing 1080 poison, PAPP baits can pose a risk to goannas and bandicoots. While uptake of buried baits by these species is low, additional care should be taken in application of baits in areas where these native species are present. Baits should not be laid at times when, or in locations where, non-target wildlife are

likely to be harmed by them. Where appropriate, risks should be reduced by correct bait placement, selection of the minimum effective rate and avoidance of baiting during the main breeding season. Use of PAPP baits in winter months (when goannas are less active) is preferred in areas of high goanna abundance. PAPP can pose a risk to some birds (including ducks) if they access baits. Burial of baits should minimise this risk.

In order to assess the risk posed by baiting programs, consult local government agency, the ACTA web site (www.animalcontrol.com.au) or Feral.org web site for information on non-target animal distribution, conservation status, habitat preference, diet, tolerance to PAPP, body weight and size of home range. Most non-target animals are not readily susceptible to the dose of PAPP used for wild dog or dog management. A sub-lethal exposure to PAPP is rapidly metabolised, excreted and an affected animal recovers quickly.

To the extent possible, recover untaken baits at the end of a baiting campaign. Untaken baits and animal carcasses should be destroyed by burning or burial according to the requirements of the State/Territory in which use has occurred.

STORAGE AND DISPOSAL: Do not store PAPP WILD DOG BAIT in a position accessible to children, livestock or domestic pets. This pesticide is only to be kept, stored or transported in a container bearing this APVMA approved label, as supplied by the manufacturer. Store in a secure locked facility. Store in the closed, original container in a dry, cool, and well-ventilated area out of direct sunlight. DO NOT allow baits to contaminate foodstuffs, or feed, for human or non-target animal consumption. DO NOT reuse containers for any other purpose.

Triple or pressure rinse empty containers before disposal. Break, crush or puncture and dispose of empty containers in an approved waste management facility. Deliver remaining baits in the original and labeled container to an approved waste management facility. If an approved waste management facility is not available, bury the PAPP WILD DOG BAIT any PAPP contaminated rinsate and empty packaging 0.5 m below the surface in a disposal pit at the site of use specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots in compliance with relevant Local, State or Territory government regulations. DO NOT burn empty container or product unless authorised by relevant Local, State or Territory Government Authority and as per the relevant Local, State or Territory Government Authority instructions.

SAFETY DIRECTIONS:
Harmful if swallowed. Do not touch or rub eyes, nose or mouth with hand. Avoid contact with eyes and skin. If on skin and after each baiting, wash thoroughly with soap and water. When opening container and using the product wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. After each days use, wash gloves and contaminated clothing.

FIRST AID: If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126, New Zealand 0800 764766. Remove from contaminated area. Apply artificial respiration if not breathing. If poisoning occurs get to a doctor or hospital quickly.

MATERIAL SAFETY DATA SHEET.
Additional information is listed in the Material Safety Data Sheet (MSDS).

CONDITIONS OF SALE and DISCLAIMER:
Animal Control Technologies (AUST) Pty Ltd (ACTA) will not accept responsibility for losses or damage arising for the supply or use of these goods other than the responsibility for the merchantable quality of the goods. To the extent allowed by the relevant laws in each State/Territory, the liability of ACTA is limited for the replacement of goods in the event that a valid claim of deficiencies in merchantable quality is proven.

ABBREVIATIONS

AC/ac	active constituent
ACCS	Advisory Committee on Chemicals Scheduling
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute Reference Dose
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
BBCH	Scale used to identify phenological developmental stages of plants (Biologische Bundesanstalt, Bundessortenamt and CHemical industry)
BCF	Bioconcentration factor
bw	bodyweight
°C	Degrees Centigrade
CHO	Chinese Hamster Ovary
CIPAC	Collaborative International Pesticides Analytical Council
Croplife	Croplife Australia
cm	centimetre
d	day
DAT	Days After Treatment
DFOP	Double First-Order in Parallel (dissipation kinetics)
DE	Department of Environment
DT50	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
EbC50	concentration at which the biomass of 50% of the test population is impacted
EC50	concentration at which 50% of the test population are adversely impacted or immobilised
EEC	Estimated Environmental Concentration
ErC50	concentration at which the rate of growth of 50% of the test population is impacted

EI	Export Interval
EGI	Export Grazing Interval
ER25/50	the rate that results in an undesirable change or alteration of 25% (or 50%) in the test endpoint being measured relative to the control
ESI	Export Slaughter Interval
EU	European Union
EUP	End Use Product
Fo	original parent generation
F1	First generation
FRAC	Fungicides Resistance Action Committee
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GI	Gastro Intestinal
GJR	Global Joint Review
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
Hb	Haemoglobin
Hct	Heamatocrit
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography or High Performance Liquid Chromatography
HR	highest residue
HR-P	Calculated highest residue—processed commodity
HSIS	Hazardous Substance Information System
Idf	food ingestion rate (dry weight) in grams per day
IPM	Integrated Pest Management

iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
JMPR	Joint FAO/WHO Meetings on Pesticide Residues
Kd	distribution coefficient for adsorption
Kd(ads)	distribution coefficient for adsorption
kg	kilogram
Koc(ads)	apparent adsorption constant
Koc(des)	apparent desorption constant
Koc/ Kfoc	organic carbon adsorption coefficient
L	litre
LC50	concentration that kills 50% of the test population of organisms
LC/MS/MS	liquid chromatography-tandem mass spectrometer
LCT	Leydig Cell Tumours
LD50	dosage of chemical that kills 50% of the test population of organisms
LH	Lutenising Hormone
LLNA	Local Lymph Node Assay
LOD	Limit of Detection—level at which residues can be detected
LOAEC	Lowest Observable Adverse Effect Concentration
LOAEL	Lowest Observable Adverse Effect Level
LOEL	Lowest Observable Effect Level
logKow	Octanol-Water Partition Coefficient
LOQ	Limit of Quantitation—level at which residues can be quantified
LR50	Application rate that kills 50% of the test population of organisms
m	metre
MetHb	Methaemoglobin
mg	milligram

mL	millilitre
MMAD	Mass Median Aerodynamic Diameter
MoA	Mode of Action
MOE	Margin Of Exposure
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
nAChR	nicotinic acetylcholine receptor
NADPH	Reduced form of nicotinamide adenine dinucleotide phosphate
ND	Not Detectable
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
nm	nanometres
NOHSC	National Occupational Health and Safety Commission
NOAEC	No Observable Adverse Effect Concentration
NOEC	No Observable Effect Concentration
NOAEL	No Observable Adverse Effect Level
NOEL	No Observable Effect Level
NOER	No Observable Effect Rate
OC	Organic Carbon
OCS	Office of Chemical Safety (Department of Health and Ageing)
OECD	Organisation for Economic Cooperation and Development
OM	Organic Matter
Pa	Pascals
PAPP	4-aminopropiophenone (also known as para-aminopropiophenone)
PEC	Predicted Environmental Concentration
PHAPP	N-hydroxylaminopropiophenone

PHED	Pesticide Handler Exposure Database
PHI	Post Harvest Interval
PMRA	Pest Management Regulatory Agency (Canada)
PNPP	para-nitrosopropiophenone
Pow	octanol/water partition coefficient
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
RAC	Confined Rotational Crop
RBC	Red Blood Cell
RCP	Restricted Chemical Product
RSD	Relative Standard Deviation
s	second
SC	Suspension Concentrate
SFO	Single First-Order Rate model (dissipation kinetics)
STMR	Supervised Trials Median Residue
STMR-P	STMR corrected for processing
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SWA	Safe Work Australia
T1/2	Elimination Half-Life
TGAC	Technical grade active constituent
Tmax	Time to achieve maximum concentration
TRR	Total Radioactive Residue
µg	microgram
US EPA	U.S. Environmental Protection Agency
UTC	Untreated control
UV/VIS	Ultra Violet/Visible Light

VMT	Vehicle Mounted Tank
W	Body weight (grams live weight)
WG	Water Dispersible Granule
WHP	Withholding Period

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration.
Anaemia	Deficiency in the number or quality of red blood cells
Antidote	A medicine or other remedy for counteracting the effects of a poison
Bioaccumulation	When an organism absorbs a toxic substance at a greater rate than the rate of loss
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Cyanosis	Appearance of blue coloration of the skin due to lack of oxygen in the blood
Desorption	Removal of a material from or through a surface
Dyspnoea	Shortness of breath
Efficacy	Production of the desired effect
Erythrocytes	Red blood cells
Erythropoiesis	Process which produces red blood cells
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Haematology	Study of medicine related to the blood
Haemolysis	Rupturing of red blood cells
Hydrophobic	Repels water
Hypoxia	Lack of adequate oxygen supply to the body
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Metabolism	The chemical processes that maintain living organisms
Methaemoglobinaemia	Condition when the oxygen-carrying capacity of blood is reduced
Mutagenicity	The ability to produce permanent changes in genetic material
Photodegradation	Breakdown of chemicals due to the action of light

Photolysis	Breakdown of chemicals due to the action of light
Piloerection	Erection of the hair of the skin
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons
Transitory	of a short duration, temporary

REFERENCES

Australian Pesticides and Veterinary Medicines Authority 2008, *Ag MORAG: Manual of Requirements and Guidelines*, APVMA, Canberra now superseded by the APVMA's application requirements and data guidelines at www.apvma.gov.au/