ENVIRONMENTAL RISK MANAGEMENT AUTHORITY
NGĀ KAIWHAKATŪPATO WHAKARARU TAIAO

ERMA New Zealand

FORM HS1

Application for approval to

IMPORT OR MANUFACTURE ANY HAZARDOUS SUBSTANCE FOR RELEASE

under section 28 of the Hazardous Substances and New Organisms Act 1996

Name of Substance: PAPP Paste A
PAPP Paste B
PAPP Ready-to-use Bait

Applicant: Connovation Ltd

Office use only

Application Code: ☐☐☐☐☐☐☐☐ Date received:____/____/____

ERMA NZ Contact: _____ Initial Fees Paid: $

Application Version No: _____.

Section One – Applicant Details

1.1 Name and postal address in New Zealand of the organisation making the application:

Name: Connovation Limited
Address: PO Box 58 613, Manukau City 2141.
Phone: 09 273 4333
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1.2 The applicant's location address in New Zealand (if different from above):

Address: 36B Sir Williams Avenue, East Tamaki, Auckland

1.3 Name of the contact person for the application:

Name: Jeanette Drysdale
Position: Registration Consultant
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Section Two – Application Type and Related Approvals Required

2.1 Is the information in this application relevant to import, manufacture or both:

• Import only?	No
• Manufacture only?	No
• Import and manufacture?	**Yes**
• If import only, indicate whether or not manufacture is likely in New Zealand	N/A

2.2 If the information in the application relates to manufacture in New Zealand, provide information on the proposed manufacturing process and any alternatives.
(See comments under "Section 2.2 of Form" in the User Guide)

The three substances, PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait, contain the active ingredient para-aminopropiophenone (PAPP). The active ingredient would be imported and the PAPP Paste A and PAPP Paste B would be manufactured in New Zealand. The details of the manufacturing and proposed manufacturing batch process are provided as *Confidential Appendix 1*. The third substance, PAPP Ready-to-use Bait, would be prepared from the PAPP Paste A to form a PAPP Ready-to-use Bait that would be then used in a bait station (*Confidential Appendix 2*).

2.3 If you have reasons for not providing detailed information in this application, explain what they are and provide some justification.

N/A

2.4 If this substance(s) needs an approval under any other legislation, has an application for this approval been made?
(Optional)

Name of Approval	**Application made**
Agricultural Compounds and Veterinary Medicines Act 1997	**Yes**
Food Act 1981	N/A
Medicines Act 1981	N/A
Chemical Weapons (Prohibition) Act 1996	N/A
Radiation Protection Act 1965	N/A
Biosecurity Act 1993	N/A
Resource Management Act 1991	N/A
Other (please specify):	

Section Three – Information on the Substance(s)

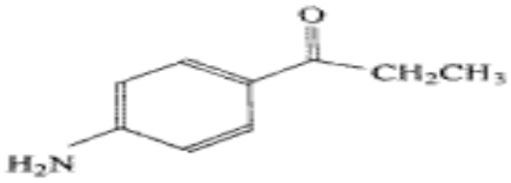
3.1 State the unequivocal identification of the substance.

The three substances, PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait, contain the active ingredient para-aminopropiophenone (PAPP).

Information on para-aminopropiophenone has been summarised as follows:

Active ingredient

Chemical name:	Para aminopropiophenone (PAPP)
Synonyms :	1, 4 para-aminopropiophenone 1-propanone, 1-4 aminophenyl 4-aminopropiophenone
CAS No:	70-69-9
Formula :	$C_9H_{11}NO$
Molecular weight:	149.19
Structure:	There is a central aromatic ring with an amino group opposite (in the para position) a propyl-phenone chain. This creates a combination of both polar and non polar sections of the molecule.



PAPP

Appearance:	Light yellow crystalline powder
Melting point:	140°C (100%); 137 – 142°C (98% min.)
Boiling point:	482 ° C

Solubility in water: 352 mg/L @ 37 ^{0}C

Log n-octanol/water partition coefficient: 1.43- 1.25

pka: 3.19

Vapour Pressure: 8.05 * 10^{-4} torr @ 25.0 °C

pH: 5.15 (as saturated solution, 0.353 g/L)

Confidential Appendix 3

3.2 Provide information on the chemical and physical properties of the substance.

PAPP Paste A and PAPP Paste B

Appearance:	Green smooth paste with grainy texture
Odour:	Nil
Specific gravity:	1.06 – 1.08
pH:	Not applicable

The PAPP concentration can be determined by HPLC and a validated analytical method has been developed (*Confidential Appendix 4*).

PAPP Ready-to-use Bait

This substance is a minced meat 'ball' that has been formed around an amount of PAPP Paste A.

3.3 Provide information on the hazardous properties of the substance.

Para-aminopropiophenone (PAPP) is listed as an approved substance [HSR006967] on the ERMA Register. PAPP is identified with both 6.1C (oral) and 9.3B hazardous classifications. Only one other component in the new substances (identified as Component C) has been identified as also having hazardous properties (*Confidential Appendix 5*).

The hazardous classifications for PAPP Paste A, PAPP Paste B and the PAPP Ready-to-use Bait have been determined using the mixture classification rules and in some instances from testing on a formulated paste in target species as a Vertebrate Toxic Agent (*Confidential Appendix 6*).

Class 1: Explosiveness

Sub Class 1.1 considers that explosive properties are associated with the presence of certain defined chemical groups. PAPP contains none of the chemical groups in its structure that are associated with explosive properties.

Sub-class 1.2 considers that if a substance contains the chemical groups associated with explosive properties, but if the calculation of oxygen balance of these groups is less than –200, then that substance is unlikely to have explosive properties. The calculated oxygen balance for PAPP is –36000 so is less than –200. PAPP therefore has neither the chemical groups associated with explosive properties, nor an adverse oxygen balance

Sub-class 1.3 also relates to the presence of chemical groups associated with explosive properties (linked to exothermic decomposition). PAPP does not appear to have any of these properties that would be associated with a potential for an explosion or flammability hazard.

Sub-class 1.4 requires that compounds included in chemical mixtures to be assessed for explosiveness. In the case of PAPP, the substance will be in the form of paste. Neither PAPP (on the basis of chemical structure) nor any of the other components in the paste formulations have explosive properties.

In summary, the PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait would not trigger an explosive classification.

Class 3: Flammability

Subclass 4.1.1 deals with flammable solids and substances liable to spontaneous combustion. The data on the flash point, vapour pressure, ignition temperature or flammability limit for PAPP indicates this compound would not trigger a flammable/combustible classification.
The information on the other components in the substances, also indicates no flammability property should apply. In summary, the PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait do not trigger a flammability classification.

Class 5: Oxidizing properties

Class 5 relates to the oxidizing capacity of substances. The classifications distinguish between solids and liquids (5.1.1), gases (5.1.2) and organic peroxides (5.2). The information available for PAPP and the other components in the substances, do not identify any as having oxidizing properties.

In summary, the PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait have not been identified with an oxidizing classification.

Class 6: Toxicity

Sub class 6.1 Acute toxicity

(i) Oral

The active ingredient, para-aminopropiophenone (PAPP) is identified with a 6.1C (oral) classification on the ERMA database [refer approved substance HSR006967 on www.ermanz.govt.nz]. This indicates an oral LD_{50} value of > 50 to ≤ 300 mg/kg. The actual toxicity data points are not listed.

From the literature the acute toxicity for PAPP is known for laboratory animals and other species including rodents and canines via oral and parenteral administration (intravenous and intraperitoneal) exposure routes. The PAPP acute oral toxicity (LD_{50}) varies with species (Saverie *et al*. 1983), sex (Bright *et al*. 1987) and route of administration (Scawin *et al*. 1984). The toxicity of PAPP is highest via intravenous administration, followed by intraperitoneal then by oral administration.

A review of the literature (refer Table 1) shows acute oral toxicity values for a number of species. The toxicity of PAPP (LD_{50}) via the oral route characterizes the relative sensitivity of animals into three general groups;

1. LD_{50} <50mg/kg
   with cats the most sensitive followed by stoats> dogs >bobcats>kit foxes and coyotes;
2. LD_{50} 100-500mg/kg
   encompassing the majority of species tested; and
3. LD_{50} >1000mg/kg
   represented by female mice and female guinea pigs.

The variations in the LD_{50} (oral or parenteral administration) values can generally be expressed as a function of differences in the metabolism of PAPP between species and in the metabolism and excretion of the degradation products, PAPP and PHAPP (Wood *et al*. 1991), differences between species in the rates of haemoglobin oxidation (Smith and Beutler, 1966), and to a lesser extent in the relative capacity of species to reduce methaemoglobin to haemoglobin.

The LD_{50} values summarized in Table 1 which show a variation in susceptibility between animals, is also relevant to the new substances in this application where the intended use is as VTA. Cats and stoats are identified as two susceptible species. The 4-aminopropiophenone (PAPP) LD_{50} value of

9.3.mg/kg for stoats (*Mustela erminea*) was determined in an acute toxicity study undertaken in New Zealand.

A 6.1C (oral) classification applies where an oral LD_{50} value is $\geq$ 50 mg/kg b.w. but < 300 mg/kg bw. The data in Table 1 shows that for laboratory rodents species (i.e. the mouse and rat) LD_{50} values fall within these limits. However data for the cat, stoat and dog show lower LD_{50} values and with cat and stoat LD_{50} values being < 50 mg/kg b.w. this indicates a 6.1B classification would be applicable to the active ingredient PAPP.

Table 1: Oral LD_{50} values available for PAPP on a range of animal species

Animal	Route of Admin.	LD_{50} mg/kg (95% C.I.)	Reference
Cat	p.o.	5.6	Savarie *et al*, 1983
Stoat	p.o.	9.3	Fisher *et al*, 2005
Ferret	p.o.	29	O'Connor, 2002
Dog (*Canis familiaris*- male)	p.o.	30-50	Vandenbelt *et al*. 1943
Wallaby	p.o.	89	O'Connor, 2002
Mouse (male)	i.v.	145 (82-217)	Scawin *et al*, 1984
Rat (*Rattus Norvegicus* - male)	p.o.	177 (119-262)	Savarie *et al*, 1983
Rat (Swiss Webstar)	p.o.	221	Pan *et al*, 1982
Mouse (female)	i.v.	200 (175-310)	Scawin *et al*, 1984
Mouse (*Mus musculus* - male)	p.o.	233 (186-292)	Savarie *et al*, 1983
Rat (female)	p.o.	224 (169-308)	Scawin *et al*, 1984
Rat (male)	p.o.	475 (89-2525)	Scawin *et al*, 1984
Mouse (female)	p.o.	> 5000	Scawin *et al*, 1984
Possum	p.o.	$\geq$ 500	O'Connor, 2002
Guinea pig	p.o.	1020 (760-1520)	Scawin *et al*, 1984

i.v. = intravenous
p.o. = oral

N.B There are no single dose LD_{50} value in primate species, however given that cynamolgus monkey was administered 150 mg/kg/day without mortality (*Confidential Appendix 11-16*) the single dose oral LD_{50} value for this species is clearly well in excess of this 150 mg/kg.

All the other components in PAPP Paste A and PAPP Paste B have been reviewed for acute oral toxicity. Only Component C has also been identified as being toxic if swallowed and would by classified as a 6.1D (an oral LD_{50} value of 335 mg/kg was the lowest value found) (*Confidential Appendix 5*).

The acute oral toxicity for the PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait has been assessed by mixture calculations using scenarios of both the component concentration minimum

and maximum limits in combination with the lowest LD_{50} values found in the literature (*Confidential Appendix 6*). The hazardous classifications for the three new substances are summarised in Table 2.

Table 2: Hazardous classifications determined using acute oral LD_{50} values determined by mixture calculation rules

Substance	Oral LD_{50}	Hazardous classification
PAPP Paste A	5 > $\leq$ 50 mg/kg	6.1B
PAPP Paste B	300 > < 2000 mg/kg	6.1D
PAPP Ready-to-use Bait	300 > < 2000 mg/kg	6.1D

(ii) Dermal

There is no information on which to classify PAPP for dermal toxicity. It is noted ERMA have also previously not classified PAPP as dermal toxicant. Component C has also been identified as being toxic by dermal contact and would by classified as a 6.1C with a dermal LD_{50} value of 223 mg/kg being lowest value found (*Confidential Appendix 5*) .

The acute dermal toxicity for the PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait has been assessed by mixture calculations at the component concentration minimum and maximum limits and using the lowest LD_{50} values found in the literature. None of the three substances has been determined as triggering an acute dermal classification (*Confidential Appendix 6*).

(iii) Inhalation

The active ingredient PAPP is a solid, and therefore any relevant inhalation toxicity would be expected to be from fine dusts. The low vapour pressure of PAPP would suggest that the inhalation exposure route would be most unlikely. No specific inhalation data was found and it is also noted PAPP has not been given an acute toxicity by inhalation classification previously by ERMA.

No acute inhalation data has been found for any of the other components used to manufacture the new substances. Component C may be toxic by inhalation but specific data could not be found. However this component is present in the three substances at a low concentration so is considered unlikely to have any impact on overall classification of the mixtures. Therefore PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait were determined not to trigger an acute inhalation classification.

Sub-class 6.3 Skin irritation

PAPP has not been identified as a skin irritant (*Confidential Appendix 3*). Component C was identified as a possible skin irritant (*Confidential Appendix 5*). However the concentration is low and would be below the concentration threshold to trigger a 6.3 classification for any of the mixtures. A 6.3 classification is not triggered for the PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait

Sub-class 6.4 Eye irritation

PAPP has not been identified as an eye irritant (*Confidential Appendix 3*).Component C was identified as a possible eye irritant (*Confidential Appendix 5*). However the concentration is low and would be below the concentration threshold to trigger a 6.4 classification for the new substances. A 6.4 classification is therefore not triggered for the PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait.

Sub-class 6.5 Sensitisation

There is no evidence of any sensitising properties (contact or respiratory) for PAPP from reported studies that involved repeated exposure to animals (Menton *et al*., 1997) , to humans (Tepperman *et al*., 1946) or from multi-dose studies on rats and monkeys (e.g., Wood *et al* ,1991). Furthermore ERMA has not classified PAPP as a sensitizer on the ERMA database. None of the other components in the mixtures have been identified as sensitizers (*Confidential Appendix 5*). Therefore no 6.5 classification has been applied to the PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait.

Sub-class 6.6 Mutagenicity

In vitro and *in vivo* studies on PAPP as reported in the literature and confidential contract reports *(e.g. Confidential Appendix 11-18)*, show PAPP is not identified as a mutagen. PAPP has been determined as non–mutagenic in the mouse micronucleus test and the human lymphocyte test. In the forward gene mutation mouse lymphoma test there were ambiguous results possibly implying weak mutagenic activity. However in further studies to clarify the genotoxicity and mutagenicity of PAPP it was shown not to be mutagenic in the Ames test and Unscheduled DNA synthesis test. Key studies from the literature are summarized in Table 3. In conclusion the weight of evidence from these results indicates that PAPP is not mutagenic and is not likely to cause cancer.

Table 3: Genotoxicity tests on PAPP

Test system	Result	Reference
Mouse micronucleus	No increase in micronuclei. Not mutagenic	*Confidential Appendix, Section 11-2*
Metaphase analyses in human lymphocytes	No clastogenicity Non-mutagenic	*Confidential Appendix, Section 11-3*
Forward gene mutation in mouse lymphoma	Weak indication of mutagenicity	*Confidential Appendix, Section 11-18*
Ames Test	Not mutagenic	Baskin & Fricke, 1992
Unscheduled DNA synthesis in rat	Not evidence of unscheduled DNA synthesis. Not mutagenic	Baskin & Fricke, 1992

None of the other components in the mixtures have been identified as being mutagenic (*Confidential Appendix 5*). A 6.6 classification was therefore concluded to not be triggered for the PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait.

Sub-class 6.7 Carcinogenicity

There is no indication from the information available in the literature to indicate PAPP has carcinogenic properties. None of the other components in the mixtures have been identified as being carcinogenic either (*Confidential Appendix 5*). Consequently no 6.7 classification is triggered for the PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait.

Sub-class 6.8 Reproductive/developmental effects

PAPP has not been identified as a having a 6.8 classification. The only study reported that specifically addresses any reproductive/developmental effects of PAPP was an exposure study by Schafer *et al* (1982) and that was on a bird species (quail). PAPP was reported as having an LD_{50} of > 316 mg/kg (a dose of 316 mg/kg resulted in no observed deaths of male quail). Testes weight in the quail was reported to average 3.670 g, which was heavier than the control value of 2.854 g. The viability of eggs fertilised by exposed males was reported to be 81% and 82% after 1 to 35 and 20 to 35 days of exposure, respectively. The data did not indicate PAPP to be an effective sterilant for birds (effective sterilant criteria being 40% fertility reduction or testes weight less than 1.1 g).

None of the other components in PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait have been identified as having adverse reproductive/developmental effects (*Confidential Appendix 5*). Therefore no 6.8 classification has been determined for PAPP Paste A, PAPP Paste B and the PAPP Ready-to-use Bait based on the information available.

Sub-class 6.9 Target organ systemic effects

Multi-dose studies in animal have covered a range of time-frames with periods of exposure of 14 and up to 30 days duration (Doull and Plzak, 1963; Baskin and Fricke, 1992: Blickenstaff et al., 1994). Most studies address the effect of PAPP on red blood function, specifically the capacity of haemoglobin to carry oxygen and the formation of methaemoglobin by the action of PAPP or its principal metabolite, PHAPP. It appears that the action of PAPP on blood and specifically haemoglobin, is rapid but also is short -lived. In a 14 day study on rats (35 to 140 mg/kg day) the test animals became pale and/or cyanotic appearance and lethargic. At high doses some rats were found to have enlarged spleens. However it was concluded that as the primary purpose of PAPP is to elevate methaemoglobin levels then the effects observed were considered to be secondary to the pharmacological effects and not direct toxicological effects (*Confidential Appendix 11-15*). In the cynomolgus monkey in an equivalent 14 day study (doses up to 150 mg/kg/day) the red blood cells were again effected and no other organs/systems were affected by PAPP (*Confidential Appendix, Section 11-16)*. In addition, at least one other study has demonstrated that the carry over effects of PAPP from repeated exposures are reversible regardless of the dose level administered (Wood *et al*., 1991).

Peak methhaemoglobin concentrations in all species lag peak plasma PAPP levels by approximately 30 - 60 minutes (Paulet *et al*. 1963; Bright and Marrs, 1982; Bright and Marrs, 1983; Marino *et al*. 1997). This lag is a function of at least 3 processes: firstly PAPP/PHAPP absorption, secondly PAPP metabolism to an active metabolite, and thirdly the accumulation of PHAPP in the red blood cells to a minimum effective concentration (Marino *et al*. 1997). Thus the duration of the lag phase as expressed by clinical symptoms is dose-dependent. During the lag phase varying amounts of circulating PHAPP will have oxidised a proportion of haemoglobin to methaemoglobin. Counteracting this, PHAPP and PAPP are being metabolised to inactive derivatives prior to being cleared via the kidneys. Therefore, by the end of the first and second hours (although it is dose and species dependent) methaemoglobinaemia will have either reached peak (or lethal) concentrations, or begun to subside due to the enzymatic reduction of methaemoglobin to haemoglobin by methaemoglobin reductase at a rate that outstrips the methaemoglobin formation.

In a review paper, Baskin and Fricke (1992) also refer to the sub-acute oral toxicity data in rats and monkeys from unpublished studies in 1987 (*Confidential Appendices 11-15 & 11-16*). The authors concluded the rat and monkey studies had similar experimental designs, with a 14-day treatment period, followed by a 14-day treatment-free period. In both studies, standard haematology, clinical chemistry, urine analysis and pathology were evaluated (Baskin and Fricke 1992). The rat study consisted of four treatment groups, which were dosed daily with 0, 35, 90 or 140 mg/kg for males and 0, 20, 50 or 130 mg/kg for females. Pertinent histopathological analysis of the spleens revealed a

dose-related increase in erythroid hyperplasia, sinusoidal enlargement, erythrophagocytosis, and pigment deposition. Pigment was also evident in the Kupffer cells of the liver and in the renal proximal tubular epithelial cells of rats in the highest dose group. The pigment was still present in the liver, kidney, and spleen of rats in the highest-dose groups at the end of the treatment-free period. The hyperplasia and enlargement, however, had returned to control levels.

Sub-acute toxicity was studied in cynomolgus monkeys (both sexes) dosed daily for 17, 50 or 150 mg/kg of PAPP (*Confidential Appendix 11-16)*. Serum chemistry parameters of the treated animals showed increased LDH (lactate dehydrogenase) levels for the highest dose group after four days of treatment. After 10 days, bilirubin levels were increased in all of the treatment groups, while LDH was elevated in the 50 and 150 mg/kg dose groups. Female animals showed elevated GOT (glutamic-oxaloacetic transaminase) and GPT in the highest dose group. These changes are consistent with an effect on the liver. After 28 days, the abnormal serum chemistry values had returned to control levels. In summary, the review by Baskin and Fricke (1992) and both of these multi-dose study reports, concluded that the pathological and histopathological effects seen with PAPP treatment were to be expected consequences of high methaemoglobin concentrations, which implies the increases in GOT, LDH and bilirubin represent an indirect rather than a direct effect of PAPP on the liver. The study on PAPP in this primate species is particularly important with regards to risk assessment for humans and it is noteworthy that the doses of 150 mg/kg/ day PAPP given to monkeys for 14 days were an order of magnitude greater than the single dose LD_{50} in susceptible species such as stoats.

These studies (rat and monkey) indicate that there are no significant or severe chronic systemic toxic or target organ effects from prolonged sub-lethal doses of PAPP, other than secondary effects of methaemoglobinaemia. Based on the data reviewed available from the literature no 6.9 classification has been assigned to PAPP.

Potential effects on other components in the new substances were also considered. Component C is available for medicinal purposes in NZ and its effects on organs/systems have been well-documented and are transient unless there is a deliberate (toxic) over-dose (*Confidential Appendix 5*).

On the basis of the information available, no 6.9 classification has been applied to the PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait.

Class 8 Corrosive properties

There is no data to suggest that any component including the active PAPP is corrosive to metals, dermal or ocular tissue. Therefore no 8.1, 8.2 nor 8.3 classification has been applied to the PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait

Class 9 Ecotoxicity

Sub-class 9.1 Aquatic toxicity

Much of the aquatic toxicity information on PAPP is derived from quantitative structure activity relationship (QSAR) models. The statistic of interest is the coefficient of determination (r^2 value) which provides an estimate of the degree to which the defined model relationship (or regression) describes the data. Most of the relationships have been described for Log ($1/LC_{50}$) where the LC_{50} value is described in mmol/L. Conversions have been made to express this as an LC_{50} value in mg/L. Where this has been done, both values are presented.

Predicted LD_{50} values for fathead minnow or guppy have been predicted by QSAR analysis to be in the range of 22 mg/L to 623 mg/L with several studies suggesting values around 120 mg/L to 160 mg/L. Newsome et al. (1987) evaluated the use of QSAR equations to predict the toxicity to guppy (*Poecilia reticulata*) of a group of compounds (aniline derivatives) and used basic physical chemical parameters (i.e., K_{OW} and the dissociation constant) to predict toxicity. These parameters describe the affinity a compound will have for organic materials, particularly lipids, and the extent to which a compound will dissociate into reactive ions in an acidic solution. Newsome *et al*. (1987) established criteria for the acceptance of toxicity data and used four databases as the source information. The QSAR equations assessed were derived by three previous authors. For PAPP and the related compound 4-aminoacetopropiophenone, Newsome *et al.* (1987) presented the following predictions of toxicity to guppy (*Poecilia reticulata*) shown in Table 4.

Table 4: QSAR prediction of toxicity of PAPP to guppy (Poecilia reticulata), based on published models of activity

Compound			**LC_{50} (mg/L)**		
	Kow	PkA	Eq 1	Eq 2	Eq 3
PAPP	1.43	3.19	623	60.4	22.7
4 aminoacetopropiophenone	0.91	3.22	1632	179	34.2

Eq = equation

Kulkarni *et al.* (2001) investigated QSAR for a number of organic compounds, including PAPP. The approach used by these authors considered both functional groups as well as overall molecular structure in a regression analysis, but added consideration and assessment of data characteristics such as co-linearity of factors, and factors contributing most to the overall variance within the dataset. By eliminating outliers through this system, the authors refined the precision of estimates of key

properties, such as environmental partitioning coefficients (K_{OW}) and toxicity to fathead minnow (*Pimephales promelas*). These estimates were calibrated against a set of compounds with previously published partitioning coefficients and toxicity. Kulkarni *et al* (2001) reported very high coefficients of determination values for the predictions of their model approach (r^2 for benzene derivates over 0.91). PAPP was included with ketones for which the reported r^2 value was 0.9532 and an adjusted r^2 of 0.9426. The aquatic toxicity estimates of PAPP to fathead minnows derived by Kulkarni *et al.* (2001) are shown in Table 5.

Table 5. QSAR prediction of toxicity of PAPP to fathead minnow (*Pimephales promelas*)

	Reported log ($1/LC_{50}$)	**Predicted 1**	**Predicted 2**
As reported	0.01	-0.013	-0.08
mol/L	0.001023293	0.00097051	0.000831764
mg/L	152.7	144.8	124.1

Karabunarliev *et al.* (1996) also investigated the use of QSAR approaches for predicting the toxicity of a wide range of organic compounds using two related equations. Through use of terms to estimate a compounds electrophilic nature and tendency to have delocalised electrons, this research group achieved a high correlation (r^2=0.855) of structural attributes with toxicological response in guppy (*Poecilia reticulata*). Previous studies had suggested that much of a compound's toxicity could be explained on the basis of the hydrophobic nature of the molecules (e.g., the log K_{ow} values). Using this approach Karabunarliev *et al.* (1996) reported values as log ($1/LC_{50}$). These were converted and shown in Table 6.

Table 6: QSAR estimate of toxicity of PAPP to both guppy (*Poecilia reticulata*) and fathead minnow (*Pimephales promelas*)

		Guppy		**Fathead minnow**	
Log KoW	1.43	Method 1	Method 2	Method 1	Method 2
GMW	149.19				
Reported log ($1/LC_{50}$)		3.378	3.642	3.009	3.146
LC_{50} mmol/L		0.000418794	0.000228034	0.00097949	0.000714496
LC_{50} mg/L		62.5	34.0	146.1	106.6

Admans *et al.* (2001) also used a QSAR approach to estimate the toxicity of organic compounds. Using the presence of each chemical's reactive group (e.g., rings, aldehydes, amines, esters, etc) a stepwise regression was conducted to evaluate the overall contribution to toxicity from 478 compounds with known toxicity thresholds. This produced an equation with 16 structure descriptor terms and a correlation of structure to toxic threshold of 0.791. The results suggested that the overall

performance of this model approach could be significantly improved in some classes of compounds as the data sets develop. Admans *et al*. (2001) calculated LC_{50} values for PAPP to fathead minnow. These are shown in Table 7.

Table 7: QSAR estimate of the toxicity of PAPP to Fathead minnow (*Pimephales promelas*)

Log KoW	1.43	**Fathead minnow**	**Calc with 16**	**Calc with reduced**
GMW	149.19	**Previously published**	**descriptors**	**model**
log ($1/LC_{50}$)		3.009	3.457	3.19
mol/L		0.00097949	0.00034914	0.000645654
mg/L		146.1	52.1	96.3

The QSAR studies provide several estimates of the aquatic toxicity of PAPP that indicate a range from being 'non-hazardous' through to a 9.1C (harmful in the aquatic environment) classification. It is noted that ERMA have previously not classified PAPP for aquatic ecotoxicity.

None of the other components in the substances have been identified as ecotoxic to aquatic life (*Confidential Appendix 4*). Using the mixture calculation rules, PAPP Paste A has been determined as a 9.1D (using worse case predictive data) while PAPP Paste B and the PAPP Ready-to-use Bait do not trigger classifications (*Confidential Appendix 6*).

Sub-class 9.2 Soil ecotoxicity

An evaluation of PAPP using OECD methodology has determined the compound as being hydrolytically stable and readily biodegradable (*Confidential Appendix 11-11*). An OECD 207 earthworm toxicity study has not been conducted on PAPP but some data is available on a PAPP chloride compound (*Confidential Appendix 11-11*). The EC_{50} (7 day) was > 86 mg/kg (the highest concentration tested). The 14 day data indicated toxicity effects at PAPP chloride concentrations of 24.4 mg/kg (80% survival) and 86 mg/kg (35% survival). An EC_{50} (14 days) was extrapolated as being 61 mg/kg. The relevance of this data to PAPP is uncertain given the water solubility of PAPP is ~230 mg/L and for PAPP chloride is 6400 mg/L and the difference in physical/chemical properties might also affect soil ecotoxicity.

The PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait have not been given 9.2 classifications.

Sub-class 9.3 Terrestrial vertebrates

There is an overlap of animal data between this 9.3 classification assessment and the assessment in Sub-Class 6.1 (acute oral toxicity). The investigations regarding the suitability of PAPP as a vertebrate toxic agent compound conducted in the United States provide alot of information on the sensitivity of a range of terrestrial vertebrates to PAPP. Data for rodents and a range of predators are summarised in Table 8 and for avian (bird) species in Table 9. Additional NZ generated data for the stoat, ferret, possum, duck and wallaby is also included in these tables.

The animal data (Table 8) shows that there are oral LD_{50} values of $\leq$ 50 mg/kg b.w. for the PAPP active ingredient for some species and that would trigger a 9.3A classification. The avian data (Table 9) shows the duck LD_{50} as $\leq$ 50 mg/kg b.w. so this also triggers a 9.3A classification.

Table 8: PAPP lowest oral LD_{50} values for animal species from literature

Animal	LD_{50} (mg/kg)	Reference
Badger	> 100	Savarie *et al*, 1983
Bobcat	10	Savarie *et al*, 1983
Cat	5.6	Savarie *et al*, 1983
Coyote	5.6	Savarie *et al*, 1983
Dog	30- 50	Vandenbelt *et al*. 1943
Dog	26 - 43	Murphy *et al*, 2007
Guinea pig	1020	Scawin *et al*, 1984
Ferret	~29	O'Connor, 2002
Kit fox	14.1	Savarie *et al*, 1983
Mouse	223	Savarie *et al*, 1983
Mouse	> 5000	Scawin *et al*, 1984
Possum	$\geq$500	O'Connor, 2002
Racoon	142	Savarie *et al*, 1983
Rat (female)	223.7	Scawin *et al*, 1984
Rat (male)	475	Scawin *et al*, 1984
Skunk	> 400	Scawin *et al*, 1984
Stoat	9.3	Fisher *et al*, 2005
Stoat	~ 25	O'Connor, 2002
Wallaby	~89	O'Connor, 2002

Table 9: PAPP oral LD_{50} values for bird species

Avian Species	LD_{50} (mg/kg)	Reference
Duck (Pekin, mallard)	32	*Confidential Appendix, Section 11-8*
Duck (Pekin, mallard)	~38	O'Connor, 2002
Eagle	> 50	Savarie *et al*, 1983
Blackbird	174	*Confidential Appendix, Section 11-4*
American crow	178	Schafer *et al*, 1983
Blackbilled magpie	178	Schafer *et al*, 1983
Crow	>178	Savarie *et al*, 1983
Magpie	178	Savarie *et al*, 1983
Magpie	~1300	*Confidential Appendix, Section 11-6*
Quail	316	Schafer *et al* 1983
Quail	> 316	Savarie *et al*, 1983
Starling	316	Schafer *et al* 1983
Starling	> 316	Savarie *et al*, 1983
Weka	568*	*Confidential Appendix, Section 11-9* *Confidential Appendix, Section 11-12*
Australian magpie	1387	*Confidential Appendix, Section 11-4*

* While the weka did not die at lower doses, it was observed at a PAPP concentration of 50 mg/kg that this species became subdued and birds lost their appetite

The toxicity of other components in the PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait was also considered. The lowest LD_{50} for Component C was 335 mg/kg indicating a 9.3B classification would apply to this paste ingredient (*Confidential Appendix 5*). The acute oral toxicity for the paste containing PAPP has been assessed by mixture calculations (*Confidential Appendix 6*) at the component concentration minimum and maximum limits and using the lowest LD_{50} values found in the literature. The terrestrial vertebrate hazardous classifications have been determined as 9.3A for PAPP Paste A, 9.3B for PAPP Paste B and 9.3C for the PAPP Ready-to-use Bait.

Sub-class 9.4 Terrestrial invertebrates

No data has been found for PAPP or any of the other components with respect to toxicity to terrestrial invertebrates. PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait have therefore not been given a 9.4 classification.

The classifications determined for PAPP Paste A, PAPP Paste B and for the PAPP Ready to use Bait are summarised in Table 10.

Table 10: Summary of hazardous classifications for PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait

Class	Description	PAPP Paste A	PAPP Paste B	PAPP Ready-to-use Bait
Class 1	**Explosiveness**	Not triggered	Not triggered	Not triggered
Class 3	**Flammability**	Not triggered	Not triggered	Not triggered
Class 5	**Oxidising properties**	Not triggered	Not triggered	Not triggered
Class 6	**Toxic properties**			
Subclass 6.1	Toxicity			
	Acute oral	**6.1B**	**6.1D**	**6.1D**
	Acute dermal	Not triggered	Not triggered	Not triggered
	Acute inhalation	Not triggered	Not triggered	Not triggered
Subclass 6.3	Skin Irritation	Not triggered	Not triggered	Not triggered
Subclass 6.4	Eye irritation	Not triggered	Not triggered	Not triggered
Subclass 6.5	Sensitisation	Not triggered	Not triggered	Not triggered
Subclass 6.6	Mutagenicity	Not triggered	Not triggered	Not triggered
Subclass 6.7	Carcinogenic effects	Not triggered	Not triggered	Not triggered
Subclass 6.8	Reproductive/developmental effects	Not triggered	Not triggered	Not triggered
Subclass 6.9	Target organ systemic effects	Not triggered	Not triggered	Not triggered
Class 8	**Corrosiveness**			
Subclass 8.1	Corrosive to metal	Not triggered	Not triggered	Not triggered
Subclass 8.2	Corrosive to dermal tissue	Not triggered	Not triggered	Not triggered
Subclass 8.3	Corrosive to ocular tissue	Not triggered	Not triggered	Not triggered
Class 9	**Ecotoxicity**			
Subclass 9.1	Aquatic ecotoxicity	**9.1D**	Not triggered	Not triggered
Subclass 9.2	Soil ecotoxicity	Not triggered	Not triggered	Not triggered
Subclass 9.3	Terrestrial vertebrate toxicology	**9.3A**	**9.3B**	**9.3C**
Subclass 9.4	Terrestrial invertebrate toxicology	Not triggered	Not triggered	Not triggered

3.4 Identification of the default Controls on the substance.

The default controls triggered by the hazardous classifications for PAPP Paste A, PAPP Paste B and the PAPP Ready-to-use Bait have been summarised in Tables 11, 12 and 13 respectively.

The 6.1B and 9.3A classifications for the PAPP Paste A, both trigger the controls for Tracking and for an Approved Handler. PAPP Paste B and the PAPP Ready-to-use Bait do not trigger these controls.

Table 11: Default Controls triggered PAPP Paste A

Class	Hazardous Classification	Default controls
Acute Toxicity	6.1B (oral)	T1, T2, T3, T4, T5 T6, T7, T8
Subclass 6.1		I1, I8, I9, I16, I17, I18, I19, I20, I21, I28, I29, I30
		P1, P3, P13 , PG2
		D4, D6, D7, D8
		EM1, EM6, EM8, EM11, EM12, EM13
		TR1
		AH1
Aquatic	9.1D	E1, E2, E6, E8
Ecotoxicity		I1, I3, I9, I11, I19, I21, I23, I29
Subclass 9.1		P1, P3, P15 , PG3
		D5, D6, D7, D8
		EM1, EM7, EM8, EM11, EM12, EM13
Terrestrial	9.3A	E1, E2, E4, E5, E6, E7, E8
vertebrates		I1, I3, I9, I11, I19, I21, I23, I29
Subclass 9.3		P1, P3, P15, PG3
		D5, D6, D7, D8
		EM1, EM7, EM8, EM13
		TR1
		AH1

Table 12: Default Controls triggered PAPP Paste B

Class	Hazardous Classification	Default controls
Acute Toxicity	6.1D (oral)	T1, T2, T4, T7, T8
Subclass 6.1		I1, I8, I9, I16, I17, I18, I19,I20, I21, I28, I29, I30
		P1, P3, P13
		D4, D6, D7, D8
		EM1, EM6, EM8, EM11, EM12, EM13
Terrestrial	9.3B	E1, E2, E4, E6, E8
vertebrates		I1, I3, I9, I11, I19, I21, I23, I29
Subclass 9.3		P1, P3, P15, PG3
		D5, D6, D7, D8
		EM1, EM7, EM8, EM13

Table 13: Default Controls triggered PAPP Ready-to-use Bait

Class	Hazardous Classification	Default controls
Acute Toxicity	6.1D (oral)	T1, T2, T4, T7, T8
Subclass 6.1		I1, I8, I9, I16, I17, I18, I19, I20, I21, I28, I29, I30
		P1, P3, P13
		D4, D6, D7, D8
		EM1, EM6, EM8, EM11, EM12, EM13
Terrestrial	9.3C	E1, E2, E4, E6, E8
vertebrates		I1, I9, I11, I19, I21, I29
Subclass 9.3		P1, P3, P15, PG3
		D5, D6, D7, D8
		EM1, EM7, EM8, EM13

3.5	**Provide information on what will happen to the substance throughout its whole life from its introduction into New Zealand, its uses, through to disposal.**

Importation

The active ingredient PAPP is to be imported into New Zealand in shipment quantities from 1 to 25 kg packed in plastic bags within another container, e.g. fibre drum (UN compliant). The material would arrive by sea or air freight and then be transported by road to the manufacturing site.

Manufacture

The PAPP and other ingredients will be delivered by road to the manufacturing site. The PAPP will be stored under lock and key in a Dangerous Goods Store. The manufacturing site already stores and manufactures other vertebrate toxic agents and has procedures and personnel in place to handle substances that require an Approved Handler and Tracking (*Confidential Appendix 1*).

The manufacture of the PAPP Paste A and PAPP Paste B is described in *Confidential Appendix 1*.
The PAPP Paste A would be packaged in:

a) Syringes (clear polypropylene; 3 ml capacity), and
b) Small pottles (white HDPE, screw top, 9 ml capacity) .

The PAPP Paste B would be packaged in HDPE screw top containers of up to 5 kg capacity.
Containers would be labelled (*Confidential Appendix 7*) and stored securely until dispatch and subsequent use.

The containers would be packed into secondary packaging (cardboard boxes) before dispatch off-site. Packaging for PAPP Paste A will be compliant with Packing Group II and for PAPP Paste B, Packing Group III.

Identification

Labels and Safety Data Sheets would be available (*Confidential Appendices 7 & 8)*. The label will identify the PAPP Paste A as a 6.1B (oral) and 9.3A. The UN DG pictogram for a Toxic (6.1) hazard will be used as will the GHS Tacking pictogram . The PAPP Paste B (and PAPP Ready-to-use Bait) would be not be required to have any transport pictograms on the label (as neither meet the criteria of

dangerous goods for transport) but the relevant GHS pictograms can be used..

Transport

A possible appropriate shipping description for the PAPP Paste A is:
UN NO. 2588, PESTICIDE, SOLID, TOXIC, N.O.S (contains para-aminopropiophenone), Class 6.1, Packing Group II..

The PAPP Paste A and PAPP Paste B would then be transported within New Zealand and be required to comply with NZS 5433; 2007, Transport of Dangerous Goods on Land. Within NZ, transportation could be via ship (across Cook Strait), rail or road provided the requirements for Approved Handlers and Tracking can be met.

Storage

The PAPP Paste A will be required to be stored in a Dangerous Goods Store in compliance with the Hazardous Substances (Packing) Regulations 2001, Hazardous Substances (Identification) Regulations 2001, Hazardous Substances (Tracking) Regulations 2001 and Hazardous Substances (Emergency Management) Regulations 2001.

PAPP Paste B and PAPP Ready to use Bait while not requiring to be 'locked up' (no Approved Handler control triggered) would still be in secure storage at the manufacturing site.

Product labels (and Safety Data Sheet) would include identification of the warning and precaution statements applicable to the substances and identify that an Approved Handler and Tracking Control applies to PAPP Paste A.

Use

The PAPP Paste A and PAPP Paste B are intended to be used as a Vertebrate Toxic Agents (VTA's). The PAPP in the paste formulation matrix has been demonstrated as being effective for the control of feral cats and mustelids (*Confidential Appendices 9 & 10*) .

The PAPP Ready-to-use bait is prepared by taking a small quantity of PAPP Paste A and enclosing this within minced meat as a 'ball' . This is then placed within the bait station for the target animal to feed on. An option is included to add a green dye to this bait.

Bait stations for stoats as an example would be laid in lines 800 to 1000 mm apart through the pest control area and with bait stations at 100 to 200 mm intervals. For feral cat control, the bait stations may be placed at more specific locations rather than as a grid pattern. Pre-feeding with a non-toxic feed is carried out to confirm the present of target species before the toxic bait is used. This pre-feeding could be for up to 2-wweks and also provides an opportunity to make observations of any non-target species that might be in the area.

As the bait may be used in remote locations a separate approval for the PAPP Ready-to-use Bait is sought to allow the preparation of this bait and then to be able to transport to the location where the pest control operation is to occur. Provision is also made for a green dye to be included in the minced meat so the PAPP Ready-to-use Bait is readily identifiable and would not be mistaken for 'food' for animal or human consumption.

All pest control operations will comply with the Hazardous Substances (Class 6) Regulations 2001, Hazardous Substances (Identification) Regulations 2001, Hazardous Substances (Emergency Management) Regulations 2001, Hazardous Substances (Tracking) Regulations 2001 and the Hazardous Substances (Personnel Qualification) Regulations 2001. In addition, any further controls set under the ACVM Act 1997 for VTA's and within the resource consent, issued under the Resource Management Act, will be followed.

The most likely non-HSNO controls (under ACVM Act 1997) for PAPP Paste A are:

2. *The product must be manufactured in accordance with ACVM Standard for Good Manufacturing Practice and to the chemistry and manufacturing specifications provided by the registrant and approved as part of the registration.*
4. *The product must only be sold or imported according to the current registration.*
31. *This product must only be used as specified in the label content.*
37. *Ongoing obligations:*

    The registrant must provide an annual summary of adverse events to the ACVM Group. Adverse events which have serious implications for the continued use of the product must be notified immediately.

    The registrant must also advise the ACVM Group of any new studies or data that contradicts information previously supplied.
43. *The product must be sold only by a person who has been approved by the ACVM Group*
51. *Vertebrate Toxic Agents: In addition to any labelling, advertising or promotion requirements specified in the current registration, labelling, advertising or promotion of the product must comply with the current ACVM - New Zealand*

Labelling and Advertising Guide for Vertebrate Toxic Agents Requiring Registration.

The PAPP Paste B is expected to have similar controls although clause 43 may not be required.

Disposal

Any paste or residues from the manufacturing process would be disposed of through an approved hazardous waste management company by incineration (in an approved facility) or by burying in a biologically active landfill.

The paste in meat bait (as used in pest control operations) would be recommended to be disposed of by burying below the ground level (recommended to be at least 60 cm depth). After a typical five to seven night interval from dispensing the paste bait as a VTA, it would be normal practice for each bait station is to be revisited and all toxic baits to be recovered and destroyed.

No specific provision for the recovery of dead carcasses of target pests (e.g. stoats, feral cats) is considered necessary as the residual levels of PAPP in animals are expected to be small. The ingestion of single bait represents 35 – 80 mg PAPP depending on the species and animal size.

Section Four: Risks, Costs and Benefits

4.1 Identify all of the potential risks, costs and benefits of the substance(s)

4.1.1 Risks & Costs

The risk identification assessment has focused on:

- Potential risks that arise from planned use;
- Potential risks that arise when the controls fail; and
- Potential risks that arise from unforeseen and unplanned events.

The risks were identified using the ERMA guidance notes, knowledge from previous applications for VTA's and taking into consideration the applicant's experience from use of existing VTA's. Potential risks at all stages of the lifecycle for the substances was prepared and are summarised in

Tables 14 &15. The magnitude of the risks identified and the effectiveness of controls to mitigate these risks will be discussed in section 4.2.

Table 14: Identification of possible events, exposure pathways and the lifecycle stage for the substance

M=Manufacture, T=Transport, S=Storage, U=Use, D=Disposal

Event	Risk pathway	Lifecycle stage
Accidental discharge into the air	Packaging damage	M,T,S
	Traffic accident	T
	Fire	M,T,S
	Safety precautions not followed	T,S,U, D
	Worker exposure	M, T, S, U, D
	Public exposure	T,S,U, D
	Spillage	M, T, S, U, D
Deliberate discharge into the air	Vandalism	T,S,U
	Eco-terrorism	T,S,U
Accidental discharge to land (soil)	Packaging damage	M,T,S,U,D
	Traffic accident	T
	Fire	M,T,S
	Safety precautions and use instructions not followed	M,T,S,U,D
	Bait not recovered after VTA operation completed	U
	Incorrect disposal	D
	Toxic bait misplaced	T, S, U, D
Deliberate discharge to land	Vandalism	T,S,U
	Eco-terrorism	T,S,U
Accidental discharge to water	Fire	M,T,S
	Packaging damage	M,T,S, U,D
	Traffic accident	T
	Safety precautions and use instructions not followed	M,T,S,U,D
	Bait not recovered after VTA operation completed	U D
	Incorrect disposal	T,S,U
Deliberate discharge to water	Vandalism	T,S,U
	Eco-terrorism	T,S,U
Risks in relation to use (as VTA) on land	Safety precautions and use directions not followed	U
	Wrong area controlled	U
	Humans eat toxic bait	U
	Domestic animals scavenge carcasses	U
	Non-target species mortality	U
Entry into human water supply	Traffic accident	T
	Safety precautions and use directions not followed	U
	Poisoned carcasses in waterway	U
	Deliberate - Eco-terrorism	T,S,U
Entry into human food supply	Dead carcasses collected/used for food	U
	Dead non-target species collected for food	U
	Spillage into water/cropped or farmed areas	U
	Contamination of food stuffs	U
	Deliberate - Eco-terrorism	U

Table 15: A summary of the potential risks, impacts and factors affecting risks for PAPP Paste A, PAPP Paste B and the PAPP Ready to use Bait

Component at risk	Type of impact	Mitigating factors
ENVIRONMENT		
Air contamination	Adverse effects to humans if product packaging damaged and substance degrades	Amount/extent limited by packaging/shipment size. Substances contain no volatiles PAPP mode of action is NOT by release of a poisonous gas. Toxic effects from PAPP require ingestion of the bait and any adverse effect is dose dependent Humans are less susceptible than target species and a heavier body weight PAPP is used as a therapeutic agent on humans for other medical conditions, i.e. cyanide poisoning.
	Non-target species potentially exposed to PAPP	Amounts likely to be available in bait/station are minimal Substances contain no volatiles Effects will be localised and small scale; amount of PAPP in each bait/station is small
Water contamination	Non-target species potentially exposed	PAPP Paste A has been classified as a 9.1D (aquatic toxicity) Neither PAPP Paste B nor the PAPP Ready –to-use Bait have been classified for aquatic toxicity Best practice is not to set bait stations within 20 m of waterways and hence PAPP is unlikely to enter water courses
Soil contamination	Non-target species potentially exposed	PAPP is formulated in a non-aqueous paste matrix. There is no evidence that PAPP would be ecotoxic in the soil environment not that PAPP will bio-accumulate nor be persistent in the soil environment . PAPP Paste A, PAPP Paste B and PAPP Ready –to-use Bait have not been identified as being ecotoxic in soil environment.
Non-target terrestrial vertebrate fauna	Non-target species, death possible for small (low weight) susceptible species	PAPP whilst highly toxic to the target species has low to moderate toxicity to other non-target species.

Component at risk	Type of impact	Mitigating factors
		PAPP Paste A, PAPP Paste B and PAPP Ready –to-use Bait have classifications of 9.3A, 9.3B or 9.3C respectively. These classifications are determined on the LD_{50} values for the most susceptible species which includes the cat. The delivery system (hand -laid ground based pest control) and application of best practices during bait application (amount of paste, use of bait stations, placement above ground if ground dwelling protected birds in area) limits exposure and therefore also risk An antidote (methylene blue) is available.
Non-target terrestrial invertebrate fauna (native and introduced)	Non-target species exposed	There is no evidence that PAPP or the paste matrix used in the new substances would be toxic to bees The 3 new substances do not contain any sweetener which might attract bees
Aquatic vertebrates (introduced and native)	Non-target species exposed	No specific data has been found on aquatic vertebrates. Limited opportunity for exposure Delivery system (bait stations) limits risks Best practice is not to set bait stations within 20 m of waterways Substances will not be applied directly onto or into water and should not get into waterways.
Aquatic invertebrates (native)	Non-target species exposed	Limited opportunity for exposure. Any effects will be localised and small scale; the amount of PAPP used in each bait/station is small. Delivery system (bait stations) limits risks
Terrestrial and aquatic flora (native and introduced)	Non-target species exposed	No evidence that PAPP is ecotoxic to flora. Delivery system (bait stations) limits risks
ECONOMIC		
Recreation	Recreational non-target species are unlikely to be killed	Removal of target species (e.g. .stoats, feral cats) likely to enhance the condition of forests for all species and in particular birds (eggs and checks not getting eaten) Delivery system (bait stations) limits access (risks) to non-target species
Tourism	Widespread use of VTA's ('chemical poisons') could be viewed negatively by tourists	Most operations would be expected to be away from the main populated/tourist areas Positive environmental effects (bird life/populations) likely after removal of target species

Component at risk	Type of impact	Mitigating factors
Non-target animals	Exposure to food producing animals (cows, sheep, goats)	PAPP Paste A, PAPP Paste B and the PAPP Ready –to-use Bait to be used only as hand laid bait in ground based pest control and placed in a bait station where access to bait is limited by target species size. Best practice procedures would also result in sensible placement of bait stations away from areas inhabited by livestock or domestic animals (cats, dogs) Deer, goats and other 'wild' animals would not have access to the bait station (size limitation) . Toxic effects in food-producing animals (e.g. pigs, sheep, cows) or game (e.g. deer, pigs, goat) are very unlikely as these animals are a significantly higher larger body weight than a stoat or feral cat. Also the animal would need first to gain access to the PAPP paste in the meat bolus which would be within a bait station. Good practise would limit baiting in areas where livestock are present. In the event of livestock ingesting PAPP residues would be rapidly eliminated.
SOCIAL AND CULTURAL VALUES		
Recreation	Recreational activities at some locations may be unavailable for a period of time	Affected parties consulted as is the case with all other toxins (poisons). Long term positive impacts (protected species) likely after removal of target pests
Use of toxicants in the environment	Public perception	PAPP is neither persistent nor bio accumulative in the environment or in dead carcasses. The amount of APP used is very small. PAPP should be viewed as viable 'safer' alternative to 1080 for some applications.
Aesthetics	May reduce the aesthetic values temporarily during operations by the presence of bait stations and possibly dead animals.	Can manage public access to sites during operations (access, signage) Positive aesthetic benefits are likely after removal of target pests
HEALTH AND WELL-BEING OF COMMUNITIES		
Public health	Oral ingestion	Very limited opportunity for exposure to PAPP No evidence that PAPP would be absorbed through skin Dose dependent and no significant level of exposure is likely.

Component at risk	Type of impact	Mitigating factors
		PAPP is used to treat some medical conditions including treatment of cyanide poisoning Any exposure likely to be a one-off encounter and of a small dose Low/negligible risk of contamination of waterway Delivery system (bait stations) and proposed use (directions/warnings on product label) limits exposure Data from the literature indicates a human dose of PAPP at 10 mg/kg b.w. will not have an effect. If a child is 10 -20 kg then theoretically 100 – 200 mg PAPP could be ingested without harm; this is equivalent to 244 – 488 PAPP Paste A A syringe (smallest packaging size) contains 2.2 g (2200mg PAPP paste) however the 6.1B classification should ensure children (and other unauthorized person) would not have access to the PAPP paste.
Occupational exposure	Oral(ingestion)	Limited opportunity for exposure if the controls set out by ERMA are followed Dose dependent, but it is likely any lethal doses would need to be deliberately ingested PAPP Paste A is 6.1B (oral). PAPP Paste B and the PAPP Ready –to-use Bait are 6.1D (oral) classifications. However these classifications are based on data for susceptible species (cats and muselids) and this group does not include humans A antidote (methylene blue) is available PAPP Paste A triggers an Approved Handler Control (from classifications based on most susceptible animal species) If an adult is 60 – 100 kg weight then a dose of 10 mg/kg bw (no effect observed) is equivalent to 600 – 1000 mg PAPP active or 1463 – 2439 mg PAPP Paste A. The smallest pack size is 2.2 g (2200 mg) so direct ingestion of this mount is unlikely to have a serious (fatal) effect. The pottle will hold 4 g so could if ingested in its entirety potentially have a toxic adverse effect on adults.

Component at risk	Type of impact	Mitigating factors
Accidental exposure	Oral (ingestion)	Limited opportunity for exposure if the controls set by ERMA are followed and substances used as hand-laid bait and placed in bait stations. A antidote (methylene blue) is available. Effects are dose and species dependent Even deliberate ingestion of a ready-to use bait is unlikely to have any effect. Fully reversible effects from non-lethal doses.
Foreseeable needs of future generations	Targeted (specific species) effect	Short-term effects Positive benefits if native plant and animal communities are maintained No evidence that PAPP will be bio-accumulative or persistent in environment Toxic effect is concentration/species dependent
Loss of value in ecosystems	Loss of non-target species at a site possible	Short-term effects , if any. Positive benefits if native plant and animal communities maintained/enhanced by removal of predators (stoats, feral cats) Does not bio-accumulate nor persist in environment The toxicity of PAPP to birds has also been considered. The mallard duck is a species that seems to be susceptible to PAPP. If a duck were killed or adversely affected by a sub-lethal dose of PAPP, and the duck were eaten, the PAPP concentration is insufficient to harm a human. Murphy *et a*l (2005) considered the impact of a range of NZ native bird species ingesting equivalent to 17 mg PAPP active. Species identified as potentially at risk because of low body weight were the long-tailed cuckoo, kingfisher, robin and tui. Ground dwelling birds such as weka that could also be attracted to a meat bait containing the PAPP paste would potentially to be at risk were the bait to be accessible, i.e. . not contained in bait station with a aperture to restrain the non-target species. Residue analysis on weka have shown the PAPP residues are very low (0.03 – 0.3% by weight of liver) . While a LD_{50} has been estimated for weka,

Component at risk	Type of impact	Mitigating factors
		a cage trial has shown that at sub-lethal doses, e.g. 61.7 mg/kg or higher, weka became subdued and lose their appetite. The symptoms of PAPP in weka are more prolonged than in other bird species.. To mitigate risk despite the higher LD_{50} value in birds t presentation of the bait in bait stations is important to preventing/restricting limit access by birds. Risk would be mitigated by use of a bait station limiting access to non-target species (size) and care in the placement/location of the bait stations.
Development of persistence in soils and waterways	Ecotoxicity	No evidence that PAPP will bio-accumulate nor persist in environment. No evidence that expected use rates of substance will result in ecotoxicity hazard.
Disposal	Ecotoxicity	Untaken bait is recommended to be collected and disposed of by burying under at least 60 cm of soil. The paste can also be disposed of by incineration. Birds (weka, hawks) might be able to scavenge a dead carcass. A study was undertaken on weka after ingestion of PAPP bait of up to 480 mg/kg. Two birds (given doses of 400 and 200 mg PAPP respectively were analysed for residues. It was found after 30 hours that 0.03 - 0.3% of the original dose concentration was in the liver and in muscle was below the method detection limit.

No significant costs have been identified from the future potential use of PAPP Paste A, PAPP Paste B or the PAPP Ready to use Bait as Vertebrate Toxic Agents (VTA's). There has however been already a significant cost in the research and development of PAPP containing VTA toxicants to get to this point. Existing manufacturing equipment can be used. The quantities of bait to be transported are small given the species specificity to the toxin. There is no evidence that PAPP (or even the other components in the paste matrix) would be persistent or bio accumulative in the environment which might result in a cost to future generations.

Additional comment to the summary points given in Tables 14 & 15 has also been considered under the headings of:

- Primary exposure
- Secondary exposure
- Manufacturing
- Application
- End-use
- Disposal
- Post-application

4.1.1.1 Primary exposure

This section summarises the potential risk of humans, other animals or birds directly ingesting PAPP (the active ingredient in PAPP Paste A, PAPP Paste B or the PAPP Ready to use Bait).

4.1.1.1.1 Humans

The PAPP active ingredient was originally developed as a treatment for cyanide poisoning in the United States. PAPP administered parenterally or orally causes the oxidation of haemoglobin to methaemoglobin.. Since the latter has an increased affinity for and sequesters absorbed cyanide, the initial overseas studies on PAPP were focused on its potential use in humans as a prophylactic for cyanide poisoning. PAPP-induced partial methaemoglobinaemia in humans protects against cyanide toxicosis. Early studies therefore provided data on the effects of PAPP as a therapeutic agent in humans. The typical methhaemoglobinaemic response can be expressed in terms of the factors which are simultaneously acting to promote or depress methaemoglobin concentrations in red blood cells. Typically, during the first 30 minutes following ingestion or injection, a majority of the chemical has entered the circulation. During this time circulating PAPP is exposed to the action of the liver, which converts a proportion of it to the active metabolite PHAPP, and begins the process of chemically degrading PAPP and PHAPP principally to inactive amino acid conjugates.

Animal including human toxicity data for PAPP has been summarized by Baskin and Fricke (1992). In one referenced study, volunteers were given between 50-100 mg PAPP in water and the maximum methaemoglobin levels occurred within one to two hours with levels elevated for 4 hours. Other than elevated methaemoglobin levels and mild haemolyses at high doses, no other adverse effects were observed. In particular no change in ventilation rate, arterial pressure, electrocardiograms, appetite or

renal function have been observed (Paulet *et al*. 1963).

In further studies, exercise tolerance has been assessed with minimal or no effects detected (Tepperman *et al*, 1946 and Marino *et al*, 1997). A study with chronic administration designed to produce steady state methaemoglobin levels have been conducted with a focus on red blood cell survival (Beulter and Mikus, 1961). No systemic toxicity effects were reported.

PAPP Paste A will have a 6.1B (oral) classification however this is based on the toxicity of the most susceptible animal species. Humans are much less susceptible. The mode of action of PAPP on species including humans is well-understood. Humans along with the majority of other species possess key enzyme systems that have evolved to metabolise and detoxify PAPP that makes them less susceptible to its oxidising action on haemoglobin and readily able to metabolise and excrete sub-lethal doses. This makes PAPP and these new VTA baits less acutely toxic to humans and therefore pose less of a hazard to humans compared to the target species (feral cats, mustelids). Humans should not be exposed to PAPP in sufficient quantity to cause an ill-effect but if there was unintentional exposure; metabolism and excretion would be rapid accompanied by a mild and transient methaemoglobinaemia.

Methylene blue could be used an antidote although PAPP-induced methaemoglobinaemia in humans has not been treated with methylene blue. However, a variety of idiopathic and acquired methaemoglobinaemias have been reported as successfully treated effectively with methylene blue (Anon, 1993; Greenberg, 2001; Boylston and Beer, 2002) and in clinical practice methylene blue is a standard treatment for individuals with idiopathic [genetic polymorphisms] and acquired [drug induced] conditions (Bodansky and Gutmann, 1947; Stossel and Jennings, 1966; Anon, 1993).

Therefore in summary, although the PAPP Paste A has been classified as a 6.1B (oral) and both the PAPP Paste B and PAPP Ready-to-use have been determined as a 6.1D (oral) category , these classifications are based on data from the oral LD_{50} for the most susceptible animal species (cat) and therefore the classifications are not truly indicative of the lesser acute toxicity to humans and reversible effects. Any risk to humans (deliberate or involuntary exposure) is not considered to be a significant risk even though the PAPP Paste A is a 6.1B (oral) and will trigger an Approved Handler Control under the HSNO Regulations.

4.1.1.1.2 Other animals

In the species that have been studied (rats, guinea pigs, rabbits, dogs, monkeys, humans) for toxicological effects, the routes of excretion are generally similar being water soluble conjugates. However, due to the different metabolic pathways for PAPP between species the forms of PAPP

metabolites differ significantly (Tepperman and Bodansky, 1945; von Jagow and Kiese, 1967; von Jagow *et al*. 1966; Wood *et al*. 1991). Species variation can generally be expressed as a function of differences in the metabolism and excretion of PAPP/PHAPP (Wood *et al*. 1991), differences between species in the rates of haemoglobin oxidation (Smith and Beutler, 1966), and to a lesser extent the relative capacity of species to reduce methaemoglobin to haemoglobin. The principal route of excretion of PAPP is via the kidneys in urine (between 65% and 90%), with excretion via faeces and in expired air contributing minimally (Tepperman and Bodansky, 1946; von Jagow and Kiese, 1966; von Jagow *et al*. 1966; Wood *et al*. 1991).

Baskin and Fricke (1992) reviewed PAPP as a prophylactic treatment to counter the effects of cyanide toxicity and this included a review on effects on a variety of animals species (rodents, sheep, dogs, guinea pigs, rabbits). Early investigations into the effects of PAPP noted that lethal doses were far lower in some species (e.g. dogs and cats) than other species. (Savarie *et al*., 1983; Scharf *et al*., 1992). Fisher and O'Connor (2002) revisited this observation and also reported low oral LD_{50} values for cats and dogs compared to other mammals, birds or other non-target species. The reason for the differential sensitivity is linked to differences in sensitivity to PAPP induced methaemoglobinaemia. By implication methaemoglobinaemia occurs in all species but reaches lethal concentrations most readily in stoats and cats even after low doses of PAPP, and not so readily in other species.

As already reported there are very extensive data from the literature on the acute oral toxicity of PAPP. Oral gavage of single doses of PAPP to animals has followed standard toxicology protocols to determine acute toxicity (Scawin *et al*., 1984; Savarie *et al*., 1983, Plzak and Doull, 1962). The earlier Table 8 showed some LD_{50} values for PAPP in different mammalian species and highlights the susceptibility of canids, including cats versus other mammals. In most canids the LD_{50} value is around 10 mg/kg or less whereas in other the species it is usually > 100 mg/kg. The selective toxicity of PAPP to mustelids and cats means that PAPP can be utilized as a selective toxin as a VTA for stoats and feral cats.

PAPP Paste A has been classified as a 9.3A , PAPP Paste B as a 9.3B and the PAPP Ready-to-use Bait as a 9.3C, for toxicity to terrestrial vertebrates. However as has been explained susceptibility between species varies. Feral cats are a target species for these VTA products. A risk to domestic cats is possible and this potential risk will be mitigated by the use of bait station placement away from domestic homes. As the baits are particularly targeted to pests in bush/forested areas where bird populations are at risk from the pests, the chance of a domestic cat being in the control area is less, although if present is at an equal risk as feral cats/stoats .

4.1.1.1.3 Birds

Table 9 provides a summary of PAPP acute oral toxicity data in birds. The mallard duck was found to have the lowest LD_{50} value (30 – 50 mg/kg b.w.). In addition studies have assessed the potential acute toxicity risks to the weka, a ground-dwelling bird and a species that might be attracted to meat baits. The LD_{50} for the weka was calculated as 568 mg/kg but there were further investigations on the susceptibility of weka to PAPP in the paste matrix as adverse effects had been observed (loss of appetite, subdued) at the lowest PAPP dose and affected weka did not recover (within 30-hours) and were euthanized. It was concluded that weka were less susceptible than the duck species although it was observed symptoms of poisoning were apparent at 61.7 mg/kg b.w. or higher. Consequently it will still be important to minimise risks by using the PAPP baits in a bait station that limits access by non-target species and that the location of bait stations takes into account the potential access by non-target species.

4.1.1.2 Secondary exposure

Secondary exposure specifically addresses any potential risk to non-target species by secondary poisoning (from residues).

Dogs are a species that show moderate susceptibility to PAPP with a LD_{50} of 26 -50 mg/kg (Table 8). Dogs could potentially try to access the meat bait or more likely try to scavenge a dead carcass. There is data available on the effects of PAPP on dogs which are helpful in assessing the possible implications of secondary exposure (poisoning).

Secondary poisoning risk is determined by the extent that residues exist in poison carcasses and this is low in the case of PAPP as it is a compound that is readily metabolised and excreted. The absorption, metabolism and excretion of PAPP in animals was originally studied by Wood *et al*. (1991) using radio-labelled PAPP. The experiments were undertaken on Sprague-Dawley rats, beagles and cynomolgus monkeys. Peak plasma concentrations in dogs occurred in 30 minutes to one hour, and similar rapid absorption was observed in other species after oral ingestion of PAPP. Wood *et al* (1991) concluded that different species appear to produce different metabolites. Species variation in the metabolism of xenobiotics is a common phenomenon, sometimes linked to differences in toxicity (*Confidential Appendix 11-5)*. Metabolic activation by the liver and associated hepatic enzyme system that converts PAPP to *p*-hydroxylaminopropiophenone is the required pathway for activation of the compound in target species. In this case aliphatic oxidation appears to be important in dogs, whereas oxidation N-acetylation is more important in rats and monkeys (and probably also humans). Regardless of this species variation in metabolism, all species appear to rapidly metabolise

and eliminate PAPP. The data is summarised in Table 16. This data, coupled with the experience from acute toxicity studies indicates that unless a dog ingested a high single bolus dose toxicity will not occur. At sub-lethal concentrations, PAPP will be rapidly excreted with non long term effect on the animal.

Table 16: Percentage excretion of PAPP in rats, dogs and monkeys over time.

	Time (hr)	**Male rat (n=4)**	**Female rat (n=4)**	**Dog (n=4)**	**Male monkey**	**Female monkey**
Urine	0-6	57.6 +/- 11.4	46.4 +/- 10.3	50.9 +/- 6.9	72, 77	54, 69
	6-24	24.4 +/- 10.6	42.1 +/- 11.7	25.3 +/- 4.2	13, 17	16, 15
	24-48	1.2 +/- 0.7	2.4 +/- 1.0			
Faeces	0-120	9.1 +/- 0.3	3.7 +/- 1.2	7.9 +/- 1.5	0.4, 1.9	13.9, 1.2

Data from Wood *et al*. (1991)

In conclusion PAPP and other phenones are bio-labile with relatively short half-lives of between 1 and 3 hours (Paulet *et al.* 1963; Marino *et al.* 1997). Furthermore, the active hydroxylated metabolite PHAPP has an exceedingly short half-life of approximately 1 minute (Wood *et al.* 1991). This rapid metabolism and clearance is a great advantage in the context of the application of PAPP as prospective predacide as the risks of secondary poisoning are significantly reduced.

A comparison has been made (Table 17) between different VTA active ingredient's persistence as residues at sub-lethal doses. There is a huge variation in the way that the different vertebrate pesticides are absorbed, distributed, metabolised and excreted. At one end of the spectrum there are compounds that are very water soluble, rapidly absorbed, well distributed and equally rapidly excreted, such as 1080 and cyanide. There are others such as cholecalciferol, para-aminopropiophenone (PAPP, a candidate predacide) and diphacinone which are extensively metabolised to more hydrophilic metabolites, and others which are lipophilic and poorly metabolised and exhibit unique receptor binding characteristics. To help distinguish between different compounds and add some clarity, Eason *et al* (2008) have classified the vertebrate pesticides into 4 groups based on their persistence in sub-lethally exposed animals:

Group 1:-Sub-lethal doses of these poisons are likely to be substantially excreted within 24 hours. e.g. cyanide, zinc phosphide, PAPP and 1080. Whilst most of a sub-lethal dose of all these poisons is likely to be substantially excreted within 24 hours, in the case of 1080, complete excretion of all residues may take up to 4 to 7 days.

Group 2:- Residues resulting from sub-lethal doses of these poisons are likely to be substantially cleared from the body within 2 to 4 weeks. e.g. pindone and diphacinone.

Group 3:- Residues resulting from sub-lethal doses of these toxins are likely to be cleared from the body within 2 to 4 months. e.g. cholecalciferol and coumatetralyl.

Group 4:- Residues resulting from sub-lethal doses of these poisons may not ever be completely cleared from the body. e.g. bromodiolone, brodifacoum, difenacoum and flocoumafen.

PAPP is likely to be slightly more persistent that cyanide or zinc phosphide but less persistent than all the other toxins.

Table 17 : Summary of VTA actives with comparison of pharmacokinetics and expected persistence of residues in target species

Group	Active ingredient	Half-life values	Likely persistence of residues after sub-lethal exposure
1	cyanide	+	12 to 24 hours
	zinc phosphide	+	12 to 24 hours
	para-aminopropiophenone	+	4 days
	1080	< 11 hours	7 days
2	pindone	2.1 days	4 weeks
	diphacinone	3 days	6 weeks
3	cholecalciferol	10-68 days	3 months
	coumatetralyl	50-70days	4 months
4	brodifacoum	130 days	24 months or longer
	bromodiolone	170 days	24 months or longer
	flocoumafen	220 days	24 months or longer

+ No published value but likely to be < 12 hours

In the event of secondary poisoning from PAPP Paste A, PAPP Paste B or the PAPP Ready to use Bait, e.g. to dogs, an antidote is presently available in hospitals and is well understood by veterinarians. Methylene blue has been recognized as an effective antidote for methaemoglobinaemia in animals (nitrate and nitrite poisoning) in cattle. The mode of action of methylene blue is as an intermediate in the transfer of electrons from pyridine nucleotides to a suitable electron acceptor, thereby stimulating the hexose monophosphate shunt (HMPS) pathway in a variety of cell systems (IPCS/CEC, 1993). In the red-blood-cell this results in the reduction of methylene blue to leucomethylene blue by NADPH-dependent diaphorase (dihydrolipoamide dehydrogenase). This diaphorase is reduced via oxidation of NADPH, which in turn stimulates the HMPS and the leucomethylene blue transfers electrons to methaemoglobin. This series of reactions reduces the ferric haem to ferrous haem iron, which converts methamoglobin back to haemoglobin (Anon, 1993).

The effectiveness of methylene blue as an antidote to PAPP-induced methaemoglobinaemia was assessed in dogs by Bodansky and Gutmann (1946) and Stossel and Smith (1966) who showed that it was highly and rapidly effective in counteracting the symptoms of severe methaemoglobinaemia. The

majority of dogs that received the life-saving treatment recovered fully within hours and appeared physiologically normal days after the methylene blue intervention (Bodansky and Gutmann, 1946). In addition, healthy dogs (anesthetized) who were given methylene blue intravenously at doses exceeding 30 mg/kg responded only with a rise in total circulating haemoglobin but were otherwise unaffected (Stossel and Smith, 1966). A study by Bright and Marrs (1987) with PAPP on beagle dogs also found survival after exposure to at least 2 ½ times a lethal dose of cyanide. A more recent study has examined PAPP effects on dogs when intravenously or orally followed by administration of methylene blue (*Confidential Appendix 11-1*). The effectiveness of the antidote and its relatively wide therapeutic window make it the clinical treatment of choice and it remains current best practice for the treatment of all methaemoglobinaemias. The treatment indication involves intravenous administration of methylene blue 1-2mg/kg of body-weight formulated as an aqueous solution and administered over a 5 minute period (Anon, 1993; Greenberg, 2001; Boylston and Beer, 2002). Doses of methylene blue should not exceed 7 mg/kg. This also the dose range that is used in veterinary medicine in the treatment of methaemoglobinaemia (Bodansky and Gutmann, 1946).

Treatment with the antidote is contraindicated at methaemoglobin concentrations below approximately 30%, which generally do not result in clinical symptoms and resolve themselves naturally once the causative agent is removed. Doses may be administered intravenously or orally following dilution of the stock solution.

4.1.1.2.2 Potential for residues in the food-chain or environment

If recommended practices are followed in pest control operations, PAPP is highly unlikely to be present in meat for human consumption. PAPP Paste A, PAPP Paste B and the PAPP Ready-to-use Bait are not proposed to be used on crops, fodder, other plants or livestock. Data on the metabolism of PAPP in laboratory animals and on target species are available in the literature which demonstrate rapid excretion with no persistence in animal tissues or tendency to accumulate should there be accidental ingestion. Where any contact of livestock (farm animals or animals intended for slaughter) with PAPP is suspected, an adequate margin of safety could be achieved by imposing a minimum withholding period of 5 days. This is similar to the withholding period recommended for 1080 (Rammell, 1993) which is erring on the side of safety since studies have shown that any animals receiving sub-lethal doses of PAPP excrete between 75-85% of a dose within 24 hours (Wood *et al*. 1991).

The possible effects of PAPP residue being in present in a ground-dwelling bird (weka), a non-target species, was also investigated (*Confidential Appendix 11-14*). PAPP concentrations in the liver and muscle tissue were determined after doses well in excess of what would be used for either stoats or

feral cat control. The PAPP residual concentrations were extremely low and extrapolations for dogs indicate many carcasses would need to be ingested at the same time to have any potential ill-effect.

4.1.1.3 Manufacture

The manufacturing site is already used for the storage and manufacture of VTA products including highly toxic active ingredients. Site approvals and operating procedures are in place. Existing controls and procedures will effectively manage the storage of the PAPP active and manufacture of the new PAPP substance. No additional risks have been identified.

4.1.1.4 Application

PAPP Paste A with both the 6.1B (oral) and 9.3A hazardous classifications will require to be under the control of an Approved Handler or locked up. For use as a VTA, a small amount of paste would then be taken from the packaging container and enclosed within a small minced meat bait to form the PAPP Ready-to –use Bait. This bait is then placed in the bait station. Where the bait is prepared before entering the pest control site, these meat baits could be prepared, put in another container and refrigerated (e.g. overnight). A green dye would be added to ensure the meat bait balls would not mistaken for meat for human or domestic pet consumption.

PAPP Paste B and PAPP Ready-to-use Bait are at significantly less PAPP concentrations than the PAPP Paste A, so have a 6.1D acute oral classification. The preparation of the baits will require the person to wear gloves and take precautions not to contaminate other surfaces or materials. No further precautions are anticipated as being necessary to prevent any secondary exposure (other non-target species, plants, soil, and water) during preparation of the bait.

4.1.1.5 End-use

The choice of bait station and the location/placement of the bit station is important. This prevents or minimises risks to non-target species (animals, birds) and to the environment (water, soil). This also assists in protecting children by restricting access to the bait. It is also normal practice to not to place bait stations within 20-metres of any waterway.

Using a non-toxic pre-feed in the bait stations and tracking cards to monitor the visiting species, e.g. rodents, birds, prior to using the toxic bait is a practice that can be used to identify the presence of non-target species . This is particularly helpful if there is any uncertainty or concern about non-target

species being in the control area and also confirm the presence of the target species (stoats, feral cats).

Murphy *et al* (2005) provided a review of PAPP as a potential toxin form mammalian predators, e.g. stoats, in New Zealand. Using the lowest LD50 (133 mg/kg) , 5 of 24 New Zealand native bird species might be vulnerable (if 17 mg PAPP were present in a bait). To overcome this potential risk, the new PAPP –paste would only be used in a bait station.

The paste bait in meat bolus will also only be used in an appropriately designed bait station.

Provision has also been made in the PAPP Ready to use Bait specification to include a green dye in the meat bolus to also act as a deterrent to birds.

4.1.1.6 Disposal

Untaken bait is recommended to be collected and disposed of by burying under at least 60 cm of soil. The paste can also be disposed of by incineration.

It is unlikely the dead target pest will be in or adjacent to the bait stations as the toxin while relatively fast-acting does not result in immediate death.

Birds (weka, hawks) might be able to scavenge a dead carcass. A study was undertaken on weka after ingestion of PAPP bait of up to 480 mg/kg. Two birds (given doses of 400 and 200 mg PAPP respectively) were analysed for PAPP residues. It was found after 30 hours from ingestion that 0.03 - 0.3% of the original PAPP dose concentration was in the liver, and in muscle was below the method detection limit.

The quantity of PAPP in any meat bolus is small and any toxic effects would require ingestion of sufficient PAPP (many baits) to produce a toxic effect. Any effect as already explained is species/body weight and concentration dependent.

4.1.1.7 Post-application

If recommended practices are followed in pest control operations, PAPP is highly unlikely to be present in meat for human consumption. PAPP Paste A, PAPP Paste B and the PAPP Ready-to-use Bait are not proposed to be used on crops, fodder, other plants or livestock. Data on the metabolism of PAPP in laboratory animals and on target species are available in the literature which demonstrate

rapid excretion with no persistence in animal tissues or tendency to accumulate should there be accidental ingestion. Where any contact of livestock (farm animals or animals intended for slaughter) with PAPP is suspected, an adequate margin of safety could be achieved by imposing a minimum withholding period of 5 days. This is similar to the withholding period recommended for 1080 which is erring on the side of safety since studies have shown that any animals receiving sub-lethal doses of PAPP excrete between 75-85% of a dose within 24 hours (Wood *et al*. 1991).

4.1.2 Benefits

There is need to for effective Vertebrate Toxic Agents (VTA's) for mammalian pests (Murphy *et al*, 2005; Murphy *et al*, 2007). Primarily the need is for a more cost effective VTA's without the side effects (e.g. persistence in environment and bioaccumulation) characteristic of some of current approved toxins. There is also a potential and significant benefit to conservationists following the development of VTA's containing PAPP as the active ingredient, for these users with products that can deliver targeted solutions to specific pest problems especially in sensitive environments. The ability to develop cost effective, humane, species specific tools with minimal environmental risks is important. The conservation outcomes are expected to be achieved without many of the difficulties, side-effects, controversies and failures associated with existing products. In the words of one of our customers, we want "no pests with no hassles".

The benefits of having PAPP available as a VTA in the form of PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait have been summarised in Table 18.

Table 18: A summary of potential benefits for the PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait

BENEFITS	DIMENSION	TYPE OF IMPACT and CONTRIBUTION
ENVIRONMENTAL	Native species	• Reverse the decline in indigenous biota (specifically protected bird species, breeding)
	Invasive Species	• Effective and humane management (refer Tables 17 & 18) • Impacts minimal (i.e. secondary poisoning/persistence when compared with 1080) • Eradication /control of target pest (e.g. stoat, ferrets,feral cats) • Intervention tool (VTA) which is environmentally and economically sustainable
	Water/Soil/Non-Targets	• Reduced non-target effects with small quantity of paste in each bait and placed at specific places in bait station • Secondary poisoning risk reduced versus 1080 • Concentration/persistence risks reduced versus 1080 and brodifacoum
ECONOMIC	Viability	• Cost effective tool for target pests • Use of a known toxin with a well understood mode of action

		(absorption, metabolism, excretion)
	Growth	• Stimulate innovation in NZ Pest Control industry • Application of more effective VTA tools/methods • Development of toxin for pest where there is currently no registered product(i.e. stoats)
	Employment	• Create new employment opportunities as the new PAPP substances will be less hazardous for professionals to handle than 1080 • Maximise opportunities for local employment in use of ground control VTA products
SOCIAL	Awareness and support	• Create opportunities for involvement with an alternative to 1080 • PAPP can be used as humane toxin (VTA) on target species • Antidote (methylene blue) available for non-target species, e.g. dogs
	Enhancing sustainability of livelihoods	• Promote a healthy and safe living environment with minimal risks of secondary poisoning
	Humaneness	• PAPP is a relatively humane toxin when compared with other approved VTA toxins
CULTURAL	Sense of place "Turangawaewae	• Helping recreate/protect a distinctive (unique) habitat
CONSENTS / REGULATORY	Consents for control	• PAPP Paste B does not trigger hazardous properties that justify need to be registered as a restricted poison therefore there should not be a need to add PAPP Paste B to 'Controlled Substances Licences' • As an unrestricted poison there will not be the protracted consent process that causes long delays to using/control with restricted poisons • This would not pre-empt need to obtain other consents, e.g. DoC or consultation where needed, e.g. iwi

4.1.2.1 Mode of action, metabolism and species selectivity of PAPP is known and understood

PAPP has a known mode of action that is well-understood and has/is used already as a therapeutic agentPAPP administered parenterally or orally causes the oxidation of haemoglobin to methaemoglobin. Since the latter has an increased affinity for and sequesters absorbed cyanide, the initial overseas studies on PAPP were focused on its potential use in humans as a prophylactic for cyanide poisoning. PAPP-induced partial methaemoglobinaemia in humans protects against cyanide toxicosis.

Early studies on PAPP therefore provided data on the effects of PAPP as a therapeutic agent in humans. It was then discovered that the extent to which a given dose of PAPP induces methaemoglobin formation varies between species. Notably, it was found that the extent of methaemoglobinaemia induced by PAPP in canids (members of the dog family including foxes) was considerably higher on a dose per kilogram of live-weight basis than for other species. This is because canids have a higher capacity than humans or rodents to convert PAPP by hydroxylation at the para amino position to form parahydroxylamino propiophenone (PHAPP). This is the agent primarily responsible for the catalytic oxidation of the haem group in haemoglobin to

methaemoglobin. This, in addition to their relatively low levels of methaemoglobin reductase (an enzyme which reduces methaemoglobin back to normal haemoglobin), means canids are more susceptible to ingested PAPP than many other animals. This conclusion has led on to the evaluation of PAPP as a new and somewhat target-specific toxicant in bait for use as a vertebrate toxic agent.

4.1.2.2 Availability of antidote

In the event of accidental poisoning, PAPP has an antidote. The antidote is methylene blue and has been used for over 100 years for the treatment of nitrate poisoning in ruminants and is currently registered as a pharmaceutical in the US for the treatment of methaemoglobinaemia in humans. The effectiveness of methylene blue as an antidote has been demonstrated (*Confidential Appendix, 11-1)*.

4.1.2.3 Control of target pests (stoats, feral cats) and protecting native species.

The proposed use of a PAPP paste for mustelids, e.g. the stoat (*Mustela erminea*), or for feral cat (*Felis cattus*) control is for application in a ground meat bait placed in bait stations by ground-based hunters. The doses of toxin required are small. The recommended bait dose for stoats for example is small; ~35 mg bait (no more than half size of standard green pea in size) of PAPP Paste A enclosed in ~ 1 tsp of minced meat.

Stoats

The stoat is about 300 mm long, and is light brown colour with a black tip on the tail. They are widely distributed, throughout the New Zealand mainland and also on many inshore islands within 1.2 km of the mainland shore. Stoats are carnivores, existing on eggs, birds, rats, mice, lizards, and insects. They will take almost any live prey up to a kilogram in size. The stoat is also a prolific breeder having 6-12 kits in a single litter per year, but the breeding actually takes place, in the early summer of the previous year. Young females are generally inseminated in the nest prior to weaning and are able to keep the fertilized egg implanted, but not active, until they permit it to gestate up to a year later. Gestation takes approximately 30 days. Kits are able hunters from 5 weeks of age and have generally begun dispersing by 2 months.

Since their introduction in the 1860's, this successful breeding strategy has made stoats one of the primary causes of extinction for many of New Zealand's ground nesting and cavity nesting species and is responsible for the continued decline of such species as kaka, kiwi, takahe, whio (blue duck) and remnant mainland seabird colonies. They also limit options for recovery of many critically

endangered species, such as kakapo, by occupying key habitats that are critical to the expansion of these populations.

Significant conservation effort is expended in the localized control of stoats to benefit threatened species. Much of this work is undertaken by community initiatives on both private and public land. The Department of Conservation undertakes wide spread stoat control to protect kiwi, whio and kaka populations at many sites throughout New Zealand. Stoats have also been eradicated from several islands within the Fiordland National Park and this programme continues with the ongoing efforts to remove stoats from the 22,000 ha Resolution Island. Additionally, stoats along with other pests are to be eradicated from Rangitoto Island in the Hauraki Gulf as part of a restoration programme.

Currently there are between 85,000 to 90,000 humane stoat traps deployed throughout New Zealand. These traps kill the animal by crushing its skull after which the animal needs to be removed and the trap re- set and re-baited by hand. To ensure traps operate effectively traps are cleared on average 10 times per year. At current contract rates of $6 per service of each trap, approximately $5.4M worth of effort is expended annually to treat around 540,000 hectares or 2% of the total land mass of NZ.

The major cost associated with stoat control is the frequent servicing requirement of each trap to ensure it is clear of dead animals.

Trials with PAPP (as PAPP Paste A) carried out with the Department of Conservation have clearly demonstrated that 5 days baiting using a PAPP Paste for stoat control equates to approximately 3 months of an equivalent trapping regime. This means that by using the new PAPP bait, conservation organisations will be able to control 13,500,000 hectares, an increase in the control area of 500%, for the same budget currently expended on 540,000 hectares. This increase in the control of stoats will have a significantly beneficial effect on the recovery and preservation of indigenous New Zealand wildlife. Scarce conservation funding will be better utilized through the use of the new substances. Kiwi and other native birds will be protected over larger areas.

Feral cats

Feral cats are probably the descendants of those left by sealers and whalers early in the settlement of New Zealand. At present feral cats are found throughout the country, both in forested areas and on farmlands of the North and South Islands, Stewart Island and on some of the outlying islands. Cats were deliberately released to the wild in the 1800's to control rabbit populations. However, the value of feral cats in controlling rabbits is far outweighed by the effect they have had on some native birds and reptiles. Cats have been credited with causing the extinction of the Stephen Island wren and the Chatham Island fernbird.

Feral cats have also been instrumental in the declines of kakapo, black petrel, yellow eyed penguin, kiwi, and weka, as well as grand and Otago skinks. In combination with other predators (mustelids and rodents) cats are accelerating the declines of threatened fauna in NZ. For example, bird counts undertaken subsequent to the eradication of cats from Little Barrier Island showed significant increases in many species including the stitchbird.

Control of cats has been undertaken at many sites throughout New Zealand for conservation purposes. Cats are under ongoing control at some mainland seabird colonies, kiwi sanctuaries and reptile management sites and have also received long term management on Stewart Island to stabilise the decline in kakapo prior to transfer to predator safe sites. Cats have been eradicated from Little Barrier Island and also from islands within the Kermadec group.

However, current control methodology is via kill traps and leg hold traps. These control methods are labour intensive and as such with budget restraints, mean that these efforts while admirable do not have any significance for large parts of our conservation estate. In addition, few, if any, meet current humane standards. Welfare is understandably an important issue particularly when cats are targeted for control.

4.1.2.4 Animal welfare

PAPP has also been demonstrated to be a very humane toxin. Table 19 summarises data from three studies on target species (two on stoats and one on feral cats) that monitored the inset of symptoms and time to death. The key parameters of note in welfare assessment of a VTA are the time to onset of symptoms, the duration of symptoms and the severity of symptoms induced by toxic doses in target species. When these symptoms and times are compared to other VTA toxins (Table 20) it is clear PAPP is a most humane toxin. It is the only VTA which has been developed with humaneness as a primary consideration. Intoxicated stoats and feral cats become sleepy and lethargic before lapsing into unconsciousness followed by death.

Table 19: Effects and time to mortality for target species (i.e. stoats, cats)

Reference	Species	Onset of symptoms	Duration of symptoms prior to unconsciousness	Time to death	Signs prior to unconsciousness
Fisher, O'Connor, Murphy (2005)	Stoat	20 min	~ 15 -20 min	40 min	Lack of co-ordination and lethargy
Confidential Appendix 11-7	Stoat	17 min	~ 20 -27 min	44 min	Lack of co-ordination and lethargy, sleepy; no nausea or vomiting
Confidential Appendix 11-	Cat	36 min	~ 40 – 46 min	82 min	Lack of co-ordination and lethargy, sleepy, short

13					period of retching in some animals (one minute); reduced by low fat bait

Table 20: Comparison of mean times to onset of symptoms, effect on target species and times to death in possums following ingestion of toxic baits (from Morgan *et al,* 2001)

Toxicant & ranking of humaneness	Mean time until onset of sickness	Sickness behaviour	Duration of sickness behaviour	Mean time until death
Cyanide	2 min	Ataxia, impaired co–ordination, breathlessness, muscular spasms	12 min	14 min
Zinc phosphide (70-80 mg/kg)	1.5 hrs	Anorexia, vomiting, dyspnoea, slight convulsions, ataxia	1.9 hrs	3.4 hrs
1080	3 hrs	Anorexia, ataxia, occasional retching, spasms, breathlessness, laboured breathing	8.5 hrs	11.5 hrs
Phosphorous	5 hrs	Retching, vomiting, hunched posture, intermittent repositioning, ataxia	13 hrs	18 hrs
Cholecalciferol	5 days	Loss of appetite, lethargy, breathlessness	3.5 days	8.5 days
Brodifacoum	16 days	Anaemia, haemorrhage, loss of appetite, hunched posture, anorexia.	3 days	19 days

4.2 Provide an assessment of those risks, costs, and benefits identified in Section 4.1 which might be significant.

Significant Risks

The identification of the risks of manufacturing PAPP Paste1 or PAPP Paste 2 and when using within a meat bolus (PAPP Ready-to-use Bait) considered these substances through the product life cycle from manufacture, storage, transport, use as VTA and then disposal. The most significant risks are summarised in Table 21 and the likely magnitude of these risks in Table 22.

PAPP Paste A is classified as a 6.1B (oral toxicity), 9.3A (for terrestrial vertebrates) and 9.1C (for aquatic toxicity). However it is clear from a review of the toxicity data available on PAPP that the

6.1 oral classification arises from the susceptibility of a few species (e.g. cats, stoats) that metabolise PAPP differently to other species such as humans. This indicates that the risk to people from exposure to PAPP Paste A during manufacture, from an accidental spillage, or occupational exposure, or in use as a VTA, is not as potentially serious or significant as the 6.1 classification might otherwise indicate. PAPP is also used as a medical (therapeutic) treatment for administration to animals including humans in the event of cyanide poisoning. Furthermore the amount of paste to be used in a bait (i.e. enclosed in a meat bolus) is very small (~35 - 40 mg PAPP Paste for a stoat and ~ 80 mg for a feral cat) so any potential adverse effects arising from the accidental contact or ingestion will be minimised by the concentration/amount (relative to body weight) and the species (how PAPP is metabolised). The 9.3A classification for PAPP Paste A is also a consequence of the susceptibility of the same aforementioned species to PAPP and to specific bird species (duck LD_{50} 38 mg/kg/b.w.). However the risk can be managed by default by the small amount of PAPP needed for the target species, but also specifically by using the substance for ground-based pest control where a bait station can be used that can exclude non-target species and also be located where there is nil or limited access to domestic animals. Carnivores are more susceptible that birds to PAPP and the hand placement of baits in appropriately designed bait stations can manage this risk.

PAPP Paste B and the PAPP Ready-to-use Bait have 6.1D acute oral classifications and these lower classifications arise from the lower PAPP active ingredient concentration. Potential risks for these substances would be managed as already described for PAPP Paste A as the amount of PAPP active in the bait station for a target species would be the same.

Table 21: Summary of potential significant risks of PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait assuming the HSNO default controls are applied

Potential significant risk	Lifecycle step	Hazardous Property	Potential adverse effect/impact
Accident or packaging failure causing spillage (land, water)	Manufacture Storage Transport Use Disposal	Toxic (PAPP Paste A -6.1B oral) (PAPP Paste B - 6.1D oral) (PAPP Ready-to-use Bait – 6.1D oral) Ecotoxic (PAPP Paste A – 9.1D, 9.3A) (PAPP Paste B – 9.3B) (PAPP Ready-to-use Bait – 9.3C)	Human health Aquatic environment Terrestrial environment
Occupational exposure	Manufacture Use Disposal	Toxic (PAPP Paste A -6.1B oral) (PAPP Paste B - 6.1D oral) (PAPP Ready-to-use Bait – 6.1D oral)	Human health

Potential significant risk	Lifecycle step	Hazardous Property	Potential adverse effect/impact
Contamination during dispensing of paste bait or preparation of ready-to-use bait	Use	Toxic (PAPP Paste A -6.1B oral) (PAPP Paste B - 6.1D oral) (PAPP Ready-to-use Bait – 6.1D oral) Ecotoxic (PAPP Paste A – 9.1D, 9.3A) (PAPP Paste B – 9.3B) (PAPP Ready-to-use Bait – 9.3C)	Human health Aquatic environment Terrestrial environment
Accidental poisoning of non target species (dogs, domestic cats, some bird species)	Use Disposal	Ecotoxic (PAPP Paste A – 9.3A) (PAPP Paste B – 9.3B) (PAPP Ready-to-use Bait – 9.3C)	Terrestrial environment
Incorrect disposal	Use Disposal	Ecotoxic (PAPP Paste A – 9.1D, 9.3A) (PAPP Paste B – 9.3B) (PAPP Ready-to-use Bait – 9.3C)	Human health Aquatic environment Terrestrial environment

The magnitude of risk should a potential risk event occur was then considered and summarised in Table 22.

Table 22: The magnitude of risk for each potential event

Event that leads to exposure	Distribution of effects (geographic)	Distribution of effects (demographic)	Distribution of effects (temporal)	Reversible/ Irreversible	Voluntary/ Involuntary	Magnitude (Consequence)
Accidental discharge into water, land from spillage	Localised	Manufacturing workers Users Local community and iwi	Short term	Reversible	Involuntary	Minimal
Occupational exposure	Localised	Manufacturing workers Users	Short term	Reversible	Voluntary	Minimal
Contamination (equipment, surrounding material) during use	Localised	Users Local community and iwi	Short term	Reversible	Involuntary	Minimal
Access to bait by non target species	Localised	Local community and iwi	Short term	Reversible/	Voluntary - Involuntary	Minimal - minor
Incorrect disposal	Localised	Users Local	Short term	Reversible	Involuntary	Minimal

Event that leads to exposure	Distribution of effects (geographic)	Distribution of effects (demographic)	Distribution of effects (temporal)	Reversible/ Irreversible	Voluntary/ Involuntary	Magnitude (Consequence)
		community and iwi				

Definition of the Magnitude descriptions used to assess the qualitative magnitude of risk

Description	Definition
Minimal	Mild, reversible effect on human health (1-2 people) Environmental effects highly localised/contained- minimal environmental impact
Minor	Mild, reversible effect on human health (up to 10 people) Environmental effects localised and minor - reversible environmental impact
Moderate	Reversible, adverse effect on human health (> 10 people) Environmental effects localised and moderate - reversible environmental impact
Major	Serious, reversible, adverse effect on human health (>10 people) Significant, irreversible, adverse effect on human health (up to 10 people) Environmental effects localised and irreversible - no species loss
Massive	Serious, irreversible, adverse effect on human health (> 10 people) Environmental effects widespread and irreversible - species loss

Significant Costs

No significant potential costs have been identified from the future potential use of PAPP Paste A, PAPP Paste B or the PAPP Ready to use Bait as Vertebrate Toxic Agents (VTA's). There has however been significant cost in the research and development of PAPP containing VTA toxicants to get to this point.

Significant Benefits

The hazardous classifications for PAPP Paste A are 6.1B (oral), 9.1C and 9.3A; for PAPP Paste B are 6.1D (oral) and 9.3B; and for PAPP Ready-to-use Bait, 6.1D and 9.3C. Only PAPP contributes to the overall hazardous classification of the substances a the other components in these substances are non-hazardous or are at a low concentration or under the cut-off concentrations.

The active ingredient PAPP is a chemical with a known and well-understood mode of action and long history of use. PAPP causes the oxidation of haemoglobin to methaemoglobin in the blood. Since the latter has an increased affinity for and sequesters absorbed cyanide, early documented studies on PAPP were focused on its potential use as a therapeutic agent in humans and specifically in cases of cyanide poisoning.

It was then discovered that the extent to which a given dose of PAPP induces methaemoglobin formation varies between species. Some species, cats and stoats, are susceptible to PAPP. This has

meant it has been possible to develop highly effective species specific VTA products while minimising potential adverse effects to other non-target species, e.g. humans, some bird species.

PAPP has been shown to be a relatively humane (observations of symptoms of poisoning) and fast acting toxin when compared to other active ingredients in existing VTA products. Anoxia is the cause of death and this occurs without appreciable pain or discomfort in much that same way as anoxia induced by carbon monoxide induced carboxaemia also causes anoxia. Less susceptible animals that are accidentally exposed to PAPP suffer only a partial methaemoglobinaemia that is transitory and causes no clinical sequalae.

In the event that that secondary poisoning did occur, either directly or indirectly, an antidote (methylene blue) is available for PAPP. A further advantage in the use of PAPP is that its effects can be reversed, even in late stages of toxicosis, by the administration of methylene blue. Animals treated promptly and effectively with the antidote can fully recover even from near terminal late stage toxicosis induced by PAPP. Such antidotes are not available for existing canid control agents such as sodium fluoroacetate ("1080"). The availability of an antidote is also considered advantageous where there is a risk of exposure to working dogs to the bait.

There is no evidence to suggest that PAPP (as PAPP Paste A, PAPP Paste B or the PAPP Ready-to-use Bait) is bio accumulative or persistent in the environment.

There is no evidence that ingestion of sub-lethal doses of PAPP would have a detrimental (irreversible) effect on the target pest species or non-target species (including humans).

PAPP Paste A, PAPP Paste B or the PAPP Ready-to-use Bait are effective as a VTA for the target pest species. These substances offer an alternative pest management tool to the use of 1080 in ground-based operations. These substances would be the first approved VTA's specifically designed for stoat control and would also have potential for control of feral cats. Present pest control requires live trapping which is time-consuming and costly. A species specific VTA using PAPP as the toxin would mean more effective utilisation of resources so more forested area with at risk bird species can be protected from the predator pests. This will assist in the natural recovery of bird populations by protection of eggs and chicks.

4.3 Provide an assessment of any particular risks, costs and benefits which arise from the relationship of Māori and their culture and traditions with their taonga, or which are, for other reasons, of particular relevance to Māori.

At the inception and during the continuing development of these new PAPP baits there has been on-going dialogue (communications and presentations) with the ERMA Maori Advisory Group, iwi and other interest groups (Table 23 and *Confidential Appendix 10*)

Consultation with Maori on early cage trials on PAPP in stoats and cats and on small scale field trials was undertaken through discussion with the Ngai Tahu HSNO committee and by Department of Conservation with iwi at Waitutu. In addition, the research programme was discussed in detail with iwi on the Chatham Islands where a small weka study was undertaken to monitor potential effects on a non-target ground dwelling bid species that might eat meat bait if they were able to access the bait.

One of the drivers for the research on PAPP has been to respond to the desire by Maori for new ecofriendly humane toxins with minimal non-target side effects to complement trapping for the protection of *taonga.* This was illustrated by PAPP being included in the future focused parts of Objective 3 in a Lincoln University FRST programme entitled Smart Pest Control (PROJ-12023-ECOS-LIN), which was initiated in 2007. In this programme a goal for community and Maori-led pest control was to include evaluation of the suitability and effectiveness of new ground control tools for feral cats and stoats using cost-effective and efficacious alternatives to 1080 and brodifacoum.

PAPP is specifically a focus in this objective and has been discussed alongside other tools at hui during 2007-2009.

The Science Leader of the FRST programme, Dr Shaun Ogilvie, is Maori (Te Arawa and Ngati Awa) and has committed his research career to ecological issues that are of direct relevance to Maori. Prior to the development of this programme that involved Connovation Ltd there was much dialogue with Maori. The key point for Maori is that taonga species are under serious threat from animal pests, and Maori have made it clear that they have a need for technologies that can reverse this threat. A focus is on developing smart tools for the control of vertebrate pests. The smart tools such as PAPP that arise from research and development are outcomes that are of direct relevance to Maori groups involved in this collaborative research programme, and to other kaitiaki around the country that have concerns about the impacts of animal pests.

Also ERMA has had a representative on the task force for this FRST programme and has visited Connovation with Maori colleagues from ERMA. PAPP was a focus for discussions at these meetings.

In 2008 the applicant had several contacts with the HSNO Advisory Committee at Ngai Tahu. A discussion was held on PAPP, feedback received and a presentation on PAPP was provided including a briefing paper on PAPP specifically for the Ngai Tahu HSNO committee.

Products that are alternatives to traditional vertebrate pest control tools (such as 1080 bait) are favoured by many Maori. The use of PAPP baits will have significant cultural outcomes for Maori in the protection of native flora and fauna.

Table 23: Some examples of Consultation during the development of PAPP for predator controls.

Date of interaction.	Focus	Outcome
Sept/Oct 2006	Discussions between Connovation and the Maori Advisory Groups at ERMA including a visit to the Connovation site in Auckland.	Summary information provided to ERMA Maori group and advice received on development plans. Ngai Tahu HASNO committee recommended for future contact
March-May 2008	Discussion re PAPP development and early field trails in stoats and cats with Ngai Tahu HASNO committee.	Questions raised and answers provided at a meeting at Ngai Tahu. The importance of mitigating non-target effects was noted. Briefing paper provided to Ngai Tahu.
Dec- April 2009	Presentation and discussion re PAPP development and early field trials in stoats and cats with Tuhoe	Tuhoe do not favour any poison use. Preference is for trapping but Tuhoe are cautiously considering the merits of PAPP if it will enable greater areas of land to be protected from stoats impacts on kiwi.

4.4 Provide an assessment of any risks, costs or benefits to New Zealand's international obligations.

NZ has international obligations regarding welfare and also residues in meat. The VTA products containing PAPP has benefits for both, and assists in our obligations with regard to international biodiversity.

4.5 Provide information on the proposed management of the substance.

The PAPP Paste A triggers the hazardous classifications of 6.1B (oral), 9.1D and 9.3A , the PAPP Paste B has classifications of 6.1D (oral),and 9.3B and the PAPP Ready to Use Bait has 6.1D and 9.3C classifications. Controls require Tracking and for the substance to be under the control of an Approved Handler if not locked up apply only to the PAPP Paste A.

The HSNO Default Controls are expected to safely and effectively manage the potential adverse effects, as identified in Sections 4.1 – 4.4 of this application. Pest control contractors would be anticipated to be required to add PAPP to their controlled substances licence if using as PAPP Paste A but not necessarily for PAPP Paste B nor the PAPP Ready to use Bait. Other non-HSNO controls (e.g. ACVM Act 1997) would have conditions of use and sale applied but these would need to be compatible with the hazardous classifications and proposed use.

The PAPP Paste A and PAPP Paste B would be required to be approved as Vertebrate Toxic Agent s(VTA) under the ACVM Act 1997 before being offered for sale for the control of any target species. An application specific to one of the target species has already been submitted.
The product label will provide information about the product, what to use for and how, and advice on other life cycle stages (storage, handling, and disposal) and first aid information.

The applicant will be manufacturing the PAPP Paste A or PAPP Paste B at a facility approved for the storage and manufacture of toxic VTA's. The applicant has a current NZFSA Good Manufacturing Practice (GMP) approval.

Health and Safety in Employment Act

This legislation covers the need to safeguard employee's safety and well-being. The applicant provides training, provides personal protective equipment and has operating procedures as examples.

Any waste, residues or contaminated packaging from the facility are disposed of through a licensed waste management operator.

Land Transport Act

The requirements of NZ5433:2007, Transport of Dangerous Goods on Land, will be followed. These include controls for labelling, storage, packaging size and type.
PAPP Paste A will be identified as a Dangerous Good for transport and as UN NO. 2588, PESTICIDE, SOLID, TOXIC, N.O.S (contains para-aminopropiophenone), Class 6.1, Packing Group II.

The hazardous classifications for PAPP Paste B and the PAPP Ready to use Bait will mean these two substances will be non-regulated for transport.

The applicant will provide Safety Data Sheets for the substances.

In addition to the default codes that are triggered by the HSNO classifications for the substances the applicant and users would be required to comply with additional statutory requirements that relate to the use of VTA's in NZ:

Wildlife Act 1953;
Wild Animal Control Act 1977;
Reserves Act 1977;
National Parks Act 1980;
Land Act 1948;
Ministry of Agriculture and Fisheries Act 1953;
Animal Pests Destruction Act 1967;
Local Government Act 1974;
Agricultural Pests Destruction Act 1967;
Animals Act 1967,
Biosecurity Act 1993;
Health Act 1956;
Health and Safety in Employment Act 1992;
Dairy Industry Act 1952;
Food Regulations 1983;
Meat Act 1981;
Agricultural Compounds and Veterinary Medicines Act 1997; and,
Hazardous Substances and New Organisms Act, 1996.

Users of VTA's on some lands will require an approval (AEE), where appropriate, under section ss.5, 6, 30 and 31 of the Resource Management Act 1991. Consultation with iwi may be required as part of this process. Accordingly, it is possible that at some sites it may be unacceptable to iwi for a specific bait type to be used.

Users of any of the VTA baits on the conservation estate will have to comply with s26ZR of the Conservation Act 1987 which permits only warranted officers, or any person authorised by the Director General of Conservation, to control pests using a hazardous substance. If the Department of Conservation considers using any PAPP bait, it may be expected to consult with iwi as part of its obligations under section 4 of the Conservation Act 1987.

4.6 Provide an overall evaluation of the combined impact of all of the risks, costs and benefits set out in sections 4.2, 4.3 and 4.4.

The next table summarises the assessment of residual risk assuming the HSNO Default Controls are followed. The level of risk at each life cycle stage for PAPP Paste A, PAPP Paste B and as PAPP Ready-to-use Bait are summarised (Table 24).

Table 24: Level of risk at each life cycle stage for PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait

Lifecycle Stage	Potential Adverse Effect	Magnitude of Adverse Effect	Likelihood of Adverse Effect Occurring	Level of Risk
Manufacture, storage, transport	Spillage /exposure resulting in adverse human health effects (PAPP Paste A as 6.1B (oral), or PAPP Paste B or a Ready-to-use Bait as 6.1D (oral); or adverse effects to organisms in the environment (PAPP Paste A as 9.3A and PAPP Paste B as 9.3B, PAPP Ready-to-use Bait is 9.3C)	Minimal to Moderate	Highly improbable	Negligible to Minimal
Preparation of ready-to-use bait, storage, transport	PAPP Ready-to-use Bait resulting in adverse human health effects or adverse effects to organisms in the environment.	Minimal to Moderate	Highly improbable	Negligible to Minimal
Use as VTA	Spillage resulting in adverse human health effects or adverse effects to organisms in the environment.	Minimal	Improbable	Negligible to Minimal
	Poisoning of non target species, specifically birds	Moderate	Possible	Minimal to moderate
Disposal	Disposal resulting in death or adverse effects to organisms in the environment.	Minimal to Moderate	Improbable	Negligible

Section Five – International Considerations

5.1 ERMA New Zealand is interested in whether this substance (or any of its components) has been considered by any other regulatory authority in New Zealand or by any other country. If you are aware of this, please provide details of the results of such consideration. (Optional)

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Section Six – Miscellaneous

6.1 Provide a glossary of scientific and technical terms used in the application.

ACVM	Agricultural Compounds and Veterinary Medicines
Anorexia	Type of eating disorder
Ataxia	Lack of co-ordination, unsteadiness
Bilirubin	Yellow-orange compound produced by breakdown of haemoglobin in red blood cells
Canids	Dog family; also includes wolves, foxes, coyotes, jackels
Carnivorous	Meat eating
Cyanotic	Showing bluish colour in skin or mucous membranes due to not enough oxygen in blood
Cynmolgus	Type of monkey; long-tailed monkey or macaque
DNA	Deoxyribonucleic acid ; one of two types of molecules that encode genetic information
Dyspnoea	Difficult or laboured breathing; shortness of breath
EC_{50}	The molar concentration of a chemical, which produces 50% of the maximum possible response for that chemical
Epithelial	Outside layer of cells
ERMA	Environmental Risk Management Authority
Erythroid	Relating to red blood cells (erythrocytes)
Erythrophagocytosis	Disease of red blood cells
Excretion	Metabolic waste products eliminated from body
Exothermic	Produces increase in temperature/heat
Gavage	Material into stomach via tube
Genetic	Relating to control by genes

Haemoglobin	Protein molecule in red blood cells that carries oxygen from lungs to body tissues and returns CO_2 from tissues to lungs
Histopathological	Tissue changes that affect part or accompany a disease
HSNO	Hazardous Substances and New Organisms Act 1996
Hyperplasia	Condition in which there is an increase in the number of normal cells in tissue or organ
Idiopathic	Of unknown cause
Intraperitoneal	Within the peritoneal cavity; the area that contains the abdominal organs
Intravenous	Within a vein
Kupffer cells	Specialised macrophages in liver
LD_{50}	Median lethal dose
LC_{50}	Median lethal concentration
LOEL	Lowest observable effect level
Lymphocyte	Small white blood cell important in defending body against disease
Macrophages	White blood cells in tissues
Mammal	Animals, e.g. humans, cats, dogs, where females have mammary glands and both males and females have features such as sweat glands, hair as examples
Metabolism	A range of biochemical process that occur within living organisms; term commonly used for breakdown of food and its transformation into energy
Methaemoglobin	Brownish compound of oxygen and haemoglobin formed in blood
Micronucleus	Smaller of two nuclei
Mustelid	Member of weasel family (carnivorous mammal)
Oral	By mouth
Oxidation	Process or result of oxidising (convert to oxide by combining with oxygen , or to take away hydrogen as by action of oxygen)
PAPP	*para*-Aminopropiophenone
Parenteral	Entering the body by route other than alimentary canal
Pathological	Caused by or involving a disease
PHAPP	*p*-hydroxylaminopropiophenone; a metabolite of PAPP
Polymorphism	A variation in DNA that is too common to be due merely to a new mutation, i.e. > 1% of population

Prophylactic	A preventative measure
Proximal	Nearest too; opposite term is dsital
Renal	To do with the kidney
RMA	Resource Management Act
Ruminant	Mammal that digest plant-based food in first stomach (rumen), e.g. cattle, sheep
Serum	Fluid component of clotted blood
Sequesters	Binds or 'locks up' so not accessible or available
Sinusoidal	In form of a wave
Sub-chronic	Term 'chronic' refers to long-lasting or recurrent effect
Therapeutic	Beneficial or desirable effect/treatment
Tubular	In form of cylinder or tube
VTA	Vertebrate toxic agent

6.2 Provide here any other information you consider relevant to this application not already included.

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Section Seven – Summary of Public Information

7.1 Name of the substance(s) for the public register:

PAPP Paste A

PAPP Paste B

PAPP Ready-to-use Bait

7.2 Purpose of the application for the public register:

To manufacture PAPP Paste A, PAPP Paste B and a PAPP Ready-to-use Bait containing para-aminopropiophenone (PAPP) to be used as vertebrate toxic agents (Category B)

7.3 Use Categories of the substance(s):

Main category

3. Non-dispersive use

Industry category

0. Other

Function/Use category

39. Pesticides non-agricultural

Subcategory: Pest control products

7.4 Executive Summary:

The PAPP Paste A has hazardous classifications of 6.1B (oral) , 9.1D and 9.3A, the PAPP Paste B has hazardous classifications of 6.1D (oral) and 9.3B, and the PAPP Ready-to-use Bait has a hazardous classifications of 6.1D and 9.3C.

The active ingredient, para-aminopropiophenone (PAPP) is to be imported and used to manufacture PAPP Paste A and PAPP Paste B for use as Vertebrate Toxic Agents (VTA's). The PAPP Ready-to-use bait is manufactured by enclosing a small amount of PAPP Paste A within a minced meat ball (5 – 10 g). Typically this would occur just prior to placing the bait in the bait station under field conditions, but might need to be prepared prior to use and then transported to the site, so a separate approval is required. Efficacy data has been generated on PAPP paste as a hand laid bait in bait stations for the control or eradication of mustelids and feral cats. The hazard classifications indicate only the PAPP Paste A would trigger the HSNO Default Controls for an Approved Handler or Tracking. Default controls including those for Tracking and being under the control of an Approved Handler and as a Tracked substance can effectively manage any hazard and life cycle risk. The PAPP Paste A and PAPP Paste B would be subject to relevant controls under the HSNO Act and other statutory controls including but not limited to, the ACVM Act, and under some circumstances the RMA Act.

The PAPP Paste A, PAPP Paste B or PAPP Ready-to-use Bait can be disposed of by burying, e.g. 60 cm below ground level. Unused material, waste or residues containing PAPP can also be burnt in appropriate licensed incinerators. Compliance with these controls will safely and effectively manage any risk during the life cycle of the PAPP mixtures when used as a Vertebrate Toxic Agent.

Data available on PAPP indicates it is neither persistent nor bioaccumulative. PAPP is stable in the non-aqueous paste matrix under a range of conditions applicable to the proposed packaging types and storage conditions.

A PAPP containing bait would be particularly useful for stoats, because currently there are no toxins registered for use for this pest. Stoats continue to have an impact on a wide range of threatened birds, lizards and invertebrates in New Zealand, and there are few effective techniques available to control them. There is also potential to use PAPP as a toxin for feral cats. Therefore registration of an effective toxin that appears to show some relative specificity for certain animals and is lethal to stoats and feral cats at a low dose would be a significant advance for pest control. The development of PAPP as a toxin has been driven by the search for more humane poisons which will also have low residues in animals receiving sub-lethal doses.

PAPP has additional benefits when compared to existing approved toxins as it does not bioaccumulate in animal tissue which may lead to a risk of secondary poisoning of non-target vertebrates, e.g. dogs, and nor is it persistent in the environment. PAPP is also identified as being more humane in its effects on target species than most other toxins used in existing VTA products, and would be the first approved VTA product specifically targeting stoat control. Its application in pest control will create a significant saving in control costs and this saving could be redirected to stoat control on larger areas where sensitive and at risk species are endangered.

The approval of the PAPP Pastes and use in the Ready-to-use Bait would be additional new tools in the on-going programme of sustained pest control necessary to protect key endangered species on the New Zealand mainland.

CHECKLIST

Mandatory sections filled out	Yes
Appendices enclosed	Yes
Fees enclosed	No
Application signed and dated	Yes

Signed Date

References

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Confidential Appendices

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