Australian Government

Department of the Environment, Water, Heritage and the Arts

Invasive Animals CRC

Pharmacokinetics and methaemoglobin reductase activity as determinants of species susceptibility and non-target risks from sodium nitrite manufactured feral pig baits

REPORT FOR THE AUSTRALIAN GOVERNMENT
DEPARTMENT OF THE ENVIRONMENT, WATER, HERITAGE AND THE ARTS

March 2010

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This report should be cited as: Lapidge, S,J. and Eason, C.T. 2010 Pharmacokinetics and methaemoglobin reductase activity as determinants of species susceptibility and non-target risks from sodium nitrite manufactured feral pig baits. Report for the Australian Government Department of the Environment, Water, Heritage and the Arts. Canberra, Australia.

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Abstract. Vertebrate pesticides are used in Australia to manage populations of invasive pest species, including feral pigs, which threaten native ecosystems, damage crops and spread disease. Feral pigs are currently poisoned using actives that are considered by some to be inhumane and more suitable agents are being sought. Pigs are susceptible to methaemoglobin forming compounds, due to innately low levels of methaemoglobin reductase, and research has identified that sodium nitrite is a promising humane alternative active. To attain registration, a new vertebrate pesticide must however be species-specific in its toxicity (rare), or be presented in such a manner to demonstrate that it is safe for use around non-target species. Furthermore, it should be shown to represent a low risk of bioaccumulation and secondary poisoning, as is the case with sodium nitrite which has a half-life of one hour or less in those species tested. Here we present a risk analysis for the use of sodium nitrite used in manufactured feral pig baits. As pharmacokinetics of sodium nitrite are similar in different species, and it does not require biotransformation to an active intermediate, methaemoglobin reductase activity in red blood cells from different species is directly correlated with differences in acute toxicity. Primary risks, or susceptibility, have been calculated for 28 marsupial and nine eutherian mammal, four reptile and two bird species based on published doses and methaemoglobin reductase activity levels. Those species that have been previously recorded to sample manufactured feral pig baits, and will be susceptible to the likely bait dose used, are identified along with the percentage of a bait that they will need to consume. The current steps being taken to limited potential non-target poisonings, including an appropriate active to matrix ratio, are discussed.

INTRODUCTION

Currently, sodium fluoroacetate (1080), warfarin and yellow phosphorus are the toxins used to poison feral pigs, *Sus scrofa*, in Australia. However, the use of warfarin and yellow phosphorus has recently been assessed as inhumane (Sharpe and Saunders 2004; Cowled and O'Connor 2004). Sodium fluoroacetate is the most commonly used toxin, with it being added to various palatable bait substrates for poisoning pigs, such as grain, pellets, meat and manufactured baits (Hone 1984; Twigg *et al.* 2005; Cowled *et al.* 2006a). But whilst it appears markedly more humane than other current pig toxins (Cowled and O'Connor 2004; Sharp and Saunders 2004), it has come under scrutiny and is not favoured by animal welfare groups (Sherley 2004 and 2007; Cooper *et al.* 2007).

In 2005 a search was undertaken for other potential chemicals that would be more suitable for feral pig management, with sodium nitrite proving to be the lead candidate (Cowled *et al.* 2008). Proof-of-concept pen trials showed that it was highly efficacious in euthanasing pigs whether given by gavage or eaten in PIGOUT® baits (Cowled *et al.* 2008). Ironically, it is the very chemical that is use to preserve pig meat that is also highly toxic to the live animal. Because of the widespread use of sodium nitrite as a human food preservative there is a considerable amount of data on the chemistry and toxicology of this compound. This active agent acts by the humane, and Royal Society for the Prevention of Cruelty to Animals (RSPCA) supported (Sherley 2007), mode of action of methaemoglobinaemia, and so is preferred to 1080 on welfare grounds (Marks *et al.* 2004; Cowled *et al.* 2008). Another methaemoglobin former, para-aminopropiophenone (PAPP), is currently being developed for foxes, wild dogs and feral cats in Australia (Marks *et al.* 2004; Fleming *et al.* 2006), and stoat, ferrets and feral cats in New Zealand (Fisher *et al.* 2005; Fisher and O'Connor 2007; Murphy *et al.* 2007). Pigs are highly susceptible to the effects of methemoglobinaemia as they contain uniquely low levels of methemoglobin reductase (Smith and Beutler 1966; Agar and Harley 1972), the enzyme required to reverse the methemoglobin formation process. This inherent weakness has previously resulted in numerous reported fatal cases of domestic pigs being poisoned with nitrite (Robinson 1942; Gwatkin and Plummer 1946; Winks et al. 1950; London et al. 1967).

As with PAPP, nitrite kills through terminal hypoxia caused by methaemoglobinaemia. High methaemoglobin levels reduce the oxygen-carrying capacity of the blood and at toxic doses hypoxia and central nervous system depression precede death. Time to death for feral pigs is 1-2 hours with few visual symptoms (Cowled et al. 2008; Lapidge *et al.* 2009). This is a marked improvement on conventional vertebrate poisons. A further benefit of nitrite is that it is known to break down readily in the environment through biological reduction (e.g. Wanntorp and Swahn 1953; Sofia *et al.* 2004), limiting non-target poisoning risks and environmental contamination. A further benefit of the chemical is that methylene blue will reverse methaemoglobinaemia induced by sodium nitrite, or PAPP, and is an established antidote for nitrite poisoning in livestock.

Understanding mechanisms of toxicity, pharmacokinetics and receptor level effects are important for a number of reasons. These include development of antidotes, risk assessment, defining the susceptibility of non-target species, defining the risk of secondary poisoning or bioaccumulation, and also the risk of residues persisting in non-target species, including wildlife and livestock inadvertently exposed to sub-lethal doses. In the following sections we firstly examine the basis for species variation in response to xenobiotics and then review the pharmacokinetics of sodium nitrite and then receptor level processes as determinants of species susceptibility.

It is planned that formulated sodium nitrite will be delivered using the new HOG-GONE® matrix (Animal Control Technologies Australia P/L). The concept is based on the successful PIGOUT® bait matrix which is currently used to deliver 1080 to feral pigs (Cowled *et al*. 2006a,b), but was also designed as a potential vaccine carrier (Campbell *et al*. 2006; Cowled *et al*. 2008b). Improvements to the target-specificity of feral pig baiting campaigns have been substantial in Australia when compared to the use of grain and meat baiting materials (Cowled *et al.* 2006b). Preliminary field trial results for the HOG-GONE® matrix, which is harder and less pungent, indicate that the target specificity has been increased further (S. Lapidge, unpub. data; A. Bengsen, unpub. data). Notwithstanding, a thorough risk analysis is required for the potential field use of sodium nitrite if the chemical is to gain registration as a new vertebrate pesticide. This paper predicts the innate susceptibility to sodium nitrite for 28 marsupial and nine eutherian mammal, four reptile and two bird species based on published doses and methaemoglobin reductase activity levels. It highlights non-target species potential at risk for the use of HOG-GONE baits, and the methods being employed to minimise such risk. The risks of secondary poisoning, either through the consumption of sub-lethally doses or poisoned animals is also discussed.

Primary poisoning

Pharmacokinetics and species variation.

The metabolism and pharmacokinetics of a vertebrate pesticide are often determinant factors in its ultimate manifestation of toxicity, non-target safety and residue profiles. The metabolic deactivation of toxins results from the actions of enzymes whose primary function is believed to be to protect the body against the accumulation and undesirable effects of foreign compounds naturally present in food and in the environment. Metabolism and excretion are protective processes attempting to limit persistence in the body.

Species differences in sensitivity to an individual toxicant may be linked to variation in the pharmacokinetic differences for the compound in different species. Savarie *et al.* (1983) clearly demonstrated this with PAPP, with a seventy-fold difference occurring between the LD_{50} of a coyote and a Striped skunk or Golden eagle. Wood *et al*. (1991) later detailed that this was due to the metabolic activation of PAPP to a reactive, and more toxic, intermediate metabolite in susceptible species such as dogs. This is the case with 1080 and cholecalciferol. However, as is normal with toxic intermediates of other drugs or pesticides, metabolic processes in the body then go on to detoxify these intermediate compounds as well. In the case of 1080 and sodium nitrite the parent compound is itself highly water soluble; hence the normal metabolic processes that render a toxin more water soluble are less important with regard to their elimination from the body.

Receptor site interactions and species susceptibility

Fortunately the pharmacokinetics of the direct methaemoglobin (MtHb) former sodium nitrite is similar in different species as it does not require biotransformation to an active metabolite. As with the drug amrinone, there are rapid and similar patterns of absorption and excretion across a range of different species. Hence, extrapolation of chemical-receptor interactions can be used with greater confidence to predict the innate risk of sodium nitrite to non-target species. The receptor site for sodium nitrite poisoning is haemoglobin in the red blood cell. The mode of action of nitrite is the oxidization of the haem iron in red blood cells from the ferrous state (Fe2+) to the ferric state (Fe3+) to form MtHb. MtHb is incapable of carrying oxygen and cyanosis results, with death occurring if the dose is high enough (Egyed and Hanji 1987). The pattern of methaemoglobinaemic response induced when erythrocytes are exposed to sodium nitrite oxidant challenge will be a balance between MtHb formation and its subsequent reduction back to haemoglobin by the protective enzyme MtHb reductase.

The activity of the enzyme MtHb reductase varies in different animals, and is known to determine a species direct sensitivity to a direct methaemoglobin former (Smith and Beutler 1966; Stolk and Smith 1966; Agar and Harley 1972; Board *et al*. 1977; Chun-Lap Lo and Agar 1986; Whittington *et al.* 1995; Agar *et al.* 2000*;* Rockwood *et al.* 2003). Species differences in MtHb reductase are therefore critical when evaluating the risk to different species from MtHb formers such as sodium nitrite. Under normal conditions this enzyme is the only system within the erythrocyte that maintains haemoglobin in its oxygen-carrying reduced state. Toxicologically, MtHb reductase will therefore be the rate-limiting enzyme controlling the toxicodynamics of sodium nitrite's effect on the red blood cells. In theory, species with lower MtHb reductase activity convert MtHb back to haemoglobin more slowly than do species with higher activity, and will therefore be more susceptible to sodium nitrite. Conversely animals with greater MtHb reductase activity will be at less risk of sodium nitrite induced toxicity.

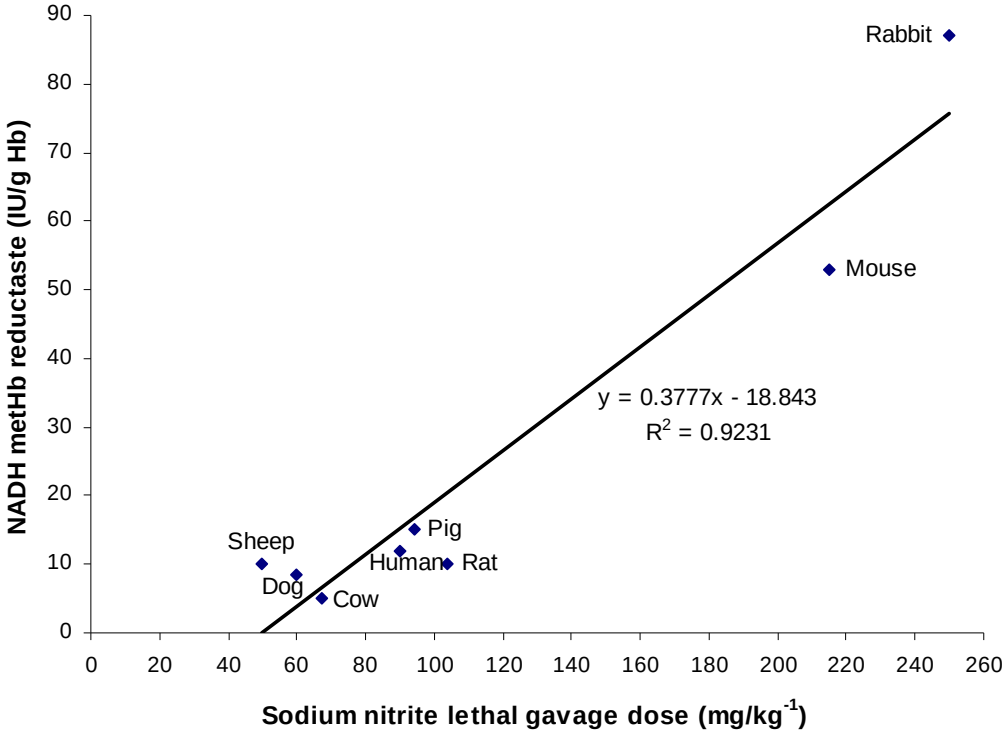
Correlating methaemoglobin reductase activity, body size, diet and risk

To test this hypothesis we collated all published acute sodium nitrite toxicity data and MtHb reductase activity, as generally determined through nitrite challenge. Data for eight eutherian mammal species were obtained (Table 1). In those species for which published data exists on both acute toxicity and on red blood cell MtHb reductase activity there is a strong correlation between susceptibility and MtHb reductase activity (r=0.961). Simple linear regression analysis revealed a highly significant ($F_{1,6}$= 72.0; $F_{0.001(1)1,6}$= 35.5; P > 0.001) relationship, with a line of best fit accounting for 92% of the variance with the equation y=0.3777x-18.843 (Fig. 1).

Table 1. Published sodium nitrite lethal gavage doses and NADH metheamoglobin reductase activities for eutherian mammals.

Species	Scientific name	Lethal gavage dose (mg/kg-1)	NADH metheamoglobin reductase (IU/g Hb)	Reference
Pig	*Sus scrofa*	90	12	Winks et al. 1950
Human	*Homo sapien*	94	15	Boink and Speijers 2001
Rat	*Rattus norvegicus*	104	10	Druckery et al. 1963
Mouse	*Mus musculus*	215	53	Rieman 1950
Rabbit	*Oryctolagus cuniculus*	250	87	Dollahite and Rowe 1974
Dog	*Canis lupus familiaris*	60	8.5	
Sheep	*Ovis aries*	50	10	Lewis 1950
Cattle	*Bos taurus*	67	5	Bartik and Pisac 1981

Figure 1. General linear regression between published sodium nitrite lethal gavage doses and NADH metheamoglobin reductase activities for eutherian mammals.



Underpinned by the comparatively straightforward nature of sodium nitrite pharmacokinetics extrapolation based on the regression analysis from individual species' MtHb reductase activity allows prediction of probable lethal doses in native Australian species. Further extrapolations are possible firstly to predict likely lethal doses of sodium nitrite in native Australian species. Secondly, based on animal size and eating habits, susceptible non-target species can be identified. The results of this modelling are summarised in Table 4 and identify susceptible non-target species that might

eat sufficient toxic pig bait. Those are Common brushtail possum, Northern brown bandicoot, Tammar and Swamp wallabies, and dogs.

Proofing model: direct non-target species testing

To examine the validity of the lethal dose predictions in Table 2 (for table2 information contact steven.lapidge@invasiveanimals.com), and to ascertain the direct risk to two key potential non-target species that have previously been observed to consume PIGOUT baits (Lapidge, pers. obs. and Cowled et al. 2006b), direct toxicity testing on Common brushtail possums and Tammar wallabies was undertaken by Landcare Research (New Zealand) and Connovation (New Zealand) respectively. Trials occurred in New Zealand where both species are invasive and the use of sufficient animals received ethics approval.

Pen trials were undertaken on 12 individually caged brushtail possums at the Landcare Research Animal Facilities in Lincoln, New Zealand. Maximum consumption by any individual possum was 229 mg/kg of sodium nitrite. Although five of the 12 possums showed visible signs of methaemoglobin formation (blue/cyanotic nose), none of the animals were affected behaviourally in terms of responses to stimuli, and as predicted no possums received a lethal dose and died. The model predicted a minimum lethal dose of 393 mg/kg. All possums were monitored for seven days following the trial, with the maximum weight changes being -3.3 % to +10.5 %, with all possums appearing healthy throughout the observation period (Fisher et al 2009).

Tammar wallaby trials were undertaken in outdoor pens in a new animal research facility at Rotorua, New Zealand. In the toxic trials nine of the 12 wallabies would not consume any toxic matrix after sniffing the mixture. Three wallabies consumed material receiving nitrite doses of 894, 335 and 625 mg/kg respectively. All doses were lethal, as predicted in Table 2 (minimum lethal dose 245 mg/kg), with the mean time to first symptoms being 63 min and 157 min to death. The three wallabies that dies all displayed lethargy, shallow breathing, slight leg spasms, and unconsciousness before death (Shapiro and Eason 2009).

Additional non toxic trials were undertaken by the Tasmanian Department of Primary Industries and Water to assess the attractiveness of the HOG-GONE® baits to Bennett's wallaby (*Macropus rufogriseus*, n=5) and Tasmanian pademelon (*Thylogale billardierii*, n=17) held at the department's Launceston facilities. Twelve HOG-GONE® baits were placed in the wallabies 0.8ha enclosure and monitored using motion sensitive video camera continually for 5 nights. Although most wallabies investigated the baits at least once, they generally recoiled abruptly once smelling the bait material (Fish and Statham 2009). No wallabies showed any inclination to consume the baits.

Although low sample sizes for possums (n=5) and tammar wallabies (n=3), results from toxic trials supported the lethal dose predictions made in Table 2, and provide some validity to the model approach presented. Results from the overall trials do however clearly indicate that marsupials are generally repelled by the HOG-GONE® bait matrix itself or the smell of formulated

sodium nitrite. Despite formulation, the nitrite smell is still present in the toxic matrix and the chemical is extremely salty to taste.

Secondary poisoning

Pharmacokinetics of sodium nitrite

There is no evidence that sodium nitrite exerts selective toxicity based on classical species variation in the metabolism or pharmacokinetics of this compound in mammals. Analysis of the publications on the fate of sodium nitrite in animals and humans enables comparisons across different species. All these publications indicate that sodium nitrite is rapidly eliminated by different animals and humans. Since sodium nitrite does not require biotransformation to be active there is a close correlation between the concentration of sodium nitrite in the blood and methaemaglobin induction. One of the more detailed recent publications in this field by Kohn et al (2002) examines time and dose-dependent relationships between exposure to nitrite and induction of methemoglobinemia in rats. The authors report the significant toxicodynamic processes as absorption of nitrite following oral ingestion, elimination from the plasma, partitioning between plasma and erythrocytes, binding of nitrite to haemoglobin and methaemoglobin, and the free radical chain reaction for haemoglobin oxidation. Peak plasma levels of nitrite were achieved in both sexes of rats approximately 30 minutes after oral exposure, and peak methaemoglobin levels were achieved after 100 minutes. The t(1/2) for recovery from methemoglobinaemia was 60 to 120 minutes depending on dose and route of administration.

We have reanalysed the raw data from Kohn et al (2002) to elucidate the time course of plasma nitrite in rats at different doses and this is summarised in Table 3. The plasma elimination t(1/2) for sodium nitrite in rats ranges from 42.0 to 62.5 minutes after oral dosing. These values are similar to those quoted in humans (Dejam et al. 2007), who showed a plasma elimination half-life of 42 minutes. They also correlate closely to plasma elimination t(1/2) values of 29.0, 30.0 and 34.0 minutes in sheep, dog and ponies reported by Schneider and Yeary (1975).

Table 3. Plasma elimination t(1/2) in minutes with lower and upper 95% confidence limits for sodium nitrite in rats (calculated by Frampton from data in Kohn *et al.* 2002).

Dose	Route	t(1/2) male	t(1/2) female
20	i.v	19.8 (16.9-23.8)	28.3 (24.4-33.8)
40	oral	42.1 (37.6-47.7)	55.5 (47.9-65.8)
80	oral	42.0 (33.9-55.0)	62.5 (58.8-66.7)

In an unpublished report (MRI 2004) confirmation that sodium nitrite is rapidly eliminated from the blood is provided in both rats and mice. In rats orally dosed with 80 mg/kg peak plasma concentrations were achieved at 30 mins after dosing and these decreased to below the limit of detection after 8 hours. In mice peak plasma concentrations occurred after 10 mins and sodium nitrite was undetectable in the blood after 4 hours. Earlier publications on the biotransformation of sodium nitrate indicate that conversion to nitrite is important for toxicity, however nitrite is very quickly converted and may not be readily detected, therefore methaemoglobin formation was often used as an indicator of nitrite formation (Ward et al 1986). The rapid elimination of nitrite predicted by Ward et al (1986) has been confirmed by Kohn et al (2002) and other research groups. Nitrite is reportedly broken down to hydroxylamine, ammonia and urea (Mascher and Marth 1993). Kovacs *et al.* (1960) reported that the concurrent administration of sodium bicarbonate was found to increase the lethality of sodium nitrite, probably due to the creation of low acid conditions in the stomach, reducing breakdown to ammonia and aiding absorption.

The pharmacokinetic data on sodium nitrite in such diverse species as mice, rats, sheep, dog, ponies and humans coupled with information on the toxicodynamics of sodium nitrite suggests similar Cmax, t(1/2), and rapid clearance would occur in other animal species and we could expect elimination of sodium nitrite following sub lethal exposure within 12 hours.

To help distinguish between different vertebrate pesticides and add some clarity to risk assessment, Eason et al (2008) has recently classified compounds used for animal pest control into 4 groups, based on their persistence in sub-lethally exposed animals. The criteria for the 4 groups and the allocation of different compounds to these groupings are described below and in Table 4.

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 4-7 days.

On the basis of what we can identify in the literature regarding sodium nitrite we believe it appropriate to include it in Group 1 and distinguish it from the more persistent compounds in Groups 2-4.

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 poisons 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

Risk to non-target species from vertebrate pesticides can be exacerbated if they bioaccumulate in the food chain. Pharmacokinetic analyses in different animals and humans have shown that unlike some common rodenticides e.g. brodifacoum, sodium nitrite is unlikely to cause secondary poisoning due to bioaccumulation. Furthermore it is unlikely to cause any significant food web contamination when used repeatedly as a vertebrate pesticide because it will be rapidly excreted.

Table 4. Summary of classification of vertebrate pesticides based on comparative pharmacokinetics and expectation for persistence of residues in sub-lethally exposed target or non-target species (adapted from Eason *et al.* 2008 to include sodium nitrite).

Group	Compound	Half-life values	Likely persistence of residues after sub-lethal exposure
1	Cyanide	+	12 to 24 hours
	Zinc phosphide	+	12 to 24 hours
	Sodium nitrite	< 60 min	12 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

DISCUSSION

Results from this analysis clearly indicate that sodium nitrite is highly toxic to most species. Although feral pigs are one of the more susceptible species on a mg/kg basis (Table 1), they are also a large animal compared to most potential non-target species, and therefore the amount of chemical required to humanely euthanase a feral pig will always mean that non-target species will be at risk unless the active can be delivered in a species specific manner. The HOG-GONE bait has been demonstrated to do this, with the exception of foxes and ravens.

In terms of ravens, out of all of the field trials ravens have only ingested non-toxic and toxic bait at one site – Glenrock Station, NSW. At this site one bird out of several hundred on bait stations was found dead. The individual had spent some time accessing toxic baits which were hidden under heavy rocks, and unlike all of its colleagues it succeeded. The exact amount of bait material consumed is unknown, and there is no published information on the toxicity of nitrite for ravens. It is recommended that if ravens are consuming non-toxic HOG-GONE baits during prefeeding then the area should not be baited or precautions (bait covering, eg. bait hopper etc) should be taken.

With regard to rodents and quolls, monitoring of baits in field trials has shown no evidence of ingestion by these species. Furthermore, quolls have never shown interest in PIGOUT baits, and are less likely to be attracted to HOG-GONE baits.

Based on their previous consumption of PIGOUT baits the non-target risk posed by a HOG-GONE baiting campaign are principally to brush-tailed possums, northern brown bandicoots, swamp and tammar wallabies, foxes and wild dogs. This is however likely an over-estimation, as recent HOG-GONE field trials have indicated that wallabies and wild dogs are less inclined to consume the new HOG-GONE bait matrix. In relation to Bandicoots, these species have consumed unprotected PIGOUT baits in the Daintree. In such areas it is recommended that a bait hopper be used, such as the HOG-HOPPER (IACRC), if baiting is ever allowed (currently not, and no sign that it will be). Methods being used to limit the risk to non-target species include:

1. the formulation of the HOG-GONE bait itself, whereby most possums and wallabies are adverse to consuming the bait, particularly when it contains sodium nitrite;
2. the size of the HOG-GONE bait, and the 10% active loading, which means smaller mammals and birds are unlikely to be able to consume enough bait, in a short enough amount of time to receive a rapid rise in methaemoglobin levels and consequently a lethal dose. The slow consumption of baits is unlikely to be lethal in most species as methaemoglobin reductase is able to keep pace with the conversion of methaemoglobin back to oxyhaemoglobin;
3. adult feral pigs are known to consume multiple HOG-GONE baits, up to 15 in one sitting, and therefore the lethal dose for particularly large (100kg+) boars can be spread over multiple baits;
4. where necessary, physical exclusion of non-target species is possible, either using large rocks, over-turned buckets pegged into the ground (as occurs in Namadgi National Park), or through a bait hopper, such as the Boar Buffet® (Lapidge *et al.* 2009), that physically excludes all non-target species.

When used as a package there is little risk from the use of HOG-GONE to non-target wildlife species or domestic stock.

Phamacokinetic analyses of sodium nitrite have demonstrated it is rapidly eliminated. Lack of persistence is an important feature in vertebrate pesticide risk assessment. Risk to non-target species from vertebrate pesticides can be exacerbated if they bioaccumulate in the food chain. Pharmacokinetic analyses in different animals and humans have shown that unlike some common rodenticides (e.g. brodifacoum) sodium nitrite is unlikely to cause secondary poisoning due to bioaccumulation. The plasma elimination half-life in a wide range of animals, including mice, rats, dog, sheep and ponies and in humans is approximately 1 hour or less, and residues will not persist in sub-lethally exposed animals for >12 hours. Given this remarkable consistency in the pharmacokinetics of sodium nitrite and the fact that biotransformation is not necessary for sodium nitrite to be active or toxic it is possible to elucidate species differences in terms of receptor differences. Building on the recognition that differences in the metabolism and excretion of sodium nitrite in different species are not important we have focused our risk assessment analysis for different Australian non-target species on differences in red blood cell MtHb reductase activity. This contrasts with species differences in toxicity to other MtHb forming agents, such as PAPP, acetanilide and acetophenetidin where rates of metabolism will largely dictate species differences in susceptibility (Marrs et al.; Stolk and Smith 1966).

In those species which have published data on both acute toxicity and on red blood MtHb reductase it has been possible to demonstrate that a correlation exists between susceptibility and MtHb reductase activity. Further extrapolations are possible firstly to predict likely lethal doses of sodium nitrite in native Australian species. Secondly, based on animal size and eating habits, susceptible non-target species can be identified, such as Tammar wallabies, as well as species most unlikely to be at risk such as the short –beaked echidna.

In this paper we have reviewed risk to non-target species linked to pharmacokinetics and also MtHb reductase activity, animal size and behaviour to determine non-target risk when sodium nitrite is used for pig control. One aspect we have not covered is the persistence of nitrite in poisoned pigs' carcasses and the rate of decay of nitrite. This will require further study to ensure persistence of nitrite is not a feature of its use. This is a recognised hazard associated with 1080 and clarification of the risk to non-targets form poisoned carcasses will be needed.

ACKNOWLEDGEMENTS

The preparation of this risk analysis, including the contact testing of possums (Landcare Research, New Zealand) and tammar wallabies (Connovation, New Zealand), was funded by the Federal Department of the Environment, Water, Heritage and the Arts. The authors thank Michelle Smith

and the team at Animal Control Technologies, Penny Fisher and team, Lee Shapiro, Duncan MacMorran, Mick Statham, Rebecca Fish for being directly involved in pen trials. Associate Prof Chris Frampton, University of Otago, is thanked for his advise on pharmacokinetics analyses on the Kohn *et al*. paper, and Jason Wishart, IA-CRC, is thanked for extracting the data from this paper which greatly assisted in our understanding of sodium nitrite pharmacokinetics.

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