REVIEW ARTICLE

Toxicology and ecotoxicology of zinc phosphide as used for pest control in New Zealand

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Abstract: Zinc phosphide (Zn_3P_2) has been used overseas as a vertebrate pest control tool for several decades. It has been favoured in the USA and Australia for the field control of rodents and other animal pest species because of its comparatively low risk of secondary poisoning and lack of environmental persistence. Zn_3P_2 paste was approved for use as a possum control agent in New Zealand by the Environmental Protection Authority in August 2011. A micro-encapsulated form of Zn_3P_2 has been developed for use in paste and in the future will be developed in solid cereal bait, initially for controlling possums and as a rodenticide. New Zealand research over the last 10–15 years has focused on several factors, including determining Zn_3P_2 effectiveness for controlling possums, animal welfare, understanding and reducing non-target risk, and environmental fate. Zn_3P_2 is fast acting when delivered at toxic doses in baits to possums, with clinical signs first appearing from 15 min, and death after a lethal dose generally occurring in 3–5 h. Its toxicity is largely mediated by phosphine, which is formed as a breakdown product when paste is digested; Zn_3P_2 interacts with stomach acid. A toxic dose for possums will be delivered in 5 g of paste containing 1.5% Zn_3P_2 w/w. When this paste is applied in bait stations in field settings following prefeeding, possum numbers will be rapidly reduced. There should be no long-term residue risks. However, considerable care must be taken when using Zn_3P_2 for the control of animal pests because, despite low secondary poisoning risks, it has the potential (like other toxins) to cause primary poisoning of non-target species, and treatment of accidental poisoning is difficult. Exposure to sublethal doses has the potential to cause adverse effects, and strict safety precautions must be enforced to protect contractors and workers in the pest control industry. Despite extensive use of Zn_3P_2 overseas there has been only limited research and practical experience with Zn_3P_2 paste in New Zealand, especially when compared with alternative tools such as baits containing sodium monofluoroacetate (1080). Additional research efforts and practical experience should enable the effective use of Zn_3P_2 in New Zealand as a tool to achieve conservation outcomes or to control vectors of bovine tuberculosis.

Keywords: efficacy; mode of action; non-target effects

Introduction

Zinc phosphide (Zn_3P_2) is a vertebrate toxic agent (VTA) with a track record of use for vertebrate pest control in many countries, including Australia and the USA (US EPA 1998). In New Zealand it offers an addition to the pest control 'tool box', especially for lethal control of brushtail possums (*Trichosurus vulpecula*), and therefore should benefit both conservation programmes and bovine tuberculosis (TB) eradication. Zn_3P_2 has a molecular weight of 258.1. It is a crystalline dark powder with a garlic-like odour. It has a melting point of 420°C and was first synthesised in the mid-1700s and used as a rodenticide in Italy in c. 1911–12 (Tickes 1985). Since then it has been used increasingly to control rodents for crop protection (Krishnakumari et al. 1980). In the 1940s, when 1080 was being researched as a candidate rodenticide (Atzert 1971), Zn_3P_2 was also being further developed. This coincided with restricted access during the Second World War to older rodenticides, such as strychnine and red squill (Tickes 1985; Casteel & Bailey 1986). Zn_3P_2 was first registered as a pesticide in the USA in 1947 (US EPA 1998).

Because of the post-war emphasis on 1080 use in the USA, Zn_3P_2 was not fully developed until many years later. In a publication in the early 1970s entitled 'Zinc phosphide–a new look at an old rodenticide for field rodents' Hood (1972) described the use of Zn_3P_2 in the USA. He noted, 'However, in recent years, as problems associated with the use of 1080 and strychnine have been recognized, interest in zinc phosphide has again increased.' It is perhaps ironic that similar difficulties with 1080 in New Zealand some 30–40 years later have led to Zn_3P_2 development as an additional tool for possum and rodent control.

Zn_3P_2 has been used in the USA to control jackrabbits, prairie dogs, gophers, rats and voles (Evans et al. 1970; Hilton et al. 1972; Fellows et al. 1988; Ramey et al. 2000). It is used as a field rodenticide in Australia (Parker & Paroz 2001; Smith et al. 2003) and the Asia-Pacific region (Tongtavee 1980), and for the control of commensal and field rodents in China (Lund 1988). For two to three decades in the 20th century, Zn_3P_2 was probably the most widely used rodenticide for all purposes, including commensal rodent control until the introduction of first-generation anticoagulant rodenticides, such as warfarin,

in the 1950s (Lund 1988). It is still used widely, and remains the toxin of choice for field use in many situations, for example mouse plagues in Australia (Twigg et al. 2002), and can be broadcast rapidly from ground spreaders or aircraft.

Anticoagulants, including second-generation compounds such as brodifacoum, have been the most commonly used rodenticides worldwide for over 50–60 years (Eason et al. 2010). However, in the last two decades there has been a shift in rodenticide use, with researchers and pest control practitioners taking a renewed interest in alternatives to anticoagulants; this stems from increased resistance in pests to first-generation anticoagulants (Quy et al. 1995), as well as concerns over the secondary-poisoning risks and wildlife contamination associated with field use of second-generation anticoagulants, in New Zealand (Eason et al. 2002) and internationally (Young & De Lai 1997; Stone et al. 1999; US EPA 2004, 2008; Thomas et al. 2011).

It is noteworthy that brodifacoum was investigated for the field control of mice in Australia (Brown & Singleton 1998) and rabbits in New Zealand (Williams et al. 1986). It is likely that an increased understanding of the toxicokinetics of brodifacoum, including its tendency to bioaccumulate, and the secondary-poisoning risks associated with regular use halted further use of brodifacoum-containing baits for the field control of mice and rabbits. As a result, 1080 has continued to be used in New Zealand and Australia for the control of rabbits, and Zn_3P_2 for the control of mice in Australia – these toxins being deemed preferable for field application. Zn_3P_2 is less commonly used in Europe, although there is occasional field use. It is registered under plant protection law in Germany for field application until 2014, but there is a desire to extend the registration beyond this date (Rolf Barten, Technical Manager Frunol Delicia GmbH, Usingen, Germany, pers. comm.)

Recommended concentrations of Zn_3P_2 in bait products vary from 0.5% to 20% for different species (Schoof 1970; Krishnakumari et al. 1980). Rodenticide baits for application usually contain 1–5% Zn_3P_2, but some paste bait types have contained 5–10% (Hone & Mulligan 1982). Formulation types registered in the USA have included solid baits (1–2%), dust (10–63%), pellets or tablets (2%), and wettable powder (80%) as a premix for bait (US EPA 1998). In Australia, 2.5% w/w surface-coated wheat bait is used effectively for field control of mice (Twigg et al. 2002), with strategies including aerial application and ground baiting (Brown et al. 2002).

The first Zn_3P_2 bait in New Zealand (a paste for possums) contains a concentration of 1.5% w/w. The flavoured paste is coloured green to serve both as a deterrent to birds and as a warning to people. The paste can be applied to trees and fence posts or used in bait stations, and can be marked and mixed with white flour as a visual lure. A micro-encapsulated form of Zn_3P_2 has been shown to be more effective for controlling possums than unencapsulated Zn_3P_2 in either paste or cereal bait (Henderson et al. 2002; Ross & Henderson 2006). Research in New Zealand has focused on determining its effectiveness for controlling possums, on animal welfare, on understanding and reducing its risk to non-target species, and on its fate in the environment. Zn_3P_2 paste was approved for use by the Environmental Protection Authority (EPA) in August 2011 and was registered for use by the Agricultural Chemicals and Veterinary Medicines Group (ACVM) at the Ministry of Agriculture and Forestry (MAF, now the Ministry for Primary Industries) in September 2011 for ground-based possum control. Further research will be undertaken on Zn_3P_2 as the active ingredient within a solid cereal-bait, initially for controlling possums and as a rodenticide. Early trials with cereal bait have shown promise (Ross & Henderson 2006); however, further research and compilation of registration dossiers are prerequisites to the use of cereal bait formulations, with a focus on stability, non-target interference, and the development of best-practice use.

As described above, the preference for the field use of Zn_3P_2 in an international context is related to a low risk of secondary poisoning compared with other VTAs, and the fact that Zn_3P_2 does not bioaccumulate, unlike many of the anticoagulants. This also makes it a suitable VTA for careful field use in New Zealand. However, all pest control toxins have advantages and disadvantages; these are summarised for Zn_3P_2 in Table 1.

Table 1. Advantages and disadvantages of Zn_3P_2 when used as a possum control tool.

Advantages	Disadvantages
Rapidly reduces possum numbers	Like most other toxins it lacks specificity
Low risk of secondary poisoning	
Less expensive than some other alternatives to 1080, e.g. cholecalciferol or brodifacoum	No antidote, and treatment of accidental poisoning is complex
No long-term residue risks	

Mode of action

The toxicity of Zn_3P_2 is principally mediated by phosphine (PH_3), which is formed following hydrolysis of Zn_3P_2 on contact with stomach acids (Johnson & Voss 1952; Krishnakumari et al. 1980; Casteel & Bailey 1986; Guale et al. 1994; Sterner 1999). (PH_3). The reaction [$Zn_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Zn(OH)_2$] is likely to be acid-catalysed and therefore to proceed faster in the acidic environment of the mammalian stomach. It is likely that substantial amounts of phosphine enter the blood following inhalation into the lungs and stomach. Phosphine is readily distributed throughout the body to major organs such as the liver and kidneys (WHO 1989; Nikolaishvili & Melashvili 1992). The cause of Zn_3P_2-induced tissue damage is thought to be linked to hypoxia, and if recovery occurs it can be complete (Sarma & Narula 1996). Zn_3P_2 and phosphine damage the heart, liver, lungs and kidney, with pulmonary oedema and tissue anoxia evident. As with all toxins, the occurrence, speed of onset, and severity of signs is dose-dependent. The onset of poisoning is rapid following ingestion of Zn_3P_2, and usually occurs within 15 min to 4 h after ingestion of a toxic amount. Death from large doses usually occurs between 3 and 5 h (Parton et al. 2006). Death results from a combination of cardiac and respiratory failure, due at least in part to phosphine-induced anoxia. There is no antidote to Zn_3P_2, so treatment is mainly symptomatic and supportive. Recommendations for treatment include induction of vomiting if ingestion was recent, administration of active charcoal and sodium bicarbonate, and fluid therapy; other supportive measures are described in full in Parton et al. (2006).

Acute toxicity

The lack of Zn_3P_2 absorption across the skin is consistent with the acute dermal LD_{50} in rabbits of 2000–5000 mg kg^{-1} (US EPA 1998). In pest species, the oral LD_{50} of Zn_3P_2 is usually 40 mg kg^{-1} or less. Although Zn_3P_2 is a broad-spectrum toxin there are some differences in the susceptibility of animal species. Some acute oral toxicity values for Zn_3P_2 available in the literature are summarised in Table 2. These examples represent a small proportion of the LD_{50} data in the literature, but are chosen for their relevance to New Zealand ecosystems. It has been noted that Zn_3P_2 has greater acute oral toxicity to small mammals, with rodents 2–15 times more sensitive than larger mammals (Johnson & Fagerstone 1994). New Zealand test data for Zn_3P_2 in possums showed a 25 mg kg^{-1} dose resulted in 100% mortality (Morgan et al. 2001); the Zn_3P_2 LD_{50} for possums of 9.6 ± 2.4 mg kg^{-1} (R. Henderson, pers. comm.) indicates they are especially sensitive to Zn_3P_2.

Ross and Henderson (2006) have suggested that the susceptibility of possums to Zn_3P_2 is most likely related to its mode of action (see above), the unique biology of the brushtail possum, and its stomach pH of 2.5, which is likely to facilitate rapid release of phosphine (Duckworth & Meikle 1995).

Table 2. LD_{50} values (mg kg^{-1}) for oral toxicity of Zn_3P_2 to mammals (after Dieke & Richter 1946; Li & Marsh 1988; Sterner 1996; US EPA 1998; Ross et al. 2000; Morgan et al. 2001; R. Henderson pers. comm.). These examples represent a small proportion of the LD_{50} data available in the literature.

Mammal species	LD_{50} (mg kg^{-1})
Brushtail possum (*Trichosurus vulpecul*a)	9.6
Ferret (*Mustela putorius furo*)	16.4
Black rat (*Rattus rattus*)	21.3
Polynesian rat (*Rattus exulans*)	23.1
House mouse (*Mus musculus*)	32.7
Norway rat (*Rattus norvegicus*)	40.5
Dog (*Canis familiaris*)	~40
Cat (*Felis domesticus*)	~40
Cattle (*Bos taurus*), sheep, goats, pigs	30–40
Sheep (*Ovis aries*)	60–70
Rabbit (*Oryctolagus cuniculus*)	75

Toxicodynamics and welfare impacts on possums

Humaneness assessments consider the type, intensity and duration of adverse effects on pest species. Observations of animal behaviour in trials with possums have demonstrated that the size of the dose of Zn_3P_2 influenced the onset of clinical signs and duration of sickness behaviour. Because possums ingesting >20 mg kg^{-1} died more quickly than individuals taking lower doses, baits were formulated with a high toxic loading to be both toxic and palatable to possums. When it comes to field use prefeeding will be important to minimise aversion and ensure a toxic dose is ingested. At doses > 20 mg kg^{-1}, possums exhibited signs of poisoning ('sickness behaviour') for 1.5–2.4 h (Table 3). The latent period until onset of clinical signs of poisoning was 1.3–1.5 h after ingesting bait. Ataxia (loss of limb muscle coordination) occurred 2.1–3.5 h following ingestion of bait, and shortly afterwards possums became recumbent and died (Ross & Henderson 2006).

The welfare impacts or degree of distress caused by possum poisons has been studied in some depth (Table 4), including for cyanide (Gregory et al. 1998), phosphorus (O'Connor et al. 2007), brodifacoum (Littin et al. 2002) and 1080 (Littin et al. 2009). Cyanide is the fastest-acting poison and causes the shortest period of distress to possums before they die (Gregory et al. 1998). It is therefore regarded as the most humane. In contrast, brodifacoum is slow-acting, with possums sometimes taking a long time to die (an average of 21 days until death), and undergoing a prolonged period of discomfort after eating baits (Littin et al. 2002). Phosphorus causes behavioural responses associated with inflammation of the stomach lining and duodenum (e.g. a crouched/hunched posture), and the time to death is greater than for cyanide and 1080, but shorter than for brodifacoum (O'Connor et al. 2007). The times to death after possums eat 1080 baits are on average less than that recorded for phosphorus (Littin et al. 2009). Although Zn_3P_2 is not as humane as cyanide, it would appear to be preferable to compounds like brodifacoum for possum control (Littin et al. 2002, 2009). In terms of welfare impacts, Zn_3P_2 could be considered similar to 1080 (MAF 2010), and might be slightly preferable when formulated into a palatable and effective bait that kills possums within 4 h.

Effectiveness of Zn_3P_2 for field control of possums

Research on safety and effectiveness, bait development, and registration processes for Zn_3P_2 paste have taken more than 14 years to complete, and initial field trials on the paste bait were conducted over 10 years ago. These trials have been reviewed previously by Ross and Henderson (2006) and are summarised in brief below. They were undertaken in

Table 3. Mean times (h) to clinical signs of toxicosis in brushtail possums (*Trichosurus vulpecula*) for different doses of Zn_3P_2 (adapted from Ross & Henderson 2006).

Zn_3P_2 (mg kg^{-1})	Time to appetite suppression	First obs. of vomiting (% vomiting)	Time to epigastric pain	Onset of dyspnoea	Onset of ataxia	Period of sickness behaviour	Time to death
<20	3.0	- (0)	2.5	6.3	8.2	16.9	19.9
20–50	1.5	2.5 (25)	2.4	3.0	3.5	2.4	4.0
50–100	1.6	1.9 (61)	1.8	2.5	2.6	2.1	3.7
>100	1.3	1.4 (92)	1.5	2.0	2.1	1.5	2.9

Table 4. Summary of mean times to onset of clinical signs of toxicosis, duration of key symptoms during sickness behaviour, and time to death in possums following ingestion of six kinds of poison baits (adapted from Eason et al. (2011); data for Zn_3P_2 are for 20–50 mg kg^{-1}).

Toxin	Mean time to onset of sickness	Sickness behaviour	Mean duration	Mean time to death	Reference
Cyanide	3 min	Ataxia, impaired coordination, breathlessness, muscular spasms-unconscious after 6.5 min	15 min	18 min	Gregory et al. 1998
Zn_3P_2	1.5 h	Vomiting, epigastric pain, ataxia breathlessness	2.4 h	4.0 h	Ross & Henderson 2006
1080	~ 2 h	Anorexia, ataxia, occasional retching, spasms, breathlessness, laboured breathing	9 h	5 h	Littin et al. 2009
Phosphorus paste	6 h	Retching, vomiting, hunched posture, intermittent repositioning, ataxia	19 h	25 h	O'Connor et al. 2007
Brodifacoum	14 days	Reduced feeding, ataxia, haemorrhages, prolonged lying down	7 days	21 days	Littin et al. 2002

Table 5. Estimated percentage kills (± 95% confidence intervals) in paired field trials comparing Zn_3P_2 and 1080 bait delivered in bait stations (adapted from Ross & Henderson 2006).

Location (ha)	Toxin	Pre-poison possum RTC (%)	Post-poison possum RTC (%)	Percentage kill (95% CI)
Site 1 (21)	Zn_3P_2	37.5	3.5	90.6 (82.5 – 98.7)
Site 1 (18)	1080	20.8	2.0	90.4 (77.6 – 99.9)
Site 2 (29)	Zn_3P_2	22.7	2.1	**91.0** (82.3 – 99.6)
Site 2 (24)	1080	28.4	7.7	**73.0** (57.8 – 88.2)

Canterbury in two exotic forest plantations containing mainly *Pinus radiata*. Each plantation was divided into homogeneous blocks (each of 15–32 ha) with a 500-m buffer zone between each block. Previous research had demonstrated that a 500-m buffer zone was sufficient to isolate possum populations in the short term (Hickling et al. 1990). Bait stations were arranged at a density of 1–2 per hectare throughout each study block, for the delivery of Zn_3P_2 and 1080 paste baits. Approximately 1200 g of non-toxic prefeed was placed in bait stations for 12 nights prior to control. Bait stations were then filled with 300 g of toxic bait (either Zn_3P_2 or 1080) and left in the field for a further 7 nights. The pre-control possum population density was estimated using 'soft catch' leg-hold traps (Victor No. 1; Warburton 1992). Percentage kill was calculated as the decline in the proportion of possums caught per trap-night compared to the proportion caught before poisoning. Confidence intervals (95%) for the kill estimates were calculated using the difference in catch rates between the trap lines (referred to as the Residual Trap-Catch (RTC) method; NPCA 2011). The field trials demonstrated that Zn_3P_2 bait had comparable field efficacy to 1080 (Table 5).

In these field studies, Zn_3P_2 paste bait was very effective, in both cases reducing the possum density by over 90%. Given that these field trials were undertaken some time ago, additional research and monitoring on Zn_3P_2 paste is anticipated in 2012/13 to ensure that the product performs and meets expectations in a wide variety of habitats before it is made more widely available for vector management or conservation purposes. Considerable efforts have been invested in over 60 years of field research to reduce the negative impacts of 1080 on non-target species (Eason et al. 2011). Lessons from research and use of 1080 must be applied to the new baits, and considerable care will be needed by users of Zn_3P_2 paste bait – and Zn_3P_2 solid cereal bait when this is developed – to increase as far as possible bait target specificity. Furthermore, prefeeding with non-toxic bait should reduce aversive behaviour in possums and improve the performance of Zn_3P_2 baits.

Toxicokinetics and exposure risk for humans and dogs

This section addresses the likely fate of Zn_3P_2 following sublethal exposure and secondary poisoning risk from poisoned carcasses. Little percutaneous absorption of Zn_3P_2 occurs (WHO 1989; Hood 1972). Once ingested, Zn_3P_2 liberates phosphine, which when inhaled or absorbed enters the bloodstream and is distributed throughout the body (Sarma & Narula 1996). Other breakdown products and metabolites include phosphoric acid, phosphate, hypophosphite, and zinc. Excretion pathways include metabolites in the urine and faeces (Johnson & Voss 1952; WHO 1976) and phosphine may be partly excreted in exhaled air (Johnson & Voss 1952; Tabata 1986). The main urinary metabolite of zinc phosphide is hypophosphite (Curry et al. 1959). Raised zinc concentrations will occur in blood and zinc will be excreted in the faeces (Johnson & Voss 1952).

In a recent review on 1080 Eason et al. (2011) used toxicokinetics to help clarify the comparative exposure risk and the risks of bioaccumulation for different VTAs. In their classification VTAs were placed in four groups based on their persistence in sublethally exposed animals, to help distinguish

between risks associated with different vertebrate pesticides. Zn_3P_2 falls into Group 1 of this classification.

Group 1. Residues resulting from sublethal doses of these poisons are likely to be substantially excreted within 24 h (e.g. cyanide, zinc phosphide, and 1080). Like other compounds in this group, Zn_3P_2 will not readily bioaccumulate.

Group 2. Residues resulting from sublethal doses of these poisons are likely to be substantially cleared from the body within 2–4 weeks (e.g. diphacinone).

Group 3. Residues resulting from sublethal doses of these poisons are likely to be cleared from the body within 2–4 months (e.g. cholecalciferol and coumatetralyl).

Group 4. Residues resulting from sublethal doses of these poisons may never be completely excreted from the body (e.g. brodifacoum), and therefore bioaccumulate (Eason et al. 2002, 2011). The risk of residues of these compounds bioaccumulating in wildlife is high if they are repeatedly used in the field.

The criteria for the four groups, and the rationale for allocation of different compounds to them, are described above and in Table 6. The inference that Zn_3P_2 is most likely to clear rapidly from the body is made on the basis of observations in poisoned animals. Following oral gavage of 80 mg kg^{-1} no detectable residues were found in muscle samples taken from 10 possums after a period of 8 h. Highest concentrations were detected in stomach contents (Fisher et al. 2005). Fisher et al. (2005) concluded that concentrations of residual Zn_3P_2 appear to be highest in possums shortly after they have ingested a lethal dose (within 1–8 h), decline between ingestion and death, and are likely to have a reduced rate of decline post-mortem. The latter was shown to be the case in a subsequent study in which the concentrations of Zn_3P_2 in the carcasses of poisoned animals declined steadily, with a half-life of 3.4 days calculated for residues in stomach contents (Brown et al. 2007). Elimination processes would likely be very much quicker in sublethally poisoned animals.

As for 1080, if recommended practices are followed in control operations, Zn_3P_2 is unlikely to be present in meat for human consumption because of its comparatively rapid elimination. However, where any contact with Zn_3P_2 by livestock (farm animals or animals intended for slaughter) is suspected, an adequate margin of safety should be achieved by imposing a minimum withholding period (prior to sending animals to an abattoir) similar to that for 1080 (5 days) (Eason et al. 2011).

There are similarities between the persistence of 1080 and Zn_3P_2 in sublethally exposed animals. However, the most significant difference between 1080 and Zn_3P_2 relates to the relative persistence of residues of these two compounds in possum carcasses. Compound 1080 can persist in possum carcasses for many months (until the carcass is broken down), and will pose a risk to scavenging dogs (Meenken & Booth 1997). Possum carcasses collected from the field can pose a serious risk to dogs even up to 75 days after the poisoning operation (Meenken & Booth 1997). In the carcasses of Zn_3P_2-poisoned animals, concentrations decline very rapidly and a half-life of 3.4 days was calculated for residues in stomach contents as indicated above. This rapid decline explains the comparatively low risk of secondary poisoning of dogs by Zn_3P_2 compared with 1080 (Ross & Henderson 2006).

Sublethal effects and the need for eliminating exposure risk in humans and non-target animals

As with other toxins, Zn_3P_2 has the potential to kill and cause sublethal effects in humans, but exposure of individuals to amounts of Zn_3P_2 that would cause such effects is unlikely if users of Zn_3P_2-containing baits follow established safety procedures. The acute toxicity of Zn_3P_2 is well documented (Dieke & Richter 1946; Li & Marsh 1988; Sterner 1996; US EPA 1998; Morgan et al. 2001; Ross et al. 2000; Henderson et al. 2002), and the toxic manifestations of sublethal effects are also described in the international literature.

There are a number of references to studies on the effects of Zn_3P_2 that demonstrate that known target organs in animals comprise the lungs, liver, kidneys and central nervous system (Stephenson 1967). As described earlier, the cause of Zn_3P_2-induced tissue damage is thought to be linked to hypoxia, and if recovery occurs it can be complete (Sarma & Narula 1996). Acute toxicity is associated with pulmonary oedema (Mannaioni 1960; Puccini 1961; Stephenson 1967), and cerebral oedema (Mannaioni 1960; Puccini 1961). In rats exposed to Zn_3P_2 vapour for over 2 weeks lung damage was evident with alveolar capillaries congested with blood, some haemorrhage, and exudation into the alveolar spaces. Mononuclear infiltration was observed around the smaller bronchi and bronchioles (Johnson & Voss 1952), and mild cellular infiltration in the bronchioles (Krishnakumari et al. 1980).

Sublethal doses have been associated with liver and kidney damage (Stephenson 1967). In laboratory trials, fatty degeneration and hepatocellular damage have been reported

Table 6. Comparative pharmacokinetics and expectation for persistence of residues in sublethally exposed target or non-target animals (adapted from Eason et al. 2011). Values are mostly based on data from rats as surrogates for non-target species.

Group	Compound	Half-life values in blood or liver	Likely persistence of residues after sublethal exposure
1	Cyanide	+	12–24 h
	Zinc phosphide	+	12–24 h
	1080	<11 h	7 days
2	Pindone	2.1 days	4 weeks
3	Cholecalciferol	10–68 days	3 months
	Coumatetralyl	50–70 days	4 months
4	Brodifacoum	130–350 days	24 months or longer

+ No published value but likely to be < 12 h.

(Johnson & Voss 1952; Fitzpatrick et al. 1955) and confirmed by increases in serum alkaline phosphatase (ALP) in rats fed a diet containing 500 mg kg^{-1} Zn_3P_2 for 13 weeks (Bai et al. 1980). The kidneys of rats fed with Zn_3P_2 have shown signs of haemorrhaging in glomeruli and tubules (Krishnakumari et al. 1980). Hydronephrosis (cystic distension of blocked kidney) and pyelonephritis (inflammation) were detected by histopathology in males in the 3.0 mg $kg^{-1}day^{-1}$ group, and hydronephrosis was also observed in rats receiving 1.0 mg $kg^{-1}day^{-1}$. No kidney lesions were found at 0.1 mg $kg^{-1}day^{-1}$; accordingly, the US EPA (1998) established a no observed adverse effect level (NOAEL) of 0.1 mg $kg^{-1}day^{-1}$ and a lowest observable effect level (LOEL) of 1.0 mg $kg^{-1}day^{-1}$ based on increased mortality and on kidney pathology in male rats (Siglin 1994). Following a 13-week administration of Zn_3P_2 to rats, neurobehavioural changes were observed and the US EPA (1998) also set a NOAEL for these effects at 0.1 mg $kg^{-1}day^{-1}$, the lowest dose tested. There are also references in the literature to reproductive and developmental toxicology with Zn_3P_2. For example, male and female rats were exposed to 0.03% w/w Zn_3P_2 in their diet for 22 days; surviving treated rats were mated with untreated rats and all proved to be fertile (Henwood 1993). In a further developmental toxicity study, mated female rats (25 per dose group) were orally administered 0, 1, 2 or 4 mg kg^{-1} day^{-1} Zn_3P_2 on Days 6 through 15 of gestation (Henwood 1993). Nine rats in the 4 mg kg^{-1} day^{-1} dose group died between Days 10 and 16 of gestation. Mean body weight and food intake in the 4 mg kg^{-1} day^{-1} dose group were significantly lower between Days 6 and 10 of gestation, but not significantly different by the end of the treatment period. There were no significant differences in the gravid uterine weights, corrected body weights, and net body weight changes from Day 0. Mean post-implantation loss at the 4 mg kg^{-1} day^{-1} level was higher, although not statistically different from that of the control dose group. Percent post-implantation loss in the 4 mg kg^{-1} day^{-1} females was similar to that of the control group. There were no test-substance-related external, soft tissue, or skeletal abnormalities in foetuses of the treated dose groups. The NOAEL for maternal toxicity was 2.0 mg kg^{-1}, based on mortality, which occurred at the LOEL of 4 mg kg^{-1} day^{-1}. The NOAEL for developmental toxicity was 4.0 mg kg^{-1} day^{-1} or above (Henwood 1993). The US EPA (1998) waived the requirement for further studies, as Zn_3P_2 residues in the environment and therefore exposure risk are expected to be minimal.

The cancer-inducing potential of Zn_3P_2 has been evaluated by in vitro and in vivo testing. Zn_3P_2 has been shown to be non-mutagenic in two out of three toxicology studies (Bigger & Clarke 1993; San & Wyman 1993; US EPA 1998). Thus, Zn_3P_2 was negative in both Ames tests and mouse micronucleus tests, but produced a positive result in a mouse lymphoma assay. Salmonella TA-strains of bacteria were exposed to Zn_3P_2 at doses of up to 5000 μg $plate^{-1}$, with and without metabolic activation (San & Wyman 1993). No increase in the number of revertants was induced; hence Zn_3P_2 was negative for gene mutation in the Ames test (US EPA 1998). Mouse lymphoma cells were exposed to Zn_3P_2 with and without mammalian metabolic activation (Bigger & Clarke 1993). Increased mutants at the thymidine kinase locus were induced in a dose-dependent manner at doses of 10–80 μg ml^{-1}; Zn_3P_2 was positive for gene mutation, in both the presence and absence of exogenous metabolic activation (US EPA 1998). In the third test, mice were treated with Zn_3P_2 by intraperitoneal injection to deliver doses of 38, 75 or 150 mg kg^{-1}. No increased aberrations were induced 24, 48 or 72 h after dosing, indicating that Zn_3P_2 was negative for mutagenicity in the micronucleus test (US EPA 1998). The implications of these findings and other sublethal effects described in this section are that careful handling of Zn_3P_2 and baits is needed, including the use of protective clothing. This is also the case for 1080, a known testicular toxin and teratogen (Eason & Turck 2002). These findings do not prevent the proper use of these chemicals, but influence the controls applied by New Zealand regulatory authorities and best handling practice.

Fate in the environment, toxicity to aquatic organisms and risk of exposure from contaminated water supplies

Persistence in soil and plants

Zn_3P_2 is unstable in soil (US EPA 1998). This has been shown experimentally with Zn_3P_2 mixed with three soils at five moisture levels decomposed with the liberation of variable amounts of phosphine. The rate of Zn_3P_2 decomposition increased with increasing moisture (Hilton & Robison 1972). Phosphine will either be absorbed by soil or discharged into the atmosphere where it is degraded by photolysis. Appreciable amounts of phosphine evolve in moist, acidic or basic soils (US EPA 1998). Hence any Zn_3P_2 leaching from bait to soil is likely to be quickly dissipated. In assessments of the weathering characteristics of Zn_3P_2 paste bait formulations in soil, residual concentrations of Zn_3P_2 were measured over 20 days and a half-life in soils was estimated to be in the range of 10–20 days (R. Henderson pers. comm.). The sensitivity of plants and microorganisms to phosphine was summarised by WHO (1988) with effects on lettuce growth being seen at 3–8 mg m^{-3} and on respiration and growth of microorganisms at 10 mg l^{-1}. However, phosphine concentrations arising from the use of Zn_3P_2 paste should be negligible given the small amounts of paste being used. No studies in New Zealand have looked at Zn_3P_2 uptake into plants. Overseas studies are numerous because of the use of Zn_3P_2-containing baits in food crops (e.g. Hilton & Mee 1972; Tickes 1985) and all indicate that uptake of Zn_3P_2 residues into food plants should not be a major concern in the New Zealand context. For example, when Zn_3P_2 grain baits were applied to wheat, sorghum and sunflower plants at 100 times the recommended field application rate (1 kg ha^{-1}), plants harvested 14 days after application had residues below the maximum residue levels (not specified) for each crop type (Parker & Paroz 2001). Earlier research produced similar results and Goodall et al. (1998) concluded that the use of Zn_3P_2 to control rodent pests in cornfields poses little threat of contamination of corn products intended for animal or human consumption.

Although significant residues of Zn_3P_2 in soil are unlikely, research in New Zealand has established the acute and chronic effect levels of Zn_3P_2 on earthworms (*Eisenia fetida*) (O'Halloran & Jones 2003). Although no earthworm mortality was found, a LOEL of 3200 mg kg^{-1} was calculated for growth, 1000 mg kg^{-1} for the number of juveniles produced, and 32 mg kg^{-1} for cocoon production. Given the proposed use pattern of the Zn_3P_2 paste, and taking into account the above studies, negative effects on plants, earthworms and soil micro-organisms are unlikely.

Water and Zn_3P_2

Zn_3P_2 and its degradation products appear to have low potential for ground and surface water contamination (US EPA 1998). Zn_3P_2 is highly reactive and hydrolyses in water. Since the initial use of Zn_3P_2 is for ground control in paste, contamination of water is unlikely. If aerial application of a Zn_3P_2 bait was to be considered in the future then additional water monitoring and research would be warranted. Aquatic ecotoxicology data exist; for example, an LC_{50} for Zn_3P_2 of 0.8 mg L^{-1} for bluegill sunfish (*Lepomis macrochirus*), and 0.5 mg L^{-1} for rainbow trout (*Oncorhynchus mykiss*) (BCPC 2000). For phosphine, the 96-h LC_{50} for rainbow trout is 9.7 $\times 10^{-3}$ mg L^{-1}, and for *Daphnia* the 24-h EC_{50} for phosphine is 0.2 mg L^{-1} (BCPC 2000).

Non-target responses

Effects on birds and invertebrates

Controlling introduced animal pests can enhance and restore New Zealand ecosystems, but careful use of any tool, including Zn_3P_2 baits, will be essential to ensure that non-target effects are minimised and that the benefits of pest control outweigh adverse effects. A major concern when using toxins in this context is that they are not selective to the target species; birds and non-target mammals that feed on baits are potentially at risk. With regard to field use of Zn_3P_2 for rodent control, the majority of agricultural operations conducted in Australia, Canada and the USA are for open-field uses with the application of Zn_3P_2 surface-coated grains, which have killed birds (Hayne 1951; Orr 1952; Rana et al. 1990; Ramey & Sterner 1995). In New Zealand, application techniques should be more discrete and in common with other toxic baits. Considerable effort will be needed to reduce the negative effects of Zn_3P_2 baits by choice of bait matrices and baiting practices. The risk of non-target poisoning is reduced by using Zn_3P_2 baits in bait stations, or other dispensers on trees or posts where they are less accessible to non-target species than baits on the ground. The LD_{50} values (Table 7) for birds tend to fall into a similar range as those for mammals. These examples represent a small proportion of LD_{50} data in the literature and are also chosen for their relevance to New Zealand ecosystems. Waterfowl, gallinaceous birds, and some passerines are described as relatively sensitive to Zn_3P_2 (Kulczycki 1985; Johnson & Fagerstone 1994). At higher doses Zn_3P_2 repels, and has an emetic effect on birds (as it does with many mammal species other than rats). This emetic effect partially protects non-target species, and is not reduced by microencapsulation (Ross & Henderson 2006). No LD_{50s} have been calculated for New Zealand native species. Monitoring for non-target interaction with baits, and robust information on bird mortality, including long-term monitoring, will be important in the future, particularly if bait types and baiting procedures change. Studies on introduced earthworms indicated low toxicity (O'Halloran & Jones 2003), but research into the impacts on other invertebrates following field use would be advisable.

Table 7. LD_{50} values for oral toxicity of Zn_3P_2 to six bird species (after Janda & Bösseová 1970; Janda 1972; Rogers 1977; Shivanandappa et al. 1979; Glahn & Lamper 1983; Kulczycki 1985; US EPA 1998, 2004; BCPC 2000).

Species	LD_{50} mg kg^{-1}
Pigeon (*Columba livia*)	7.2
Canada goose (*Branta canadenis*)	12
California quail (*Lophortyx californica*)	13.5
Mallard duck (*Anas platyrhynchos*)	13.0 – 67.4
Pheasant (*Phasianus colchicus*)	7.7 – 26.7
Chicken (*Gallus domesticus*)	24–26

Effects on feral animals

There are no LD_{50} values for oral toxicity of Zn_3P_2 to deer. However, their susceptibility to Zn_3P_2 is likely to be similar to that of cattle, sheep, goats and pigs, which are reported to have LD_{50} values of 30–40 mg kg^{-1} (Casteel & Bailey 1986). Poisoning of these species is possible, but the risk will be reduced by the use of bait stations. Only 5 g of paste bait containing 1.5 % Zn_3P_2 is needed to kill a possum, but substantially more would be required to kill a larger mammal.

Risk of secondary poisoning of dogs

This section has two parts: initially, publications on secondary poisoning from the USA are reviewed, and are followed by a synopsis of recent New Zealand research. Secondary poisoning following Zn_3P_2 baiting is less likely than with 1080, and Johnson (1992) and Johnson and Fagerstone (1994) concluded there is a low risk of acute secondary poisoning to dogs. There is some variability in results reported in the USA, however. For example, Colvin et al. (1991) demonstrated a low risk of secondary toxicity to both birds and mammals from Zn_3P_2 whereas Savarie (1981) noted some degree of acute secondary poisoning of carnivores. Nevertheless, the weight of evidence from the US studies indicates a low risk. This would in part be explained by the fact that neither Zn_3P_2 nor phosphine accumulates in the tissues of target animals. Furthermore, there is a marked difference in the persistence of 1080 residues and Zn_3P_2 residues in poisoned animals. The most hazardous part of a carcass to a scavenger is the digestive tract of a poisoned animal, as it may contain Zn_3P_2 for a period after baits have been eaten. Sterner and Mauldin (1995) noted that potential secondary hazards to scavengers included the amount of undigested material present at time of death, the parts of a carcass ingested, and weather affecting carcass decomposition. Emesis may also provide some protection from secondary poisoning, as may the development of aversion following the occurrence of sublethal symptoms from an initial exposure. In general, sublethal effects of secondary exposure are more probable than lethal ones and include illness, listlessness, and regurgitation (US EPA 1998).

In 2004, the EPA updated its earlier assessment of the potential for mammalian secondary poisoning by Zn_3P_2 (US EPA 2004). In a total of 10 studies, 77 animals were presented with carcasses of poisoned animals. Three test animals died. These were either cats or dogs fed freshly-poisoned animals. These North American results, which focused on wildlife species and only a small number of dogs, underpin the importance of the New Zealand research.

Because of concerns relating to secondary poisoning of domestic dogs, working dogs on farms, and dogs used for hunting, the secondary poisoning studies previously reviewed by Ross and Henderson (2006) are reported in some detail below. In their experiments 65 acclimatised possums were presented with Zn_3P_2 bait. Twenty-two dogs used in the

study were unwanted animals designated for euthanasia by city dog control authorities. All dogs were medium-sized breeds with bodyweights in the range 15–32 kg (i.e. the size of farm dogs). They were randomly allocated to one of four equal-weight groups:

1. Four to a control group eating the muscle and viscera of non-poisoned possums.
2. Six to a group eating the muscle and viscera equivalent to one poisoned possum.
3. Six to a group eating the muscle and viscera equivalent to two poisoned possums.
4. Six to a group eating the muscle and viscera equivalent to four poisoned possums.

Half the dogs in the low-dose group (one possum eaten) showed no overt clinical signs of poisoning throughout the study. However, about 2 h after eating, dogs in this low-dose group appeared to become slightly dehydrated, and most were observed to drink water with half of them eventually vomiting. A dog in the intermediate group (two possums eaten) vomited after 1 h 40 min, with all other dogs in the intermediate and high dose groups (four possums eaten) vomiting between 7 and 12 h after consumption. Once dogs had vomited they became slightly lethargic, but no other overt clinical signs of poisoning were apparent during the following 48 h.

Freshly killed possum carcasses present the greatest risk of causing secondary poisoning of dogs, although this risk will be reduced in the days after a possum has been killed. Studies show that the risk of secondary poisoning with Zn_3P_2 is low when only a single carcass is eaten (Ross & Henderson 2006). Repeated consumption of poisoned carcasses by dogs over several days will induce signs of poisoning such as loss of appetite and lethargy (Ross & Henderson 2006). 'Low risk' of secondary poisoning with Zn_3P_2 does not imply there is no risk to pets and farm dogs, which should be discouraged from eating potentially poisoned possum carcasses.

Conclusions

A micro-encapsulated form of Zn_3P_2 has been developed for use in paste and will be incorporated with a solid cereal bait, initially for controlling possums and as a rodenticide (Ross & Henderson 2006). It is fast-acting when delivered at toxic doses in baits to possums, with clinical signs first appearing after 15 min, and death generally in 3–5 h. Its toxicity is largely mediated by phosphine, which is formed as a breakdown product when Zn_3P_2 interacts with stomach acid. Zn_3P_2 is a broad-spectrum poison that has been used since the early 1900s. Toxic doses result in circulatory changes, cardiac abnormalities, pulmonary oedema, and death. Sublethal doses of zinc phosphide are unlikely to persist in meat or major organs. Secondary poisoning is theoretically possible if cats and dogs eat the stomach or intestine still containing toxic baits. However, the main advantage of Zn_3P_2, as illustrated by the trials described above, is that this risk appears to be small and that the risk of secondary poisoning is likely to be considerably lower than that of 1080. Considerable care must be taken when using Zn_3P_2 for the control of animal pests. Despite low secondary poisoning risks, it has the potential (like other toxins) to cause primary poisoning of non-target species and treatment of accidental poisoning is difficult. Exposure to sublethal doses has the potential to cause adverse effects, and strict safety precautions are enforced to protect contractors and workers in the pest control industry. Despite extensive use of Zn_3P_2 overseas there has been only limited research and practical experience with Zn_3P_2 paste in New Zealand**.** Additional research efforts and practical experience should enable its effective use as a conservation tool, or for TB vector control, and plans are being developed to extend its registration in New Zealand to include rodents as well as possums as target species.

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