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Introduction

The focus of this manual is on the properties of poisons used for mammalian pest control. Intensive measures have been devised, and implemented on an unprecedented scale in New Zealand, to control a wide variety of introduced mammals. These include aerial application of 1080 bait on mainland New Zealand, and baits containing brodifacoum to kill rodents on islands. Such measures are amongst the most aggressive taken world-wide to control introduced mammals.

The risk to non-target species, from the compounds, will be determined by their intrinsic susceptibility, the properties of the poisons used, such as the toxicokinetics of these chemicals, as well as bait design and the way in which toxic baits are used in the field, which may limit or exacerbate the exposure of non-target species. The manual documents in detail the different properties of the different poisons. All have advantages and disadvantages, which make them more or less effective or appropriate for different use patterns. There is a massive literature on these compounds generated around the world, which is complemented by New Zealand-based research. A review was undertaken of the first edition of this manual and additional details with regard to the treatment of poisoning incidents were requested (Moffat 1999). In response to this review, the second edition contains more details on symptoms, diagnosis, and treatment for those poisons extensively used: 1080, cyanide, cholecalciferol, and brodifacoum. There is a greater emphasis on comparative toxicokinetics, and a new section at the end of the manual on the comparative risks associated with different poisons.

The first edition of this manual has frequently been referred to as the 'Toxins Manual' (Haydock & Eason 1997). This reflects some confusion with regard to the following terms: toxins, toxicants, poisons, and vertebrate pesticides. Toxic substances of natural biological origin, principally derived from microbes, plants, and animals are usually described as toxins (e.g. cholecalciferol (vitamin D_3), cyanide, and 1080). Toxicants are considered to be substances that are toxic in relatively small doses and do not originate from microbes, animals, and plants (e.g. brodifacoum, phosphorus, and pindone). The term 'poison' or 'vertebrate pesticide' can be used to cover both toxins and toxicants. In the context of this manual, compounds such as cholecalciferol and warfarin are considered as vertebrate pesticides, whereas the former is commonly regarded as a vitamin and the latter as a drug used to treat blood clotting disorders in humans. This should not be that surprising since 'All substances are poison and it is only the dose that makes a distinction between one which is a poison and one which is a remedy.' (Paracelsus c. 1500) Vertebrate pesticides (sometimes referred to as rodenticides) are distinguished from insecticides (toxic to insects), herbicides (toxic to plants), and fungicides (toxic to fungi). In this regard 1080 is unusual as it is known to be toxic to both insects and mammals and could therefore be classified as an insecticide, a vertebrate pesticide, or a rodenticide.

We[1] hope that compiling the significant toxicological features of these vertebrate pesticides in one document will assist all those directly or indirectly involved in the application of toxic baits for wildlife management. The focus of the document is the toxins and toxicants commonly used by the Department of Conservation (DOC) in New Zealand, for example, 1080, brodifacoum, cyanide, and cholecalciferol. Other, less widely used, anticoagulants and poisons no longer used by the Department are covered only briefly. Toxicology is the study of the fate and effects of compounds with a toxic potential. The manual follows the same general structure as that requested by the Department of Conservation in the first edition. However, a new section has been added to assist with the comparison of the key features of the different toxins and toxicants. Also new, Appendices 1–3 present specifications for 1080 bait, and baits per lethal dose. A Glossary of terms follows the Appendices. Note that many common names for animals are used throughout the manual. Those interested are referred to the original research for the scientific names where these are not cited.

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1. Acute poisons

1.1 SODIUM MONOFLUOROACETATE (1080)

Chemical Name: Sodium monofluoroacetate.

Synonyms: monofluoroacetate or Compound-1080 or 1080 ('ten-eighty')

Sodium monofluoroacetate (1080) is still the most widely used poison for possum control in New Zealand (in carrot, cereal, paste, and gel baits) for situations where possum numbers need to be reduced rapidly over large areas. Carrot baits are screened to remove small pieces so that the risks of birds eating baits is reduced. Cereal baits are used for both aerial and bait station control. Paste baits, and more recently gel bait, are used for ground-based follow-up maintenance control. Cinnamon is usually added to baits to mask the taste of 1080, and may be a partial deterrent to birds. Sodium monofluoroacetate can only be used by licensed operators.

1.1.1 Physical and chemical properties

The empirical formula for 1080 is $C_2H_2FNaO_2$ and the molecular weight is 100.3. It forms an odourless, white, non-volatile powder that decomposes at about 200°C. Although the compound is often said to be tasteless, dilute solutions are thought to taste like weak vinegar. Sodium monofluoroacetate is very water-soluble but has low solubility in organic solvents such as ethanol and oils. Monofluoroacetates are chemically stable, hence 1080 as a pure compound in powder form—or when prepared in an aqueous stock solution—will not readily decompose.

1.1.2 Historical development, use, and occurrence in nature

Sodium monofluoroacetate was first used in the United States about 50 years ago to control gophers, ground squirrels, prairie dogs, field mice, and commensal rodents. In New Zealand it is a pivotal component of pest control and has been developed specifically for aerial control of possums (Morgan 1994a, b), though it is increasingly being used for predator control through primary (E.B. Spurr pers. comm.) and secondary poisoning (Alterio 2000). Currently in New Zealand the principal target species are possums (Thomas 1994) and rabbits. Overuse of 1080 baits may result in bait shyness, but this may be avoided or mitigated by adherence to high-quality baiting practices and use of different bait types (Morgan et al. 1996b; Ogilvie et al. 2000; Ross et al. 2000) or additives to the baits (Cook 1999; Cook et al. 2000) Despite this risk of 'shyness' 1080 remains a highly effective tool for possum control. Manufactured 1080 for use in toxic baits has been shown to be chemically identical to the toxic compounds found in a poisonous plant; naturally produced 1080 induces the same signs and symptoms in animals (de Moraes-Moreau et al. 1995). Highly toxic fluoroacetate-producing plants are globally distributed with species on several major continents. Research in the 1940s identified monofluoroacetate,

the active toxin in 1080, as the toxicant in the South African plant gifblaar (*Dichapetalum cymosum*), long recognised as a hazard to livestock. Since this discovery, monofluoroacetate has been identified as the toxic agent in many other poisonous plants, such as rat weed (*Palicourea margravii*), native to Brazil (de Moraes-Moreau et al. 1995); and ratsbane (*Dichapetalum toxicarium*), native to West Africa (Atzert 1971).

Monofluoroacetate also occurs naturally in some 40 plant species in Australia. Air-dried leaves of *Gastrolobium bilobum* (heart-leaf poison) and *G. parviflorum* (box poison), for example, can contain up to 2600 mg/g of monofluoroacetate, and seeds of *G. bilobum* can have in excess of 6500 mg/kg of monofluoroacetate (Twigg 1994; Twigg et al. 1996a,b; 1999). The highest monofluoroacetate concentration so far reported from a living source is 8000 mg/g in the seeds of *Dichapetalum braunii* (Meyer 1994).

Monofluoroacetate would appear to be one of the many secondary plant compounds that have evolved at high concentrations as a defence mechanism against browsing invertebrates and vertebrates. Most studies assessing monofluoroacetate concentrations in plants have focused on those species that are overtly toxic to mammals. However, it would appear that the ability of plants to synthesise monofluoroacetate is more widespread than generally supposed, since monofluoroacetate occurs at extremely low concentrations in some Finnish plants (Vartiainen & Kauranen 1980), in tea leaves (Vartiainen & Kauranen 1984), and guar gum (Vartiainen & Gynther 1984; Twigg et al. 1996b). In addition some plants, when exposed to fluoride ion, can biosynthesise fluoroacetate, albeit at very low levels. Fluorocitrate, the toxic metabolite of monofluoroacetate, has also been detected in tea leaves (Peters & Shorthouse 1972). Fluoroacetate biosynthesis can also occur in some bacteria, notably *Streptomyces cattleya* (O'Hagan & Harper 1999). Resistance in mammals, birds, and insects occurs in areas where there is continued exposure to the toxin. Interestingly, the caterpillar moth, *Sindrus albimaculatus*, which feeds on *Dichapetalum cymosum*, can not only detoxify fluoroacetate, but also accumulate it (probably in vacuoles) and uses it as a defence against predation (Meyer & O'Hagan 1992).

1.1.3 Fate in the environment

Persistence in soil

Presumably, naturally occurring monofluoroacetate is diluted by rainwater and breaks down in soil after leaves and seeds drop to the ground or when the plants die. Not all micro-organisms can readily defluorinate monofluoroacetate and the rate of metabolism differs with different species of soil bacteria and fungi (King et al. 1994). Sodium monofluoroacetate, the sodium salt of this natural toxin, can certainly be metabolised by some soil micro-organisms, such as *Pseudomonas* and *Fusarium* species (Walker & Bong 1981; King et al. 1994). Enzymes capable of defluorinating fluoroacetate have been isolated from several micro-organisms. The active site of the enzyme attacks fluoroacetate. The fluoride carbon bond is cleaved and ultimately enzyme-bound intermediates form non-toxic metabolites such as glycolate (O'Hagan & Harper 1999).

Sodium monofluoroacetate derived from baits will also be dispersed by water since it is highly water soluble and mobile (Parfitt et al. 1995). In older

literature, it was suggested that 1080 is retained in solid particles and does not leach. This conclusion was based on the mistaken assumption that 1080 would not be held on cation-exchange sites in soil. However, monofluoroacetate is an anion and New Zealand-based research has demonstrated that it could potentially be leached through soil by water (Parfitt et al. 1995). If heavy rainfall follows the use of 1080 baits, dilution to unmeasurable concentrations (<0.0001 ppm) may precede biodegradation. In comparison to cereal bait, 1080 is retained in carrot baits and will only slowly leach from carrots into the soil (Bowen et al. 1995). However, control operations are planned to coincide with periods of dry weather, and some defluorination by micro-organisms on the decaying baits and in the soil around baits is probable, particularly if the baits become moist. Under favourable conditions, such as 11–20°C and 8–15% moisture (King et al. 1994), 1080 may be significantly defluorinated in 1–2 weeks. In less favourable conditions breakdown might take several weeks and, in extreme cold and drought, 1080 residues might persist in baits or in the soil for several months.

Sodium monofluoroacetate that has leached into soil may be absorbed by plants (Atzert 1971; Rammell & Fleming 1978). Cabbage (*Brassica oleracea capitata*) has been shown to systematically accumulate 1080 through its roots, and subsequently become toxic to aphids (Negherbon 1959). To investigate whether herbivores may be at risk of secondary poisoning if they consume plants that have taken up 1080 leached from bait, concentrations of 1080 have been assessed in broadleaf (*Griselinia littoralis*) and perennial ryegrass (*Lolium perenne*) following simulated baiting (Ogilvie et al. 1998). The observation in both species that 1080 was absorbed, reached a peak, and then decreased to near the limits of detection, supports previous findings that plants can degrade 1080 (Preuss & Weinstein 1969; Ward & Huskisson 1969). The concentration achieved in broadleaf and ryegrass would be most unlikely to cause poisoning (Ogilvie et al. 1998).

Monofluoroacetate appears to be defluorinated by plants (Preuss & Weinstein 1969; Ward & Huskisson 1972) and animals (Eason et al. 1993a), which may make a small contribution to the removal of monofluoroacetate from the environment following the use of baits containing 1080.

The gene encoding for the bacterial enzyme capable of defluorinating fluoroacetate in soil has been cloned and expressed in the rumen bacteria, *Butyrivibros fibriscolens*. This organism has then, in an experimental setting, been employed to infect the gut of sheep in an attempt to protect against dietary poisoning by fluoroacetate-containing plants. Early indications are that the genetically modified organisms become established sufficiently well to give the sheep a degree of resistance to fluoroacetate (Annison & Bryden 1998; Gregg et al. 1998). Currently there are no plans to introduce genetically modified organisms into New Zealand livestock to protect them from 1080 baits.

Water and 1080

Communities in New Zealand have expressed considerable concern with regard to their potential exposure to 1080 after aerial application of 1080 bait. Between 1990 and 2000, field monitoring programmes of 1080 were

undertaken after more than 25 possum and one rabbit large-scale control operations using aerially sown 1080 baits. These recent surveys are summarised in Table 1. There has been no evidence of 1080 presence in reticulated water and no evidence of significant or prolonged 1080 contamination in surface or ground waters (Eason et al. 1992; Hamilton & Eason 1994; Parfitt et al. 1994; Meenken & Eason 1995; Booth et al. 1997; Eason 1997; Eason et al. 1999b).

Trace amounts of 1080 have been found close to the limit of detection (of 0.0003 mg/L) in approximately 5% of over 1000 water samples. The occurrence is transient and has frequently been associated with the visible presence of baits in small streams. Further surveys in New Zealand continue to show that significant contamination of waterways is unlikely after carefully conducted control operations.

A series of laboratory studies have shown that 1080 would be biodegraded by aquatic plants and micro-organisms if small amounts entered waterways. The rate of breakdown would be temperature-dependent, and in fast-running streams dilution of the toxin would be more important in reducing the presence of 1080 to toxicologically insignificant concentrations. The breakdown of this toxin has been found to occur more rapidly at higher temperatures, but still occurs at <7°C within 1–2 weeks (Ogilvie et al. 1996). Fluorocitrate (the active metabolite of 1080) has been detected in aquaria spiked with 1080. Its disappearance paralleled that of 1080, hence absence of 1080 in environmental samples would indicate that there would be a very low risk of fluorocitrate being present (Booth et al. 1999b).

When considering the risks posed to humans from exposure to 1080 through drinking water it is worth exploring the process of risk assessment, which typically involves hazard identification and exposure assessment. The risks associated with 1080 to human health (or livestock or non-target wildlife) is determined by the innate toxicity of 1080 and the potential for exposure:

$$\text{Risk} = \text{Hazard} \times \text{Exposure}$$

In a recent review Beasley (1996) pointed out that human exposure to 1080 might arise from drinking contaminated water, ingestion of toxic baits, consumption of food contaminated by contact with bait, or by inhalation of bait dust or contact with 1080 solution by pest control operators and bait manufacturers. Potentially the most significant source of general public exposure was considered to be contamination of surface water in public-water-supply catchments by aerially sown 1080 baits.

As indicated above, 1080 has never been detected in reticulated water at the point of consumption. The highest concentrations measured in surface water within the boundaries of pest control areas following aerial 1080 bait distribution are between 3.5 and 4.0 µg/L (ppb) (Table 1). If this concentration is chosen as a worst-case exposure scenario, the potential risk of adverse developmental effects from exposure of pregnant women to drinking water following possum control operations can be crudely assessed, based on recent observations in rats (Eason et al. 1999b). (For further details of recent regulatory toxicology studies on 1080, see the Pathology Section of 1.1.4.)

The assumptions used in these calculations are those recommended by the Ministry of Health (Drs G. Durham and N. Foronda pers. comm.), and are

TABLE 1. WATER ANALYSIS AFTER MAJOR 1080 OPERATIONS.*
(Adapted from Eason et al. 1999b with some recent results spanning 1998–99 added)

LOCATION	DATE	TOTAL NO. OF SAMPLES TAKEN IN OPERATION AREA	NO. WITH RESIDUES	HIGHEST CONCENTRATIONS (μg/L OR ppb)
Waipoua	1990	36	0	–
Rangitoto	1991	20	0	–
Blackstone Hill	1992	23	11	0.6
Mt Taranaki	1993	125	15	<0.3
Woodside	1993	55	0	–
Hunua Range	1994	136	7	0.7
Mt Taranaki	1994	63	0	–
Marlborough Sounds	1994	26	5	3.4
Wairarapa	1994	31	0	–
Hawke's Bay	1994	15	0	–
Ohakune	1994	6	1	0.2
Whangarei	1994	18	0	–
Karioi	1994	10	1	0.8
Manawatu	1994	21	0	–
Waimakariri	1995	4	1	0.2
Manawatu	1995	48	0	–
Hawke's Bay	1995	8	1	0.3
Ohakune Erua Forest	1995	3	0	–
Tongariro National Park	1995	8	0	–
Northland	1995	11	0	–
Tararua Ranges	1995	11	0	–
Hawke's Bay	1995	9	0	–
Waimarino Forest	1995	4	0	–
Wairarapa	1996	7	0	–
Pirongia	1996	7	0	–
Raukumara Ranges	1996	37	1	0.2
Waikato	1996	4	0	–
Levin Buffer	1996	8	0	–
Erua State Forest	1996	3	1	3.5
Waitohu Stream	1996	4	0	–
Wairokau Stream	1997	4	0	–
Raukumara Ranges	1997	12	0	–
Ohakune	1997	10	0	–
Pareora River, Timaru	1997	2	0	–
Rangataua Forest	1997	40	0	–
Te Whaiau Spillway	1997	3	1	2.4
Raukumara Ranges	1997	9	1	0.5
East Cape	1997	12	0	–
Warawara Forest	1997	4	0	–
Mt Bruce/Mikimiki	1998	10	0	–
Mawheraiti, West Coast	1998	1	0	–
Kuharua Tb	1998	1	0	–
Manawatu-Wanganui	1998	6	0	–
Toko	1998	3	2	9.0†
Wairarapa	1998	8	0	–
Manawatu-Wanganui	1998	8	0	–
West Taieri Stream	1998	4	0	–

Continued next page>

* Further water sampling and residue analyses are anticipated as part of standard operating procedures enforced by Medical Officers of Health when granting approvals for aerial 1080 operations.

† This sample is included in the table, but not included with regard to our risk assessment extrapolations under Section 1.1.3. Enquiries from Landcare Research's senior chemist identified that the sample had been collected by a worker with 1080 dust on his overalls and hands.

TABLE 1. *(Continued)**

LOCATION	DATE	TOTAL NO. OF SAMPLES TAKEN IN OPERATION AREA	NO. WITH RESIDUES	HIGHEST CONCENTRATIONS (µg/L OR ppb)
Hook Bush, Timaru	1998	2	0	–
Haurangi Crown	1998	6	0	–
Northland	1998	9	0	–
Otorohanga, Te Tahi	1998	3	0	–
Ahuroa/Maungatoroto	1998	2	0	–
Levin Buffer	1998	2	0	–
Lawrence/Waitahuna	1998	8	0	–
Northland	1998	5	0	–
Masterton	1998	6	0	–
Richmond	1998	9	0	–
Porangahau	1999	3	0	–
Northland	1999	7	0	–
Waipoua Forest	1999	1	0	–
Waipa River	1999	2	0	–
Holdsworth/Woodside	1999	3	0	–
Manawatu-Wanganui	1999	2	0	–
Hawke Hills	1999	2	0	–
Warawara Forest	1999	1	0	–
Waima	1999	2	0	–
Riwaka Forest	1999	2	0	–
Eastern Tararua R.	1999	7	0	–
Takaka	1999	6	0	–
Amuri Range	1999	1	0	–
Hawkins River	1999	1	0	–
Wakamarama	1999	15	0	–
Northland	1999	8	0	–
Wainuiomata	1999	26	0	–
Aorere	1999	2	0	–
Hauturu/Honikiwi	1999	2	0	–
Otorohanga	1999	1	0	–
Wainuiomata	1999	25	0	–
Pembroke Wilderness	1999	6	0	–
Aorere	1999	6	0	–
Rotomanu	1999	2	0	–
Kaiiwi	1999	4	0	–
Inland Paparoa	1999	12	0	–
Te Kopia Scenic Res.	1999	10	2	4.0
Marlborough	1999	1	1	0.2
Tapu River/Te Mata Str.	1999	7	0	–
Te Kopia Scenic Res.	1999	1	0	–
Benhopai	1999	1	0	–
Eastern Tararua R.	1999	4	0	–
Hauhungaroa Range	1999	8	0	–
Hampden, Herbert	1999	14	0	–
Manawatu-Wanganui	1999	2	0	–
Waingawa	1999	1	0	–
Tapanui	1999	1	0	–
Murupara	1999	1	0	–
Manawatu-Wanganui	1999	1	0	–
Wairarapa	1999	2	0	–
Totals		1153	51	

* Further water sampling and residue analyses are anticipated as part of standard operating procedures enforced by Medical Officers of Health when granting approvals for aerial 1080 operations.

intended to be very conservative (i.e. protective). If a 50-kg woman consumed water containing 1080 at 3.5–4.0 μg/L to provide all of her 2-litre daily intake during the first 90 days of pregnancy (the approximate period of organogenesis during which the foetus is most sensitive to toxic insult), she would receive a daily 1080 dose of 0.14–0.16 μg/kg. The 'safe human exposure' for developmental end points is derived by applying a 1000-fold safety factor to the no-observable-effect level (NOEL) from the developmental toxicity study in rats: 0.1 mg/kg/day ÷ 1000 = 0.1 μg/kg/day. Therefore, the potential dose received under this worst-case scenario is slightly greater than the 'safe human exposure' derived from the developmental toxicity study (after application of the 1000-fold safety factor).

In light of these findings, the Ministry of Health (MOH) recommended in 1998 that potable water from catchments treated with 1080 monitored to confirm that concentrations do not exceed 2 μg/L. The likelihood of exceeding this value in drinking water is very small, since it has only rarely (i.e. in five samples out of 1153) been exceeded in small water bodies within the operational area immediately after aerial 1080 bait distribution (see Table 1). Further, these reported levels were only detected for short periods of time (days). Continuous exposure for the 90 days of the first trimester of pregnancy would be the comparable length of exposure to that experienced by the pregnant rats in recently completed regulatory toxicology studies (Eason et al. 1999b). The current provisional maximal acceptable value in the New Zealand Drinking Water Standards is 5 μg/L (ppb).

In 1996–97, the Southland Regional Council monitored the fate of 1080 when 12 000 kg of 1080 bait were disposed of in a landfill. Bore water samples taken adjacent to the disposal pit contained 1080 concentrations either below or close to MOH guidelines. No 1080 was detected after 10 months. *In situ* samples of the residual waste material indicated that the 1080 concentration in the landfill decreased to less than its original level in 12 months (Bowman 1999).

1.1.4 Toxicology and pathology

Onset of symptoms

The latent period between the time monofluoroacetate is ingested and the appearance of clinical signs in mammals is between 0.5 and 3 hours. Peak plasma concentrations of monofluoroacetate occurred in possums and rabbits 0.5 hours after ingestion, 0.75 hours in goats, and 2.5 hours in sheep. This correlates with the latent period between ingestion and clinical signs and reflects the time taken for absorption and distribution of monofluoroacetate, and the conversion of monofluoroacetate to fluorocitrate. Animals receiving small sub-lethal doses of 1080 show mild clinical signs of poisoning, metabolise and excrete 1080 within 1–4 days, and then recover. Animals receiving a lethal dose usually show more severe signs of poisoning in addition to non-specific clinical signs such as nausea and vomiting. Specific signs include cyanosis, drowsiness, tremors, staggering, and death from ventricular fibrillation or respiratory failure. In general, herbivores experience cardiac failure, whereas carnivores experience central nervous system disturbances and convulsions then die of respiratory failure (Egekeze & Oehme 1979). Possums usually die

within 6–18 hours (Eason et al. 1997). The clinical signs of 1080 poisoning in birds will vary according to the species. Common signs may be lack of balance, slowness, ruffled feathers, and salivation. Vomiting will occur in some species such as raptors. In the terminal phase of poisoning, birds and mammals may exhibit convulsions and coma.

Mode of action

Monofluoroacetate is converted within the animal to fluorocitrate, which inhibits the tricarboxylic acid cycle. This results in accumulation of citrate in the tissues and plasma, energy deprivation, and death. Synthesis of fluorocitrate occurs in the mitochondria, and the fluorocitrate formed inhibits mitochondrial aconitate hydratase. There is also evidence to suggest that fluorocitrate inhibits citrate transport into and out of mitochondria, and that fluorocitrate has an inhibitory effect on succinate dehydrogenase. The high levels of citrate concentration that occur during monofluoroacetate intoxication can also have an inhibitory effect on the glycolytic enzyme, phosphofructokinase.

Death from monofluoroacetate poisoning is caused by the inhibition of energy production which, in turn, results in either cardiac or respiratory failure. Fluorocitrate is commonly described as a specific metabolic inhibitor of glial cells in the brain. Glial cells are thought to be important for extracellular fluid ion and pH regulation, and the control of breathing (Erlichman et al. 1998).

Pathology and regulatory toxicology

Known target organs in animals following 1080 exposure include the heart, lungs, liver, kidney, testes, and foetus (Annison et al. 1960; McTaggart 1970; Buffa et al. 1977; Sullivan et al. 1979; Schultz et al. 1982; Trabes et al. 1983; Chung 1984; Savarie 1984; Chi et al. 1996; Gregg et al. 1998; Twigg et al. 1988; Eason et al. 1999b). The pathological changes observed at post-mortem appear to be largely the result of progressive cardiac failure with congestion of the abdominal viscera and lungs. Examination of monofluoroacetate-poisoned mammals usually reveals cyanosis of mucous membranes and other tissues. Diffuse visceral haemorrhage has been described in some animals, particularly cattle. Subepicardial haemorrhages on the epicardium and endocardium as well as on the epiglottis and trachea have been observed in sheep and possums poisoned with monofluoroacetate. The presence or absence of tissue damage is likely to be dose-related, and subepicardial haemorrhages have been observed in rabbits receiving a lethal dose of monofluoroacetate but not in those receiving a sub-lethal dose. It is apparent that the target organs vary to some extent in different species, which may relate to the citrate response in different species, or the metabolic activity in different tissue. In birds a target organ appears to be wing muscle (Ataria et al. 2000) as well as the heart, which is a more common target in other species.

Repeated exposure of rats to small doses of monofluoroacetate appears to afford some protection to subsequent challenge (Atzert 1971). However, at a histopathological level, this is not the case in sheep, probably because even small doses of monofluoroacetate result in myocardial damage in this species, and this damage will be cumulative with subsequent exposure (Annison et al. 1960). In sheep that had received multiple sub-lethal doses of 1080, myocardial degeneration has been reported as well as necrosis of individual or small groups

of myocardial fibres (Schultz et al. 1982). Researchers in Australia noted macroscopic lesions in the heart of sheep, described as acute multifocal injury to the myocardium, after doses as low as 0.11 mg/kg/day for 3–7 days. A dose of 0.1 mg/kg is approximately equivalent to a 30-kg sheep eating one 4-g 1080 possum bait containing 0.08% 1080 w/w. Mild cardiac histopathology at doses of 0.055 mg/kg/day has been reported, but the duration of treatment was not specified (Whitten & Murray 1963). Although 1080 itself is not cumulative (Rammell 1993; Eason et al. 1994c), these reports in sheep clearly demonstrate that cumulative damage to the heart or other organs from repeated exposure to large sub-lethal doses of 1080 can occur.

A recent study demonstrated that ewes surviving a single exposure to 1080 did not experience any adverse long-term effects (Wickstrom et al. 1997b). Nevertheless, pathological abnormalities related to 1080 exposure were found in the heart and brain. Glial cells in the brain are particularly sensitive to fluorocitrate (Erlichman et al. 1998; Hulsmann et al. 2000). Obviously livestock must not be allowed access to toxic baits, and even partially degraded baits should be regarded as hazardous. Pregnant ewes are more susceptible to the acute toxic effects of 1080 than non-pregnant animals (O'Connor et al. 1999).

Many regulatory toxicology studies were completed in the USA before 1995, as 1080 is still used there in livestock protection collars. They included 17 studies on product chemistry, six studies on wildlife hazards, and four studies relevant to human health. The results from these studies were summarised in the Science Workshop Proceedings on 1080 (Fagerstone et al. 1994) (Table 2).

The most important of these studies to the health of those involved in pest control in New Zealand was on acute dermal toxicity of 1080 in rabbits. In this test, five male and five female rabbits for each of four dose levels were treated dermally with 1080 paste. The estimated LD_{50} was 324 mg/kg for females and 277 mg/kg for males. It had long been known that 1080 can be absorbed through the gastrointestinal and respiratory tracts, open wounds, and mucous membranes, but is less readily absorbed through intact skin (Atzert 1971). However, the results of this study demonstrated that poor dermal absorption of 1080 (Atzert 1971) does not imply no absorption, and there are obviously implications with regard to enforcing strict codes of practice and appropriate protective clothing for those involved in the manufacture or handling of 1080 baits.

Regulatory (laboratory-based) toxicology studies of this type are usually conducted before the launch of new drugs or pesticides, and are used to proactively assess the risk of these compounds to humans, pets, livestock, and wildlife. Alternatively, they may be conducted on older products, such as 1080, to provide an update to the toxicology data generated to meet new standards and data requirements that are now commonplace internationally.

The new regulatory toxicology studies (targeting human health concerns) listed in Table 2 were conducted following internationally recognised protocols. The methods are routine (Wilson 1965; Ames et al. 1975; Hoddle et al. 1983; Blazak et al. 1989). These data provide answers to the following general questions: does 1080 alter genetic material (mutagenic) and therefore have the potential to cause cancer; and does it cause birth defects (developmental toxicant)?

TABLE 2. TOXICOLOGY STUDIES ON 1080 RELEVANT TO HUMAN HEALTH: CURRENT STATUS.

STUDY TYPES	STATUS
Acute toxicity	Extensive database in the literature (see Rammell & Fleming 1978; Seawright & Eason 1994; Eisler 1995)
Skin and eye irritation	Completed (see Fagerstone et al. 1994)
Skin sensitisation	Completed (see Fagerstone et al. 1994)
Ames assay	Completed January 1998
Mouse lymphoma assay	Completed January 1998
Mouse micronucleus test	Completed January 1998
Developmental toxicity in rats (including pilot study)	Completed January 1998
90-day feeding study in rats* (including pilot study)	Completed March 2001
Metabolism/pharmacology studies	Extensive published database (see Eason et al. 1994c)

* The core component of the study was completed in December 1999. Histopathological assessment and a full report were completed in March 2000.

Results from a series of *in vitro* (cell culture) and laboratory animal studies (in rats and mice) to update the regulatory toxicology database for 1080 provided information on mutagenicity and teratogenicity. Results of three different, complementary tests indicate that 1080 is not mutagenic, and therefore unlikely to cause cancer. Results of a developmental toxicity study in rats indicate that 1080 causes developmental defects in rats when pregnant females are exposed to relatively high doses (0.33 and 0.75 mg/kg) on a daily basis during the period of organogenesis (from days 6 through to 17 of gestation). The developmental abnormalities observed were mild skeletal effects: slightly curved forelimbs, and bent or 'wavy' ribs. These results highlight the highly toxic nature of 1080 and the need for extreme care when handling this pesticide during the manufacture and distribution of bait, but do not preclude its proper use (Eason et al. 1999b). Spielman et al. (1973) reported that 1080 at a dose just below the maternal LD_{50} was not teratogenic to rats. The embryos in this study showed no macroscopic or skeletal abnormalities. The work by Spielman et al. involved only a single dose and the results contrast with our investigation following current international guidelines that require dosing rats from day 6–17 of gestation at three dose levels.

Comparison of the study by Spielman et al. (1973) and Eason et al. (1999b) is relevant to human risk assessment in New Zealand. It is noteworthy that the NOEL derived from the present multi-dose study (0.1 mg/kg/day) was 10-fold less than the single dose NOEL (1 mg/kg) reported by Spielman et al. (1973). In the most recent 90-day exposure study in rats, the NOEL for effects on testes was 0.075 mg/kg/day. In the high-dose group (0.75 mg/kg) gross examination revealed small testes and microscopic examination at necropsy revealed damaged sperm. Effects occurred in only one out of three dose groups and they were partially reversible on cessation of dosing. At the time of completing this edition of the manual (March 2000) the histopathology is incomplete. Possible heart defects are being reported in the males of the top-dose group, but this requires confirmation. The effects on these target organs are consistent with earlier work. The difference between these current regulatory toxicology studies and earlier animal studies are that no effect levels have been defined.

Fate in animals

Absorption, metabolism, and excretion

Sodium monofluoroacetate (1080) is absorbed through the gastrointestinal tract or via the lungs if inhaled. (While it is not volatile, the inhalation of 1080 powder must be avoided). Monofluoroacetate is not readily absorbed through intact skin, but it can be absorbed more readily through cuts and abrasions.

Studies of laboratory animals since the 1950s have shown that sub-lethal amounts of 1080 are excreted both unchanged and as a range of non-toxic metabolites. After oral or intravenous dosing of laboratory rodents, 1080 is rapidly absorbed and distributed through the soft tissues and organs (Hagan et al. 1950; Egeheze & Oehme 1979; Sykes et al. 1987). This contrasts with the action of commonly used anticoagulant rodenticides, such as brodifacoum, which preferentially bind to liver cells (Bachman & Sullivan 1983). Sodium monofluoroacetate is excreted as unchanged fluoroacetate and a range of metabolites (Gal et al. 1961; Schaefer & Machleidt 1971). Approximately 30% of a dose of 1080 administered to rats was excreted unchanged in the urine over 4 days (Gal et al. 1961). At least seven unidentified metabolites other than fluoroacetate and fluorocitrate, the toxic metabolite of 1080, were also detected in rat urine (Gal et al. 1961).

Administration of ^{14}C-labelled fluoroacetate to rats showed that fluorocitrate, the toxic metabolite of 1080, accounted for only 3% of the radioactivity (Gal et al. 1961), and this was confirmed by Schafer & Machleidt (1971). The major metabolite, unlike fluorocitrate, does not inhibit the activity of aconitase (Gal et al. 1961). Phillips & Langdon (1955) suggested that the unidentified metabolites include non-saponifiable lipids that probably serve as intermediates for cholesterol, and some radioactivity was found in fatty acids and cholesterol in the liver. Up to 3% of the radioactivity appeared as respiratory CO_2, which implied cleavage of the C-F bond (Gal et al. 1961).

Defluorination of 1080 or its metabolites, including fluorocitrate, has been demonstrated in animals and other living organisms (Kirk & Goldman 1970; Smith et al. 1977; Egekeze & Oehme 1979; Soifer & Kostyniak 1983, 1984; Twigg et al. 1986; Tecle & Casida 1989). Although fluoride is extensively excreted, primarily in urine, some deposition occurs in bone (Sykes et al. 1987; Eason et al. 1993a, b; Rammell 1993; Eason et al. 1994b).

The earliest reports on rats suggested that some 1080 is retained for 1–4 days. In a study using mice, 1080 concentrations in plasma, muscle, and liver decreased by half in less than 2 hours. Prolonged persistence of 1080 in animals after sub-lethal exposure therefore seems unlikely, and this has been confirmed for larger animals such as rabbits, goats, possums, and sheep (Gooneratne et al. 1994; Eason et al. 1994c). Sodium monofluoroacetate was readily absorbed and excreted. The highest concentrations occurred in the blood, with moderate levels in the muscle and kidneys, and the lowest concentration in the liver. In sheep, the highest concentrations in blood occurred 2.5 hours after dosing and there were negligible amounts in tissue and plasma 4 days after dosing. All traces of the toxin are, therefore, likely to be eliminated within 1 week.

If recommended practices are followed in possum control operations, 1080 is unlikely to be present in meat for human consumption. Where any contact of livestock (farm animals or animals intended for slaughter) with 1080 is

suspected, an adequate margin of safety should be achieved by imposing a minimum withholding period of 5 days. Should a death in a flock or herd be attributed to 1080, the withholding period should be doubled to 10 days for the surviving stock, which should be removed to a 1080-free pasture (Rammell 1993; Eason et al. 1994c).

Whilst 1080 is comparatively rapidly eliminated from living animals it can persist in carcasses for many months where it will break down more slowly and will pose a risk to dogs (Meenken & Booth 1997).

Limited research has been conducted on the pharmacokinetics of monofluoroacetate in invertebrates. In a laboratory study weta were dosed with 1080 and the persistence of 1080 residues at specified times after dosing was determined. In this experiment 1080 was eliminated from weta 6–10 days after exposure, and all weta survived dose levels of 15 mg/kg (Eason et al. 1993a, b). Similar results were obtained from a native ant (Booth & Wickstrom 1999). Insects have been monitored in forests for 1080 residues after toxic baits were aerially sown for possum control. No 1080 was found in living earthworms, spiders, beetles, millipedes, or centipedes. Although 1080 was found in some cockroaches, bush weta, and cave weta during the period the baits were on the ground, after 3–4 weeks all invertebrate samples were free from 1080 residues. Field and laboratory results for invertebrates do show that 1080 is taken up by some of the terrestrial invertebrate species. Its persistence in invertebrates is short-lived and the risk to insectivorous birds or other predators is therefore also confined to a short period after sowing baits for possum or rabbit control. However, large invertebrates frequently eat bait (Spurr & Drew 1999) and, since species like weta can contain large amounts of bait, the concerns regarding secondary poisoning via this route remain unresolved.

Species variation in response to monofluoroacetate

Whilst monofluoroacetate is a broad-spectrum toxin, there are some marked differences in susceptibility (Table 3). There is an extensive database on the acute toxicity of 1080 in a diverse spectrum of species, including birds, mammals, and reptiles (Atzert 1971; Harrison 1978; Rammell & Fleming 1978; Eisler 1995). Unlike most other vertebrate pesticides, 1080 also has insecticidal

TABLE 3. ACUTE ORAL TOXICITY (LD_{50} mg/kg) FOR SODIUM MONOFLUOROACETATE.

SPECIES	LD_{50}mg/kg		SPECIES	LD_{50}(mg/kg)
Dog	0.07		Wallaby	<1.0
Cat	0.3		Rat	1.2
Pig	0.3		Possum	1.2
Rabbit	0.4		Human	2.5
Sheep	0.4		Duck	9.0
Cow	0.4		Weka	8.0
Deer	0.5		Clawed toad (South Africa)	500
Goat	0.6			

N.B. These results represent a very small proportion of the LD_{50} data available in the literature. (Rammell & Fleming 1978; Hone & Mulligan 1982; Eisler 1995)

properties (Negherbon 1959; Notman 1989; Booth & Wickstrom 1999). As with other poisons, the relative susceptibility and LD_{50} values can be influenced by the vehicle used to deliver the poison, and environmental conditions (Henderson et al. 1999). **Dogs are extremely susceptible**, and most other carnivores are highly sensitive to poisoning. Herbivores are less sensitive, and birds and reptiles are increasingly resistant (Atzert 1971; Rammell & Fleming 1978; Eisler 1995). Several studies have revealed that animals that forage in areas where fluoroacetate-producing plants are common have evolved an increasing resistance to fluoroacetate compared to animals from areas where plants containing the toxin are not indigenous. This phenomenon is well-documented in Australia where the effect is most dramatic in herbivores and seed eaters, which are more directly exposed to the toxin than carnivores. The emu (*Dromaius novaehollandiae*) is the oldest seed-eating bird species in Australia, and has a very high level of resistance with an LD_{50} of 100–200 mg/kg. In contrast, seed-eating birds from regions outside the range of fluoroacetate-producing plant species have an LD_{50} in the range of 0.2 to 20 mg/kg. Similarly the brushtail possum of south-western Australia is 150 times less susceptible to fluoroacetate poisoning than the same species in eastern Australia where plant species containing the toxin are not present. The biochemical basis for tolerance and species variation is not clear. This species variation in mammals in response to monofluoroacetate poisoning may in part be due to differences in the biochemical response of different organs to the toxin, which may be linked to difference in glutathione level and a glutathione-requiring defluorinating enzyme. For example, 1080-induced changes in citrate content of the heart are more pronounced than in any other organs in sheep, and for this reason citrate concentrations in sheep hearts may have diagnostic value (Annison et al. 1960; Schultz et al. 1982). Guinea pigs and rabbits, like sheep, are sensitive to myocardial damage. In rats there is some short-lived elevation of citrate in the heart and, by contrast, in dogs elevation of citrate concentrations in heart tissue is reported to be minimal (Bowsakowski & Levin 1986). Furthermore, dogs do not show the ECG changes seen in sheep that are suggestive of cardiac ischaemia (Matsubara et al. 1986). In comparison with dogs the clinical signs in cats are less severe (Eason & Frampton 1991). In birds, damage to wing muscle is a unique feature that occurs at sub-lethal dose levels (Ataria et al. 2000). Most deaths in mammals generally occur 8–48 hours after ingestion of a lethal dose.

A recent review paper has highlighted the effects of ambient temperature on possum mortality, specifically how the acute toxicity of 1080 is reduced at low temperatures, and the importance of conducted aerial control in months with coldest average temperatures (Veltman & Pinder 2001).

Aquatic toxicology

Historical data indicate that fish are relatively resistant to 1080. Fingerling bream and bass (species unidentified) survived indefinitely, without any signs of toxicity, in water containing 370 mg 1080/L (King & Penfound 1946). In New Zealand, fingerling trout were subjected to 1080 concentrations of 500 mg/L and 1000 mg/L without any visible effect on the fish. Force-feeding pellets containing a total of about 4 mg of 1080 (two fingerling trout and five adult trout) or about 8 mg of 1080 (two adult trout) also had no visible effect (Rammell & Fleming 1978). Fluoroacetamide (a compound related to 1080) at a

concentration of 3500 mg/L killed only 50% of a harlequin fish (*Rasbara heteromorpha*) population in 48 hours. The LD_{50} of 1080 after intraperitoneal injection was approximately 500 mg/kg (Bauermeister et al. 1977). No explanation of the high resistance of fish to 1080 has been published but it is presumably associated with differences in the pathways or relative importance of the Krebs cycle in fish metabolism (Rammell & Fleming 1978).

During 1993, three aquatic toxicity tests were completed in the USA. The first estimated the acute toxicity of 1080 to bluegill sunfish (*Lepomis macrochirus*). No mortality or sub-lethal effects were observed at any concentration tested, with a highest NOEC (the no-observed-effect concentration) of 970 mg/L. Based on the results of this study and criteria established by the US Environmental Protection Agency (EPA), 1080 would be classified as practically non-toxic to bluegill sunfish. The second test, on rainbow trout (*Oncorhynchus mykiss*), used the same test conditions as the bluegill sunfish studies. Mortality ranged from 50% to 90% in four treatment levels ranging from 39 to 170 mg/L. In addition, mortality was 10% at the 23 mg/L treatment level, and sub-lethal effects were observed at levels over 23 mg/L. No mortality or sub-lethal effects were observed at the 13 mg/L level. The NOEC was 13 mg/L, which the US EPA classifies as slightly toxic to rainbow trout.

The third test estimated the acute toxicity (EC_{50}) of 1080 to the small fresh water invertebrate *Daphnia magna*. The EC_{50} is defined as the concentration in water that immobilises 50% of the exposed daphnids. Of daphnids exposed to levels of 350 to 980 mg/L (ppm), 70 to 100% respectively were immobilised. Immobilisation of 5% was observed among daphnids exposed to 220 mg/L. Sub-lethal effects were observed among all the mobile daphnids exposed to 220–590 mg/L, but not among those exposed to 130 mg/L. The 48-hour EC_{50} value for daphnids exposed to 1080 was 350 mg/L and the NOEC was 130 mg/L, making 1080 practically non-toxic to *Daphnia magna* by US EPA classification standards (Fagerstone et al. 1994). An early experiment reported that mosquito larvae (*Anopheles quadrimaculatus*) were comparatively sensitive to 1080 (Deonier et al. 1946). In 48 hours, 1080 concentrations of 0.025 mg/L were fatal to 15%, 0.5 mg/L to 40%, and 0.1 mg/L to 65% of fourth-instar larvae. Since the concentrations of 1080 described above are many times higher than the residue concentrations rarely associated with 1080 use (<0.001 mg/L or ppm), adverse effect on aquatic animals is unlikely (see Table 1). In practice this data would only be of value in risk assessment relating to a large amount of 1080 bait or stock solutions being deliberately or accidentally tipped into a waterway.

1.1.5 Diagnosis and treatment of 1080 poisoning

Diagnosis of non-target poisoning in domestic animals

Diagnosis of 1080 toxicosis is based on exposure history, clinical signs, laboratory analyses, and in lethal cases, lesions. Differential diagnoses (varies with species) include hypomagnesemia, hypocalcaemia, acute lead poisoning, cardiac glycoside toxicosis, strychnine, organochlorine insecticide or methyxanthine toxicosis, traumatic brain injury, epilepsy, and infectious central nervous system diseases such as distemper and rabies.

Clinical signs

Clinical signs of 1080 toxicosis vary with the species involved. In general, neurotoxic signs predominate in carnivores, while herbivores manifest signs of cardiotoxicity. However, there are exceptions and overlapping effects in some cases. The onset of clinical signs usually ranges from 30 minutes to 2–3 hours after oral exposure. Humans may experience nausea, vomiting, and abdominal pain initially, followed by respiratory distress, anxiety, agitation, muscle spasms, stupor, seizures, and coma. Hypertension is thought to be one of the more important predictors of mortality in 1080 intoxication (Chi et al. 1996, 1999).

Primary poisoning in sheep and cattle exposed to 1080 cereal bait is characterised initially by anorexia and depression, followed by staggering, muscle tremors, cardiovascular and pulmonary abnormalities (e.g. arrhythmias, ventricular fibrillation, tachypnoea, dyspnoea), terminal tonic convulsions, coma, and death from cardiac and/or respiratory failure. Severe trembling and sweating have been reported in horses (Beasley et al. 1997c). Death may occur within 12–24 hours. Animals alive 4 days after acute oral exposure are expected to make a complete recovery (Wickstrom et al. 1997b; O'Connor et al. 1999).

Secondary (or primary) poisoning in domestic dogs is characterised by rapid onset of anxiety, nausea, and vomiting (usually too late to prevent absorption of a lethal dose, given the extreme sensitivity of this species to 1080). These signs are followed by fits of wild barking and frenzied running (in a straight line or around the perimeter of an enclosure), with repeated urination, defecation, convulsions and paddling. Affected dogs appear to be oblivious to their surroundings. Seizures increase in frequency and severity with time until animals become exhausted. Death may occur during an extended tonic seizure, or from subsequent respiratory paralysis, usually 2–12 hours after ingestion (Lloyd 1983; Beasley et al. 1997c).

Neurological signs associated with 1080 exposure are generally less severe in domestic or feral cats than in dogs. Signs reported include depression or excitation, vocalisation, salivation, diarrhoea, and cardiac arrhythmias (Lloyd 1983; Eason & Frampton 1991; Beasley et al. 1997c).

Laboratory diagnosis

The most reliable diagnostic indicators of 1080 exposure are measurement of 1080 residues in blood, skeletal or cardiac muscle tissue, or stomach/rumen contents or vomitus. Analytical laboratories require at least 1 mL of serum or plasma, or 10 g of tissue, for residue determination. Samples should be stored at <4°C and analysed promptly[2] (Wickstrom & Eason 1997).

Ante-mortem clinical pathology changes consistent with 1080 toxicosis include increased serum citrate concentration (the most specific and reliable biomarker), hyperglycaemia, azotemia (increased serum urea nitrogen), lactic acidosis (secondary to seizure activity), and hypocalcaemia. In animals that survive, clinical pathology parameters return to baseline levels by day 3–4 after exposure (Beasley et al. 1997c; Wickstrom et al. 1997b; O'Connor et al. 1999; Ataria et al. 2000).

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[2] Contact Geoff Wright, telephone: (03) 325 6700; email: wrightg@landcare.cri.nz

Lesions

Rigor mortis occurs rapidly in animals poisoned with 1080, but distinctive, specific post-mortem lesions have not been described. Grossly, there is generalised cyanosis. The heart is usually observed in diastole with petechial subepicardial haemorrhages. Petechial haemorrhages are also often observed on the epiglottis, trachea, and abdominal viscera, and the lungs, liver, and kidney may be congested secondary to progressive cardiac failure. The stomach, colon, and urinary bladder of dogs and cats will invariably be empty (Lloyd 1983; Beasley et al. 1997c).

Histopathological lesions observed in sheep that died from acute 1080 exposure included multifocal or diffuse, severe, pulmonary oedema, and scattered foci of myocardial degeneration and necrosis (Wickstrom et al. 1997b; O'Connor et al. 1999). Cerebral oedema and lymphocytic infiltration of the Virchow-Robin space have also been described.

Treatment of 1080 toxicosis in domestic animals

Sodium monofluoroacetate poisoning is an urgent medical emergency, and veterinary treatment should be initiated rapidly in order to maximise the probability of survival. Although research continues, no specific antidote for 1080 poisoning has been identified, and treatment is largely symptomatic and supportive. Most animals that present with severe signs will die in spite of treatment, but veterinary intervention will increase the chance of survival in individuals that receive less than an LD_{50} dose.

Therapeutic goals for veterinarians are to:

- Decrease 1080 absorption and facilitate toxin excretion
- Control seizures
- Support respiration and cardiac function

Recommendations for the treatment of 1080 toxicosis in companion animals are as follows (Tourtellotte & Coon 1950; Chenoweth et al. 1951; Lloyd 1983; Beasley et al. 1997c):

- Where an owner sees the dog scavenging 1080-poisoned carcasses, giving a simple emetic like supersaturated household salt solution or washing soda within approximately an hour can help save dogs.
- Rapid onset of severe neurological signs precludes the induction of emesis as a means of decontamination in some cases.
- Induce anaesthesia and perform enterogastric lavage (after endotracheal intubation) if there is any likelihood of continued toxin absorption.
- Administer activated charcoal (1–2 g/kg) with a saline cathartic (magnesium sulphate at 250 mg/kg in 5–10 times as much water). (However, data from rodent studies indicate that activated charcoal is ineffective at reducing 1080 uptake from the gastrointestinal tract.)
- Control seizures with barbiturates (phenobarbitone or pentobarbitone as needed).
- Intravenous fluid therapy to enhance renal excretion of 1080 (proposed), treat hypotension/shock, lactic acidosis, and electrolyte imbalances (e.g. hypocalcaemia).
- Calcium gluconate at 0.2–0.5 mL/kg IV (5% solution, slowly, in fluids) to control tetany.

- Glycerol monoacetate (monacetin) at 0.55 g/kg IM has been recommended as a source of acetate (competitive inhibitor of fluoroacetate). However, it is difficult to obtain, and ineffective except when administered early to dogs with relatively low dose exposures.
- Ethanol at 1.5–8.0 mL/kg (50% solution) orally has also been recommended as an acetate donor. However, combined therapy with ethanol and barbiturates produces profound depression of the central nervous system and prolonged (days) anaesthesia, with high risk of pneumonia and other complications. Use of acetate donors does not appear to be more effective than supportive treatment alone.
- Antiarrhythmics for treatment of cardiac arrhythmias.
- Maintain normal core body temperature.
- Other symptomatic treatment, such as respiratory support, as needed.

1.1.6 Non-target effects

Non-target effects of 1080 used for possum control have been studied extensively during the last 20 years in New Zealand (Spurr 1991, 1994a, b; Eason et al. 1998a; Innes & Barker 1999; Powlesland et al. 1999). Dead birds may be found after aerial application of 1080 baits (Caithness & Williams 1970). However, cold-blooded animals such as reptiles are less susceptible than birds (Atzert 1971). Spurr has noted that fewer and fewer species of birds have been reported dead after 1080 poisoning operations since 1978. Most dead birds were found after large-scale control operations and trials using undyed, raspberry-lured, unscreened carrot bait that had a high percentage of small fragments or 'chaff'. Reductions in bird deaths can be attributed to the screening of carrot baits to remove small fragments, the banning of raspberry lure, the use of cinnamon oil as a deterrent, the reduced rates of bait application, and the increased use of cereal-based baits. Bait specifications now minimise the amount of fragments and chaff (likely to be eaten by birds and insects) in bait consignments, which in turn minimises the effects on non-target species. It is imperative that only high-quality baits (carrot or cereal baits) are used in control operations. Carrot or cereal baits containing substantial amounts of fragments or chaff will result in substantial bird deaths. For carrot and cereal-pellet bait specifications see Appendices 2 and 3. However, improvements in quality will not reduce the secondary poisoning risk for forest insectivores, such as tomtit, hedge sparrow, and short-tailed bats, which may be exposed to concentrations of ≥130 mg/kg in some invertebrates (Lloyd & McQueen 2000).

Regardless of the route of exposure, extensive monitoring indicates that populations of common birds are not adversely affected (Spurr 1994a). The impacts on non-target species of 70 aerial 1080 operations or trials carried out between 1978 and 1993 were reviewed by Spurr. Dead birds were reported from six of the 11 operations where systematic searches were made and from nine of the 59 operations where only incidental observations were made. Most birds found dead were introduced species (blackbirds and chaffinches), but some native birds were also killed. These losses were insignificant in population terms as no population reductions were detected for any of the more common bird species in the 35 operations where bird populations were monitored both before and after poisoning (Spurr 1994a). However, less common bird species (e.g. kiwi and kokako) have been less frequently monitored, at least for some

bait types. And the sub-lethal effects of 1080 in birds have received limited attention (Ataria et al. 2000). In contrast, Powlesland et al. (1999) have produced recent data to show that there can be very significant mortality of robins (43–55%) after aerial operations, even when quality control standards of bait are met. However, their data indicate that robin populations benefit in the longer term. They argue that the results suggest that as long as carrot protocols are strictly adhered to, and baits are distributed over large blocks of forest so that mammalian predator populations remain low during the next robin nesting season, robin populations will benefit from aerial 1080-carrot possum control operations (Powlesland et al. 1999).

Since 1993, radio transmitters have been increasingly used to monitor less common bird species. For example, in the Hauhungaroa 1080 poisoning operation in 1994, radio transmitters were fitted to 21 kaka and 19 blue ducks. All the radio-tagged birds survived for at least 4 weeks after the poison operation. Radio transmitters were also fitted to nine great spotted kiwi, five weka, and six moreporks on the Gouland Downs; 16 weka and one morepork in Tennyson Inlet; seven great spotted kiwi at Karamea; and eight weka at Rotomanu. One radio-tagged weka died from 1080 poisoning, but all other birds survived for at least 4 weeks after the operations. In 1995, radio transmitters were fitted to 24 North Island brown kiwi in Aponga Scenic Reserve, Northland, and all birds survived at least 6 weeks after 1080 baits were distributed in their territories (Fraser et al. 1995).

Lizards and frogs were not monitored in any 1080 poisoning operations prior to 1994; however, none have been reported killed by 1080. Hochstetters frog populations were monitored after possum control in the Hunua Ranges in 1994, and no short-term detrimental effect was observed. Whilst the primary focus on non-target species monitoring has been on birds, selected invertebrate populations were also monitored in five 1080 poisoning operations. No impact was detected on populations of weta in Waipoua Forest, a range of invertebrate species on Rangitoto Island, predatory insects in Mapara Reserve, or ground-dwelling invertebrates in Puketi Forest and Titirangi Reserve (Spurr 1994a). Recent observations of the numbers of species and number of individual invertebrates found feeding on 1080 baits has led to the prediction that vertebrate pest control operations are unlikely to have any long-term deleterious impacts on invertebrate populations (Sherley et al. 1999; Spurr & Drew 1999). However, concerns remain because of the number of taxa identified on baits, and changes in the number of invertebrates interfering with baits containing 1080. Sherley et al. (1999) suggested that the risk from carrot bait is small when compared with cereal bait. This conclusion is based on the mistaken assumption that 'rain washes 1080 from carrots faster than from pollard' and is incorrect as 1080 leaches more slowly from carrot bait than it does from cereal bait (Bowen et al. 1995). Regardless of these findings, efforts to reduce non-target exposure through the use of new bait materials, repellents, and colour continue (Morgan & Goodwin 1995; Hartley et al. 1999; Morgan 1999).

It has recently been suggested that a food-web approach may be a more rational way to evaluate 1080 movement and impact in ecosystems. Priorities suggested include measuring net ecological outcomes at the community level (Innes & Barker 1999) to provide a clearer assessment of risk versus benefit.

Dogs are extremely susceptible to 1080 and must be kept away from toxic baits and possum carcasses which can remain toxic for many months (Meenken & Booth 1997). Predators, such as stoats, ferrets, and cats, are also susceptible to secondary poisoning (Heyward & Norbury 1999; Murphy et al. 1999). Livestock must also be kept well away from baits, and even partially degraded baits should be regarded as hazardous to sheep and cattle. Although possum kills are routinely monitored, particularly for large-scale aerial 1080 operations, there have been few scientific studies of any associated deer mortality. One study in the northern part of Pureora Conservation Park in 1988 found that 43% of the red deer population were killed. Simultaneous carcass searches over the poisoned area confirmed the pellet-count result. The other study in the Hauhungaroa Range in 1994 gave deer kills in three areas of 30–40% of the population (Fraser et al. 1995). However, in a recent report 1080 carrot baits are reported to have reduced deer populations by >90% (Fraser & Sweetapple 2000). Pig mortality might also be expected but has not been reported.

There has been a sustained international trend to increase target specificity and reduce bait application rates when using any pesticide (Greig-Smith 1993; Morgan 1994a, b; Veltman & Pinder 2001) and minimum bait application rates (e.g. ≤5 kg/ha) should be used. Pest control operators should guard against the careless use of 1080, poor-quality control operations, or use of poor-quality baits. Non-target mortality can be minimised by well-planned operations using high-quality baits and by the increased use of bait stations. Provided that control operations are well planned and carefully executed by trained professionals using high-quality baits, adverse effects on ecosystems, water quality and safety, livestock, and human health can be minimised. No significant hazards exist to people drinking water from poisoned areas unless substantial amounts of 1080 have been dropped into a small stream. Nevertheless, the continued use of aerial sowing techniques is bound to cause community concern. Greater use of ground control including trapping, cyanide, and 1080 bait enclosed within bait stations has reduced the conflict between communities and pest control operators. When conducting aerial control, operators should be aware of a recent review of aerial control operations that indicate they will be significantly more successful when conducted in cold conditions. These observations are consistent with acute toxicity studies in possums that have demonstrated that the toxicity of 1080 is temperature-dependent (Veltman & Pinder 2001).

1.1.7 Summary

Advantages	Disadvantages
Highly effective for achieving a rapid reduction in possum numbers	Controversial, especially aerial operations
The only poison available for aerial application	Secondary-poison risk from possum carcasses (especially to dogs)
Cheap compared to most other poisons	No effective antidote
Biodegradable in the environment	Generates bait shyness if target animal gets sub-lethal dose
Can achieve consistently high kills	Poor-quality bait causes bird deaths
High-quality efficacy data and extensive field experience underpin both aerial and ground-baiting techniques	

- Ten-eighty is the main poison currently used for possum and rabbit control, either aerial application or ground-based operations.
- Monofluoroacetate, the active ingredient of 1080, occurs naturally in toxic plants in Australia, South Africa, and South America.
- Since 1080 is highly water-soluble, it will be dispensed in the environment by rain and stream water. Some micro-organisms, such as *Pseudomonas* species, in the soil will defluorinate 1080.
- Sodium monofluoroacetate is a relatively stable molecule that will not break down in water unless living organisms, such as aquatic plants or micro-organisms, are present. Water-monitoring surveys, conducted during the 1990s, have confirmed that significant contamination of waterways following aerial application of 1080 bait is unlikely.
- Sodium monofluoroacetate is a broad-spectrum poison that acts by interfering with the energy-producing tricarboxylic acid cycle in the mitochondria.
- Dogs are extremely susceptible to poisoning.
- If an animal has ingested a sub-lethal dose of 1080, toxin residues will not persist in meat, blood, the liver, or fat (in contrast with brodifacoum—Talon® or PESTOFF®).
- Cellular and organ damage from multiple exposure to sub-lethal doses (e.g. myocardial necrosis) could be cumulative.
- If livestock become exposed to 1080 bait, a minimum withholding period of 5–10 days should be enforced to allow for excretion of 1080, so that residues will not occur in meat.
- High-quality baits reduce non-target impacts on birds. Current evidence suggests that populations of common bird species and invertebrates are not adversely affected, but further monitoring of rarer species after aerial application of baits is still underway.

1.2 CYANIDE (FERATOX®)

Chemical Name: Sodium cyanide

Synonyms: Cyanide

Cyanide paste and pellets are favoured by commercial hunters. Because it kills so quickly, animals die no more than a few feet from where the poison was laid so recovery of carcasses and skins is easy. Cyanide can only be purchased and used by licensed operators.

Pea-sized pieces of paste are placed with a little flour and icing sugar (or other lures such as cinnamon or eucalyptus oil) on a rock, leaf, or stick. However, cyanide paste rapidly loses its toxicity in wet conditions and possums that receive a sub-lethal dose become bait shy. This shyness problem may be compounded by the hydrogen cyanide gas (also hazardous for hunters) emitted by the paste. Bait and poison shyness is a problem in many areas where cyanide paste has been used intensively.

Feratox® (a pea-sized encapsulated cyanide pellet) was developed to increase the effectiveness of cyanide and reduce the risk of exposure of operators to hydrogen cyanide gas. The pellets are placed in a bait station with either similar-sized cereal feed pellets, or in a peanut-butter paste.

1.2.1 Physical and chemical properties

The empirical formula for sodium cyanide is NaCN and the molecular weight is 49. It is a white powder with a melting point of 563°C. Potassium cyanide (KCN) is also available in New Zealand. Both compounds have similar properties. They are both highly soluble in water. KCN has a melting point of 623°C, molecular weight.

1.2.2 Historical development, use, and occurrence in nature

Cyanide has been used in New Zealand for several decades for killing possums, but has limited use in other countries. Because of its fast action, cyanide is considered in a number of countries to be too hazardous for pest control. Cyanides are used widely and extensively in the manufacture of synthetic fabric and plastics, in electroplating baths, and metal-mining operations. Other sources of cyanide in the environment include fumigation operations, cyanogenic drugs, fires, cigarette smoke, and chemical warfare agents. Although the natural occurrence of cyanide is widespread in the environment, levels tend to be elevated in the vicinity of metal-processing operations, electroplaters, gold-mining facilities, oil refineries, power plants, and solid-waste combustion.

Cyanogenic (cyanide-containing) compounds occur in plants (Table 4) and also in some fungi and bacteria. More than 2000 plants are known to be cyanogenic, including food plants and forage crops.

Some common sources for humans include cassava, sweet potatoes, yams, maize, millet, bamboo, sugar cane, peas, beans, almond kernels, lemons, limes, apples, pears, cherries, apricots, prunes, and plums. There are reports from overseas that yields of hydrogen cyanide (HCN) from common food and feed sources range from 0 to 912 mg/100 g. There are also numerous overseas reports of livestock that have been acutely poisoned by young sorghum and

TABLE 4. EXAMPLES OF PLANTS WITH CYANOGENIC POTENTIAL (Osweiler et al. 1985).

BOTANICAL NAME	COMMON NAME
Holcus lanatus	velvet grass
Hydrangea spp.	hydrangea
Linum spp.	flax
Lotus corniculatus	birdsfoot trefoil
Phaseolus lunatus	lima bean
Prunus spp.	cherry, apricot, peach
Malus spp.	apple
Pyrus spp.	pear
Sambucus canadensis	elderberry
Sorghum spp.	Sudan grass, Johnson grass
Suckleya suckleyana	poison suckleya
Trifolium repens	white clover
Triglochin maritima	arrow grass
Vicia sativa	vetch seed
Zea mays	maize

sugar gums (Towill et al. 1978; Webber et al. 1984). Young bamboo shoots and peach leaf 'tea' are examples of dietary sources of HCN poisoning in children (Hayes 1994). Cyanogenic lipids are another group of precursors from plants that contain, instead of sugars, long-chain fatty acids and yield carbonyl compound and hydrogen cyanide upon hydrolysis. Like fluoroacetate, cyanogenic glycosides are considered to be a chemical plant-defence to deter browsing animals.

Under natural conditions the hydrolysis of cyanogenic glycosides in plants is inhibited, since the degradative enzymes of plants that can cause release of cyanide from the glycoside are kept spatially separated from the glycoside in intact plant cells. Upon wilting, frosting, or stunting of the plant, free HCN may be released as a result of plant cellular damage, which allows enzymatic degradation of the glycoside.

Rapid hydrolysis and release of HCN occurs only when plant cell structure is disrupted. Thus when the leaves of cyanogen-containing plants that possess glycosidase enzyme are eaten or damaged by herbivores, HCN will be released.

Cyanide has been recognised as a poison since very early times, having been used by the ancient Egyptians and early Romans. In the USA and Australia it is used in predator control devices and in New Zealand it is used in pastes or in a pellet (Feratox®) for controlling possums. The pastes contain oil, which protects the cyanide from exposure to air and hence slow down the release of hydrogen cyanide gas. Nevertheless, cyanide paste has a characteristic smell produced by the hydrogen cyanide gas liberated on hydrolysis. It is thought that 'shy' possums avoid cyanide paste because of this smell. The paste contains 55% NaCN and Feratox® pellets contain 80 mg. Cyanide has not been the toxicant of choice in the past, because cyanide pastes are only moderately effective and some possums have an innate aversion to the smell (Warburton & Drew 1994). Feratox® became available in 1997 and has become increasingly popular as field experience with the product has been gained. Feratox® products for other species (e.g. ferrets) are being developed, but at present these are still at the prototype phase (Spurr et al. 1999). A rodent repellent has been added to the Feratox® delivery system to increase its specificity for possum control (Morgan & Rhodes 2000).

1.2.3 Fate in the environment

There are no formally published data on the fate of cyanide from possum pastes used in New Zealand. However, cyanide paste is fairly unstable. It is thought that the cyanide dissipates into the environment by gaseous diffusion as hydrogen cyanide. The stability of the cyanide is increased by the oil present in the paste bait. The length of time that baits remain toxic depends on rainfall and on how well they are protected from the rain. The baits are not considered safe until they are broken down and unrecognisable (Rammell & Fleming 1978). Feratox® pellets that fall from bait stations will disintegrate slowly over a period of 2–4 months.

Cyanide ions are not strongly absorbed or retained in soils. Leaching into water will occur. Cyanide salts may also be degraded by some soil micro-organisms (Eisler 1991). Bacteria exposed to high concentrations of cyanide can be

adversely affected, but acclimatised populations can degrade cyanide to yield a variety of products, including carbon dioxide and ammonia (Towill et al. 1978).

1.2.4 Toxicology and pathology

Onset of symptoms

Cyanide is a potent and rapid-acting asphyxiant. At lethal doses inhalation or ingestion of cyanide produces adverse reactions within seconds and death within minutes. Of all the poisons currently used for possum control, cyanide is considered the most humane (Gregory et al. 1996, 1998). However, death from lower doses can in some cases take from 1 to 4 hours, hence the importance of using high-quality baits and baiting practices to ensure maximum efficacy.

The minimal lethal dose of HCN in humans is 0.5–3.5 mg/kg. Information on the LD_{50} values of specific species is detailed in Tables 5 and 6. Signs of acute poisoning in humans are hyperventilation, headache, nausea and vomiting, generalised weakness and coma, followed by respiratory depression and death (Hayes 1994). In animals, clinical effects also occur in rapid succession. Initially there can be excitement and generalised muscle tremor. Animals may salivate, void faeces and urine, and gasp for breath. Convulsions will follow due to anoxia. In possums there appears to be minimal signs of distress, and convulsions occur after unconsciousness (Gregory et al. 1998).

The first signs of cyanide toxicosis in birds appear between 0.5 and 5 minutes after exposure, and include panting, eye blinking, salivation, and lethargy (Wiemeyer et al. 1986). Breathing becomes laboured and intermittent prior to death.

Mode of action

Cyanide disrupts energy metabolism by preventing the use of oxygen in the production of energy. Cyanide's toxic effect is due to its affinity for the ferric haem form of cytochrome a_3 (also known as cytochrome c oxidase), the terminal oxidase of the mitochondrial respiratory chain. Formation of a stable cytochrome c oxidase–CN complex in the mitochondria produces a blockage of electron transfer from cytochrome oxidase to molecular oxygen and cessation of cellular respiration, causing cytotoxic hypoxia in the presence of normal haemoglobin oxygenation. Tissue anoxia induced by the inactivation of cytochrome oxidase causes a shift from aerobic to anaerobic metabolism, resulting in the depletion of energy-rich compounds such as glycogen, phosphocreatine, and adenosine triphosphate, and the accumulation of lactic acid with decreased blood pH.

The combination of cytotoxic hypoxia with lactate acidosis depresses the central nervous system, the most sensitive site of anoxia, resulting in respiratory arrest and death (Eisler 1991). Cyanide is known to produce a range of biochemical changes in the brain associated with poisoning. Some of these changes will be associated with acute toxicity, anoxia, and death. Others, such as the depletion of dopamine (a central nervous system neurotransmitter), may be associated with chronic toxicity, such as the development of delayed progressive Parkinsonism and dystonia in humans following sub-lethal cyanide intoxication (Kanthasamy et al. 1994).

Pathology and regulatory toxicology

Cyanide causes subendocardial and subepicardial haemorrhage and petechial haemorrhage in the intestine. However, the only consistent post-mortem changes are those related to the oxygenation of the blood. Mucous membranes are pink and appear well oxygenated. The blood is usually a bright cherry-red colour. Chronic exposure to sub-lethal doses may lead to multiple foci of degeneration in the central nervous system (Osweiler et al. 1985), and histological examination of the brain has associated extensive destruction of dopaminergic neurones in the basal ganglia with neurotoxicity associated with acute cyanide intoxication (Kanthasamy et al. 1994).

The authors were unable to access regulatory toxicology studies on cyanide, which are conducted in *in vitro* test systems and laboratory animals to assess risk to humans with regard to issues such as mutagenicity, teratogenicity, and to define no-effect levels.

Fate in animals

Absorption, metabolism, and excretion

Cyanide is rapidly absorbed through the lungs by inhalation or through the gastrointestinal tract following ingestion. It is less readily absorbed through the skin. However, it should be noted that the LD_{50} for a solution of KCN on intact skin in rabbits is as low as 22.3 mg/kg (Eisler 1991). Free cyanide is rapidly distributed in tissue and body fluids, resulting in the prompt onset of the signs of acute cyanide poisoning.

TABLE 5. ACUTE ORAL TOXICITY (LD_{50}mg/kg) OF CYANIDE (Hone & Mulligan 1982; Marks & Gigliotti 1996).

SPECIES	LD_{50} (mg/kg)
Duck	1.43
American kestrel	2.12
Cattle	2.00
Sheep	2.30
Deer	Approx. 3.5–4.5
Pig	Approx. 3.5–4.5
Goat	Approx. 3.5–4.5
Rabbit	Approx. 3.5–4.5
Hare	Approx. 3.5–4.5
Japanese quail	4–5
Rodents	6.40
Possum	8.70
European starling	9.00

TABLE 6. ACUTE TOXICITY (96-hour LD_{50}) OF CYANIDE TO *Daphnia* AND FISH FROM AQUARIA (Hone & Mulligan 1982).

SPECIES	CYANIDE CONCENTRATION (ppb)
Rainbow trout	28 at 6°C
Yellow perch	76–108
Fat minnow	82–113
Daphnia magna	160

In animals surviving a sub-lethal dose, the great majority of the absorbed cyanide reacts with sulphane sulphur in the presence of enzymes to produce thiocyanate, which is excreted in the urine for several days afterwards. Owing to this rapid detoxification, animals can ingest sub-lethal doses of cyanide over extended periods without apparent harm (Mengel et al. 1989). Species vary considerably in both the extent to which thiocyanate is formed and the rate at which it is eliminated from the body. Thiocyanate metabolites resulting from the transulphuration process are about 120 times less toxic than the parent cyanide compound. However, thiocyanate may accumulate in tissues, and has been associated with developmental abnormalities and other adverse effects. The development of delayed progressive central nervous system disorders, including Parkinsons disease in humans, following acute cyanide intoxication (Kanthasamy et al. 1994) suggests that there is a risk of permanent brain damage in animals and humans after apparent recovery from acute exposure. Although cyanide is not cumulative, as with other toxic materials, the damage caused from repeated exposure could be cumulative.

Minor detoxification pathways for cyanide include exhalation in breath as HCN and as CO_2 from oxidative metabolism of formic acid; conjugation with cystine to form 2-aminothiazolidene-4-carboxylic acid or 2-aminothiazoline-4-carboxylic acid; combining with hydroxocobalamin (B_{12}) to form cyanocobalamin, which is excreted in urine and bile; and binding by methaemoglobin in the blood.

Inhalation and skin absorption are the primary hazardous routes in cyanide toxicity in relation to occupational exposure. Skin absorption is most rapid when the skin is cut, abraded, or moist. Inhalation of cyanide salts is also particularly hazardous because the cyanide dissolves readily on contact with moist mucous membranes. Regardless of route of exposure, cyanide is readily absorbed into the bloodstream and distributed throughout the body. Cyanide concentrates in erythrocytes through binding to methaemoglobin. Because of the affinity of cyanide for the mammalian erythrocyte, the spleen may contain elevated cyanide concentrations when compared to blood. Accordingly, the spleen should always be taken for analysis in cases of suspected cyanide poisoning (Eisler 1991). The brain is the major target organ of cytotoxic hypoxia, and brain cytochrome oxidase may be the most active site of lethal cyanide action, as judged by distribution of cyanide.

Species variation in response to cyanide

Cyanide is a broad-spectrum toxin and is likely to be toxic to a range of vertebrates and invertebrates. The LD_{50}s on a mg/kg basis are similar for a range of mammals and birds (see Table 5). The insecticidal properties are utilised when HCN is used as a fumigant (e.g. to kill weevils in grain warehouses).

It has been suggested that the rapid recovery of some birds exposed to sub-lethal doses of cyanide may be due to the rapid metabolism of cyanide to thiocyanate and its subsequent excretion. Species sensitivity to cyanide is not related to body size, but may be associated with diet. For example, raptors are more sensitive to cyanide than are species that feed mainly on plant material, with the exception of mallard duck (Eisler 1991).

There are limited data on the toxicity of cyanide to reptiles, though it would appear that cold-blooded animals such as frogs are less susceptible. The lethal dose in frogs is approximately 60 mg/kg (Hone & Mulligan 1982).

Aquatic toxicology

There are numerous publications on the toxicity of cyanide to aquatic invertebrates and fish, and some results from these are given in Table 6. However, these data are principally relevant to accidental spills of large quantities of sodium or potassium cyanide into rivers and streams (Eisler 1991) and are of very limited relevance to the use of cyanide baits for possum control in New Zealand.

1.2.5 Diagnosis and treatment of cyanide poisoning

First aid for human exposure

Lethal exposures to cyanide can cause unconsciousness in 10 seconds and death within a few minutes. Symptoms in humans include hot flushes with diaphoresis (perspiration), headache, nausea, vomiting, lethargy/weakness, anxiety, confusion, coma, convulsions, increased respiratory rate at low doses, but rapid onset of apnea (respiratory arrest) at high doses, tachycardia (increased heart rate) early, which progresses to bradycardia (decreased heart rate) with hypotension, arrhythmias, and asystole (cardiac arrest).

Fatalities usually result from intentional ingestion of bait or cyanide salts. By contrast, pest managers are most likely to be exposed to inhalation of hydrogen cyanide (HCN) fumes in an enclosed space, such as a storeroom or vehicle. Serious risks to health are rare under these circumstances, but prompt treatment is essential if any of the above symptoms are observed in the presence of cyanide baits.

First aid for persons who have inhaled HCN gas includes (Meredith et al. 1993):

- Move the victim to a safe environment, being careful to avoid exposing the rescuers.
- Ensure adequate ventilation.
- Establish clear airway and provide 100% oxygen, if possible.
- If victim is still breathing, break a capsule of amyl nitrite in a handkerchief and hold it under the nose and mouth for 30 seconds of every minute until the condition stabilises. Note that inhalation of amyl nitrite is rather ineffective at producing methaemoglobinemia, and is meant to be a temporising measure until intravenous sodium nitrite can be administered. In the field, it is far more important to adequately ventilate and oxygenate the victim than to administer amyl nitrite (Chen & Rose 1952).
- If breathing has ceased, begin artificial respiration, preferably with an endotracheal tube and bag, or bag-mask-valve ventilation. Hold a crushed capsule of amyl nitrite in front of the intake valve of the ventilation bag for 30 seconds of every minute. Direct mouth-to-mouth resuscitation should be avoided because of risk to the rescuers.
- Initiate cardiopulmonary resuscitation if there is no pulse.
- Remove any contaminated clothing and wash cyanide from the skin.
- Keep victim warm and transport to hospital immediately.

It is important to note that a person who has only inhaled HCN gas, but has escaped to a safe environment without becoming seriously ill, is unlikely to develop delayed adverse health effects (Peden et al. 1986).

Diagnosis of non-target poisoning in domestic animals

Cyanide poisoning is an extremely acute syndrome, and non-target animals that receive a lethal dose are usually found dead close to the source of the toxin. However, in cases where exposure is observed directly, and the dose is not immediately fatal, veterinary intervention may increase the chance of survival. Diagnosis of cyanide toxicosis is based on exposure history, clinical signs, laboratory analysis of appropriate specimens, and in lethal cases, lesions. Differential diagnoses in livestock include nitrate and urea poisoning.

Clinical signs

Clinical signs generally begin within 5–10 minutes of oral exposure to toxic levels of cyanide, and are characterised by anxiety, salivation, lacrimation (flow of tears), and tachypnoea (rapid respiratory rate), progressing rapidly to dyspnoea (difficult breathing), weakness, pink-coloured mucous membranes, muscle fasciculations and tremors, urination, defaecation, pupillary dilatation, staggering, and tachycardia (rapid heart rate). Terminal signs include lateral recumbency, cardiac arrhythmias, opisthotonus (spasm in which the head and hind legs are bowed backward), clonic/tonic convulsions, and death from respiratory paralysis. Death can occur in as little as 10–20 minutes, or more swiftly if large doses are absorbed, or up to 3–4 hours after exposure. However, most animals that survive 2 hours after exposure will recover completely without treatment (Radostits et al. 1994; Osweiler 1996a; Beasley et al. 1997b).

Laboratory diagnosis

Since cyanide exposure causes no specific, definitive pathologic changes, and many animals are found dead (rather than sub-lethally exposed), it is difficult to confirm a diagnosis of cyanide poisoning without demonstrating cyanide residues in stomach contents or blood or other tissue (Osweiler et al. 1985; Beasley et al. 1997b). Stomach or rumen contents, liver, or skeletal muscle samples should be collected and immediately frozen in airtight containers. Samples should be shipped frozen to an appropriate laboratory. Low concentrations of cyanide in tissues are indicative of intoxication. Whole, heparinised blood samples collected in airtight containers with no head space (submitted immediately or frozen) can also be analysed for cyanohaemoglobin concentration.

Lesions

Blood and mucous membranes may be bright red in colour, especially in cases of rapid death, and when post-mortem examination is performed promptly. This distinct colouration is caused by high oxygen levels in the venous blood secondary to cyanide inhibition of mitochondrial cytochrome c oxidase, with resultant inability to utilise molecular oxygen at the cellular level. Peripheral tissue oxygen rises, preventing unloading of arterial oxygen, and the consequent increase in oxyhaemoglobin in the venous return (Smith 1996). However, this clinical sign is not consistently present. In the terminal stages,

many poisoned animals become cyanotic (bluish or purple discolouration of skin and mucous membranes resulting from the accumulation of deoxyhaemoglobin in peripheral blood), as a result of respiratory paralysis, low cardiac output, and shock (Curry 1992).

Because death associated with cyanide exposure is so rapid, gross and microscopic lesions induced by the toxin are frequently absent (Jones et al. 1997). Many of the gross post-mortem changes that may be observed are attributable to death from anoxia, often accompanied by terminal seizures, and are not specific for cyanide. Subepicardial and subendocardial haemorrhage are often observed, as is congestion with petechial haemorrhages in the lungs, trachea, abomasum, and intestine. If death is somewhat delayed, or animals have been repeatedly exposed to cyanide, focal lesions of grey and white matter may be seen in the brain (Jones et al. 1997). A bitter-almond smell may be detectable in the rumen contents in some cases (Osweiler et al. 1985; Radostits et al. 1994).

Treatment of cyanide toxicosis in domestic animals

Cyanide poisoning is an urgent medical emergency, and veterinary treatment should be initiated rapidly in order to maximise the probability of survival. Therapeutic goals are to:

- Decrease toxin absorption
- Split the cyanide-cytochrome oxidase bond and facilitate cyanide excretion
- Support respiration and cardiac function.

Recommendations for the treatment of cyanide toxicosis in animals are as follows (Osweiler 1996a; Beasley et al. 1997b):

- Peracute onset of signs precludes the induction of emesis as a means of decontamination.
- Administer activated charcoal (1–2 g/kg).

  Livestock
- Sodium nitrite at 10–20 mg/kg IV (as a 20% solution) to induce measured methaemoglobinemia. The Fe^{+3} in methaemoglobin binds cyanide (forming cyanomethaemoglobin) and reduces the amount of toxin available and bound to Fe^{+3} in cytochrome oxidase. Nitrite may also act as a vasodilator.
- Sodium thiosulphate at 30–40 mg/kg IV (as a 20% solution), to provide a sulphur substrate to enable rhodanase-catalysed conversion of cyanomethaemoglobin to hydrogen thiocyanate, which is excreted in the urine. Repeat at half the initial dose in 30 minutes if no clinical response.
- Recent reports indicate that high doses of sodium thiosulphate (660 mg/kg IV) may be effective without the use of nitrites (and the attendant risk of excessive methaemoglobinemia).

  Small animals
- Administer 1.65 mL of a 25% solution of sodium thiosulphate per kilogram, and 16 mg of sodium nitrite per kilogram body weight IV over several minutes. Repeat at half the initial dose in 30 minutes if no clinical response.

1.2.6 Non-target effects

In general it is perceived that fewer land-bird species have been reportedly killed by cyanide than by trapping or 1080. Smaller numbers of individual birds have been killed by cyanide than caught in traps. The most commonly poisoned

native bird species have been weka and kiwi. For example, in 1947/48, extensive use of cyanide in Poverty Bay killed thousands of possums, but only a small number of native birds, mainly weka. However, in 1984, 66 hunters reported 37 kiwi poisoned by cyanide, about a quarter of the number caught in traps (Spurr 1991). No kiwi have been reported poisoned after 1080 operations. A short-tailed bat has been found dead, presumably poisoned on a cyanide bait laid for possums (Daniel & Williams 1984). The use of Feratox® baits and improved delivery systems should limit non-target mortality. The risks of secondary poisoning are low, but freshly killed carcasses are likely to be hazardous to non-target species.

1.2.7 Summary

Advantages	Disadvantages
Cheap (1–2 cents per bait)	Hazardous to users
Humane (very rapid action)	Toxicity of paste deteriorates rapidly in wet weather
Suitable for skin/carcass recovery	Paste can result in very poor kills if possums are cyanide-shy, hence not favoured by pest control agencies
Low secondary-poisoning risk	Can induce poison aversion
Achieves moderate to high kills (70–90%)	Antidotes are available but their use is controversial
Encapsulated cyanide does not produce HCN gas so is safer for hunters to use and is suitable for cyanide-shy possums	
Encapsulated cyanide pellets can be recovered and reused	
Encapsulated cyanide is not adversely affected by wet weather as cyanide paste is	
Biodegradable in the environment	

- Cyanide has been used since ancient times. It is used in New Zealand in a concentrated paste bait or pellet for controlling possums.
- Cyanide is the most humane poison available for vertebrate pest control.
- Naturally occurring cyanogenic compounds are considered to be a plant defence mechanism to deter browsing animals. When animals eat the leaves of cyanogen-containing plants, hydrogen cyanide gas is released.
- Cyanide in paste bait is fairly unstable and has low persistence in the environment. Cyanide dissipates by gaseous diffusion. The length of time that a bait remains toxic will depend on rainfall. Some cyanide may be washed into the ground, but it will not be strongly absorbed or retained in soil, and cyanide salts can be degraded by micro-organisms.
- Cyanide is toxic to a wide range of aquatic organisms; however, significant contamination of waterways after ground use of cyanide paste is most unlikely.
- Cyanide is a fast-acting broad-spectrum toxin and in both birds and mammals it causes tissue anoxia through inactivation of cytochrome oxidase and death due to respiratory failure.
- Sub-lethal doses of cyanide will be metabolised to less toxic thiocyanides and excreted in the urine over a period of several days.

- Cyanide biomagnification in food webs is most unlikely and has not been reported, possibly due to rapid detoxification of sub-lethal doses by most species and death at higher doses.
- Cyanide baits have been reported to kill non-target species, including kiwi, weka, and short-tailed bats.
- Cyanide bait is a potential hazard to users and the public if not handled, dispensed, and disposed of with diligence.
- Cyanide in paste can change into a gaseous state (HCN). Risk of inhalation of HCN is perhaps the greatest risk associated with cyanide. One or two cyanide capsules (Feratox®) contain enough cyanide to be lethal to humans.

1.3 CHOLECALCIFEROL (CAMPAIGN®, FERACOL®)

Chemical Name: 9,10-Secocholesta-5,7,10 (19)-trien-3-ol.

Synonyms: Vitamin D_3

This is a relatively new poison and was introduced in New Zealand in 1995. It poses a low risk of secondary poisoning. Introduced initially for possum control, it is also a rodenticide.

1.3.1 Physical and chemical properties

The empirical formula is $C_{27}H_{44}O$ and the molecular weight is 384.62. The melting point is 84–85°C. It is practically insoluble in water, soluble in the usual organic solvents, and only slightly soluble in vegetable oils. Pure cholecalciferol is oxidised and inactivated by moist air within a few days. Commercially produced cholecalciferol concentrate and baits are formulated to overcome oxidation and ensure stability.

1.3.2 Historical development, use, and occurrence in nature

Cholecalciferol (vitamin D_3) was developed in the 1980s as a rodenticide (Marshall 1984; Tobin et al. 1993). It is registered under the trade name of Quintox® (0.075% cholecalciferol) in the USA, and in Europe it has been added to baits (Racumin® plus) to overcome anticoagulant resistance in rats and mice (Pospischil & Schnorbach 1994). In 1995 a cereal bait containing 0.8% cholecalciferol (Campaign®) was registered for possum control in New Zealand. This was followed in 1999 by the development of a paste bait containing 0.8% cholecalciferol (FeraCol®). Two strengths of FeraCol® paste will be available from 2000, 0.8% for possums and 0.08% for rats and mice. Cholecalciferol is synthesised in animal skin by the action of sunlight on its precursor, 7-dehydrocholesterol. Natural dietary sources of vitamin D_3 include liver, fish oils, egg yolk, and milk fat. Vitamin D exists in two forms, vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol), each sharing the same steroid nucleus, but having different side chains. Both forms of vitamin D appear to be identically metabolised and express similar biological activity in mammalian species. Cholecalciferol seems to be more widely used as toxin, probably because it is more readily available and less expensive than ergocalciferol.

Because Vitamin D_3 is naturally occurring and is involved in calcium homeostasis, there has on occasion been a tendency to consider baits containing cholecalciferol as safe to non-target species. However, the relatively lower sensitivity of cats and dogs compared with rodents does not make this product 'safe' for pets. Inappropriate marketing of cholecalciferol-containing rodenticides in Australia in the late 1980s produced a spate of poisoning incidents and subsequent backlash against its use. While target species for cholecalciferol are amongst the most sensitive, all bait containing cholecalciferol must be treated as potentially poisonous to non-target species, and must be handled and dispensed as carefully as other types of toxic bait.

1.3.3 Fate in the environment

There are no published data on the fate of cholecalciferol in soil and water. The manufacturers of Campaign® (Aventis) have suggested that cholecalciferol residues will be degraded by sunlight. Proper use of cholecalciferol-containing baits will limit the contamination of soil. Some baits may be spilt from bait stations. Cholecalciferol leaches from cereal baits very slowly and trace amounts will be found in soil immediately underneath disintegrating baits (Booth et al. 1999a). Once cereal baits have disintegrated, low-level residues of cholecalciferol in soil are unlikely to present a significant hazard. Since cholecalciferol is licensed for use only in bait stations, any contamination will be localised. Cholecalciferol is most unlikely to be found in waterways when used in a proper manner in appropriately designed bait stations.

1.3.4 Toxicology and pathology

Onset of symptoms

Possums that receive a lethal dose of cholecalciferol bait usually die within 4 to 7 days. Clinical signs commonly expressed include loss of appetite, constipation, lethargy, tachypnea (rapid and shallow breathing), and death. Death is thought to result from hypercalcaemia, tissue calcification, and renal or cardiac failure (Jolly et al. 1993; Beasley et al. 1997a).

The occurrence, speed of onset, and severity of signs is dose-dependent. There appears to be some species variation in the clinical signs of poisoning and target organs affected by cholecalciferol (Jolly et al. 1993). The clinical signs reported in cats and dogs include nausea, vomiting, and diarrhoea, but these do not occur in possums.

Mode of action

In order to gain biological and toxicological activity, cholecalciferol must undergo metabolic conversion to 25-hydroxycholecalciferol. At toxic doses, this active metabolite mobilises calcium stores from bones into the bloodstream, and decreases calcium excretion by the kidneys. The net result is dangerously high concentrations of blood calcium (hypercalcaemia) and tissue calcification. Tissue calcification can occur in the cardiovascular system, kidneys, stomach, lungs, and muscles. Mineralisation and blockage of blood vessels, with death probably from heart failure, appears to be the mode of action of cholecalciferol in the possum, as in rodents. In other species, including cats and dogs, renal failure (caused by vessel blockage and

nephrocalcinosis) and gastrointestinal haemorrhage appear more prominent (Gunther et al. 1988; Moore et al. 1988; Jolly et al. 1993).

Sub-lethal poisoning of target species can cause prolonged anorexia and wasting, which creates ethical and animal welfare concerns. Therefore, current baits are designed with the appropriate concentration of cholecalciferol to ensure maximum potency. Calcium has been added to cereal baits in New Zealand to increase their effectiveness (Jolly et al. 1995). To avoid sub-lethal poisoning, it is particularly important for cholecalciferol baits that adequate palatability and efficacy of any new formulations are established using reliable quality assurance procedures.

Pathology and regulatory toxicology

Post-mortem examination of possums poisoned with cholecalciferol-containing bait has revealed pale, mottled hearts, oedema, and lung congestion. Histological examination has revealed widespread mineralisation of cardiac muscle fibres and calcification of blood vessel walls in the heart, kidneys, and lungs. In other species (cats and dogs) nephrocalcinosis and gastrointestinal haemorrhage appear more prominent. Necropsy shows a swollen liver with patchy congestion, pale enlarged kidneys with congested cortical vessels, pale blotching of the intestines, areas of gritty mucosa in the stomach, and pallid heart musculature. Histopathology shows widespread metastatic calcification of soft tissue (e.g. renal tubules, submucosal and mucosal regions of stomach and small intestine, heart, and arterial walls of viscera).

The authors were unable to access data from regulatory toxicology studies on cholecalciferol. Regulatory toxicology studies are conducted in *in vitro* test systems and laboratory animals to assess risk to humans with regard to issues such as mutagenicity, teratogenicity, and define to no-effect levels.

Fate in animals

Absorption, metabolism, and excretion

Cholecalciferol after absorption from the intestine is transported to the liver, where it is metabolised to 25-hydroxycholecalciferol (25OHD). This metabolite is then transferred to the kidney and converted to 24,25-, or 1,25-dihydroxycholecaliferol. The latter metabolite is the most biologically active form of the vitamin.

Half-lives of cholecalciferol of 0.8–7.9 days have been observed in vitamin D-deficient humans and rats and 3–36 days in normal humans. The half-lives of the active metabolite 25OHD are 10.5–12 days in vitamin D-deficient humans, 15–36 days in humans when vitamin D status was normal, and 25–68 days in humans and cattle during vitamin D toxicity. Interestingly the half-life of 25OHD is shorter in seals than in other mammals, which probably explains the resistance of this species to cholecalciferol toxicity (Keiver et al. 1988). The fate of the 25OHD has been studied in a dog undergoing treatment for poisoning. Levels of 25OHD decreased from >250 ng/mL to normal (i.e. <50 ng/mL) within 30 days (Dougherty et al. 1990). After possums have received a lethal dose (20 mg/kg) of 0.8% cholecalciferol, the mean concentrations of the active metabolite in the blood increased from <50 to between 600 and 1000 ng/mL (Eason et al. 1996c).

Persistence studies in possums with cholecalciferol indicated that elevated concentrations of 25OHD are likely to persist for several weeks in animals that had received sub-lethal doses. In comparison to other examples of cholecalciferol excretion in the literature, the clearance of elevated 25OHD in poisoned possums appeared to be quite slow. This is perhaps not surprising since it has been shown in other animals that clearance of 25OHD is dose-dependent (Keiver et al. 1988) and target animals poisoned with cholecalciferol receive extremely high near-lethal doses. Clearly 25OHD is more persistent than rapidly eliminated poisons like 1080 (Eason et al. 1996a), but is less persistent than second-generation anticoagulants (Eason et al. 1996b).

Species variation in response to cholecalciferol

The single-dose LD_{50} for cholecalciferol in Norway rats and house mice is very similar but there is considerable species variation in susceptibility amongst other mammals and birds (Table 7). Possums and rabbits appear to be particularly sensitive to cholecalciferol (Eason 1993; Eason et al. 1994a; Henderson et al. 1994; Jolly et al. 1995; Henderson & Eason 2000) and recent studies overseas have shown cholecalciferol to be effective in controlling rock squirrels, gophers, and ground squirrels (Beard et al. 1988; Tobin et al. 1993). Cats appear to be less susceptible than possums, but toxicity was less consistent with some cats surviving doses up to 200 mg/kg, while others died at 50 mg/kg (Eason 1991).

TABLE 7. ACUTE ORAL TOXICITY (LD_{50} mg/kg) OF CHOLECALCIFEROL (Eason 1993; Eason et al. 1994a; Jolly et al. 1995).

SPECIES	LD_{50}(mg/kg)
Rabbit	9.0
Possum	16.8 (reduced to 9.8 when administered with calcium)
Rat (Norway)	42.5
Mouse	43.6
Dog	80.0
Duck	2000.0

The relatively high LD_{50} in ducks suggests that cholecalciferol is less toxic to birds than the other toxins used for possum control. If the LD_{50} in ducks were applicable to other species, then a 500-g bird would need to eat approximately 100–150 g of bait to receive a lethal dose. However, mortalities in canaries and chickens at 2000 mg/kg indicate that some species may succumb to toxicosis after eating <100 g of bait containing cholecalciferol (Eason et al. 2000), and there are reports that calciferol (Vit D_2), which is closely related to cholecalciferol, has killed song birds when used in bait for rodent control (Quy et al. 1995). These articles suggest some level of vulnerability of non-target birds to cholecalciferol.

Aquatic toxicology

There are no published data on the aquatic toxicity of cholecalciferol. In the unlikely event of significant amounts of cholecalciferol bait being applied

directly to a small stream, poisoning of some aquatic organisms might result. However, fish are naturally rich in cholecalciferol and animals that exclusively eat fish (e.g. seals) appear to be able to cope with levels of vitamin D that would be toxic to most mammals (Keiver et al. 1988).

1.3.5 Diagnosis and treatment of cholecalciferol poisoning

Diagnosis of non-target poisoning in domestic animals

Diagnosis of cholecalciferol toxicosis is based on exposure history, clinical signs, development of hypercalcaemia, and in lethal cases, lesions. Veterinarians should note that differential diagnoses in dogs include hypercalcaemia secondary to paraneoplastic syndrome (especially with lymphosarcoma), juvenile hypercalcaemia, and hyperparathyroidism.

Clinical signs

Clinical signs in companion animals can be divided into neurologic, cardiovascular, gastrointestinal, and renal effects (Beasley et al. 1997a). Signs of poisoning usually develop within 12B36 hours after consumption of a toxic dose. Initial signs may be non-specific and moderate, and include anorexia, lethargy, weakness, nausea, vomiting (±blood), diarrhoea (±blood), polyuria (increased urination), polydipsia (increased water consumption), and rarely neurological abnormalities (e.g. seizures). Clinical signs become more severe 24–36 hours after onset, as serum calcium levels increase. Renal effects, including polyuria, hyposthenuria (decreased urine specific gravity), and azotemia (increased blood urea nitrogen (BUN) and creatinine) become more pronounced. Hypercalcaemia can result in electrocardiogram (ECG) changes, (Dorman & Beasley 1989). Heart sounds are slowed and prominent, and animals become progressively more depressed. Death usually occurs in 2 to 5 days from the onset of clinical signs.

Laboratory diagnosis

The most significant and specific clinical pathology alteration is hypercalcaemia. Serum calcium concentration begins to increase about 24 hours after exposure, and values of >11.5 mg/dL in adult dogs are highly suggestive of cholecalciferol poisoning. Elevations of serum phosphate may proceed hypercalcaemia by 12 hours, and may serve as a non-specific indicator of exposure. Renal azotemia and hyposthenuria (urine specific gravity in the 1.002–1.006 range) are common, and proteinuria and glucosuria may be seen in some acute cases. Increased tissue 1, 25-dihydroxycholecalciferol is a sensitive indicator. Kidney calcium concentrations may reach 1000 ppm in poisoned animals, compared with about 100 ppm in normal dogs (Osweiler 1996a; Beasley et al. 1997a).

Lesions

Gross lesions include roughened, raised plaques in the intima of large vessels, petechial haemorrhages in various tissues; enlarged, pale thyroid glands; and pale, mineralised streaks in renal cortical surfaces. Histopathologically, calcification and necrosis of intramural coronary arteries, gastric mucosa, intestinal wall, parietal pleura, pulmonary bronchioles, pancreas, thyroid, muscles, and bladder have been observed. Degeneration, necrosis, and

mineralisation may occur in the myocardium and especially the renal tubular epithelium (Beasley et al. 1997a; Jones et al. 1997).

Treatment of cholecalciferol toxicosis in domestic animals

Cholecalciferol poisoning is a medical emergency. Veterinary treatment of animals presented with severe or advanced clinical signs is difficult and prolonged, and the prognosis is guarded. Therefore, treatment should be initiated rapidly in order to maximise the probability of survival. Therapeutic goals for veterinarians are to:

- Decrease cholecalciferol absorption
- Correct fluid and electrolyte imbalances
- Prevent or reduce hypercalcaemia

Current recommendations for the treatment of cholecalciferol toxicosis in companion animals are as follows (treatment should be followed in order) (Dorman & Beasley 1989; Beasley et al. 1997a):

- If ingestion was recent (<3 hours), induce emesis with household salt solution or washing soda crystals, or perform gastric lavage.
- Administer activated charcoal (1–2 g/kg) with a saline cathartic (magnesium sulphate at 250 mg/kg in 5–10 times as much water).
- Continue activated charcoal (at 0.5–1.0 g/kg t.i.d.) for 1–2 days to reduce enterohepatic recirculation of vitamin D and its active metabolites.
- Determine baseline serum calcium as soon as the animal is presented (to rule out normally occurring juvenile hypercalcaemia—values up to 14 mg/dL reported in some puppies), and continue to monitor serum calcium levels every 24 hours to determine if specific therapy to reduce serum calcium is required.
- Monitor BUN and creatinine, urine specific gravity, heart sounds, and ECG parameters, beginning 24 hours after exposure.

Hypercalcaemia is treated with:

- Diuresis with IV normal saline and frusemide (5 mg/kg initial IV bolus, followed by 3–4 mg/kg orally t.i.d.) to enhance renal calcium excretion. Thiazide diuretics are contraindicated since they may decrease urinary calcium. Early diuresis (initiate within the first 24 hours) is highly recommended in all animals with potentially serious exposures.
- Corticosteroid administration (prednisone at 2–4 mg/kg, divided, b.i.d.) to inhibit the release of osteoclast-activating factors, reduce intestinal calcium absorption, and promote renal calcium excretion.
- If serum calcium is excessive (>14 mg/kg), or hypercalcaemia is prolonged and unresponsive, administer salmon calcitonin to inhibit osteoclast activity at 4–6 IU/kg subcutaneously every 2–3 hours initially, until serum calcium levels stabilise (may be increased to 10–20 IU/kg if needed). Long-term administration at increased doses may be required, and some animals become refractory to treatment. Animals should be monitored for foreign protein reactions.
- Life-threatening (>20 mg/dL) hypercalcaemia may be treated with IV sodium EDTA at 25–75 mg/kg/h (human doses), although EDTA is potentially nephrotoxic. Severely hypercalcaemic or uremic animals may also benefit from peritoneal dialysis with calcium-free dialysate solutions.
- Treatment with diuretics (frusemide at 2–4 mg/kg PO b.i.d.) and corticosteroids (prednisone at 2–4 mg/kg divided b.i.d.) should continue until serum calcium concentrations stabilise in the normal range. It is also valuable

to continue to monitor BUN as an indicator of renal function. Often treatment is administered for 2–4 weeks, followed by withdrawal of therapy, and retesting serum calcium after 24 hours. Continue treatment until serum calcium remains normal at 24, 48, and 72 hours after withdrawal.

1.3.6 Non-target effects

The use of cholecalciferol baits in bait stations should limit non-target effects. Baits in bait stations are likely to be less accessible to non-target species than baits on the ground. A reassessment of the non-target hazards associated with toxic bait containing cholecalciferol has been recently completed by Eason & Wickstrom (2000). Current and future research questions for cholecalciferol relate to further investigation of primary and secondary poisoning risks to non-target species, its relative humaneness, and its persistence in the environment and animals.

Acute toxicity

In comparison with 1080 or brodifacoum, there is limited information on the susceptibility of non-target species to cholecalciferol. Primary poisoning assessments to gauge non-target susceptibility were undertaken with weta, ducks, chickens, canaries, and weka. Following oral gavage of cholecalciferol concentrate at 2000 mg/kg, there were no adverse effects in ducks. Chickens and canaries were more sensitive and some deaths occurred at 2000 mg/kg. Weka ate over 50 g of (0.1%) cholecalciferol without ill effects. Weta were not affected by oral administration of a single dose of cholecalciferol. Campaign® baits are dyed green and contain a high concentration of cinnamon (0.5%) to deter birds. Domestic cats or farm dogs allowed access to baits containing cholecalciferol may be killed or exhibit symptoms of cholecalciferol toxicosis. Treatment of cholecalciferol toxicosis is difficult (see Section 1.3.5) (Hatch & Laflamme 1989) and prevention of exposure is critical.

Secondary poisoning

Three secondary-poisoning studies are summarised in Table 8. These assessments involved the feeding of carcasses of poisoned animals to cats or dogs as their only food source for consecutive days. Dogs and cats fed these carcasses were therefore exposed to concentrations of 25OHD residues usually

TABLE 8. SUMMARY OF SECONDARY POISONING STUDIES.

NON-TARGET SPECIES	TREATMENT	RESULT	AUTHOR
Dog	Dogs fed rat carcasses for 14 days (after poisoning with 0.08% cholecalciferol baits)	No clinical signs of toxicosis No pathological abnormalities	Marshall 1984
Cat	Cats fed possum carcasses for 5 days (after poisoning with 0.8% cholecalciferol baits)	No toxicosis Non-significant increase in plasma Ca^{++}	Eason et al. 1996a,c
Dog	Variable from single to multiple feeding of dogs with possum carcasses (after poisoning with 0.8% cholecalciferol baits)	No toxicosis in dogs receiving 1 or 2 carcasses. Exposure to 5 carcasses resulted in moderate, sub-lethal toxicosis.	Eason & Wickstrom 2000

encountered by scavengers after poisoning operations. In addition, in order to create a worst-case secondary-poisoning scenario, some dogs were fed possums 48 hours after dosing with cholecalciferol (Eason & Wickstrom 2000). The feeding study in cats appeared to confirm earlier work with dogs (Marshall 1984), which indicated that the risk of secondary poisoning with cholecalciferol is low. This is despite the presence of elevated concentrations of 25OHD in possum carcasses. Research in rats has previously demonstrated that 25OHD is active when administered orally (Rambeck et al. 1990), but is partially degraded in the intestinal tract (Frolick & Deluca 1973). Hence not all the 25OHD present in poisoned carcasses will be bioavailable to cats and dogs. The study by Eason & Wickstrom (2000) demonstrated repeated consumption of poisoned carcasses by dogs over 5 days induced hypercalcaemia and calcium deposition in the kidney. This was accompanied by partial anorexia and lethargy. Nevertheless, all affected dogs began to recover without veterinary intervention by about 14 days after exposure.

Low risks of secondary poisoning with cholecalciferol does not imply no risk, and all pets and farm dogs should be discouraged from eating animals that have been poisoned with cholecalciferol. Given that mild toxicosis can occur in dogs eating possum meat, a precautionary approach should be followed, and it would be extremely unwise for hunters to take game from areas where cholecalciferol has been used in the previous 1–3 months. Game species, particularly if they have gained direct access to bait, would be potentially hazardous to humans since they would be likely to contain abnormal levels of 25OHD for 1–2 months.

1.3.7 Summary

Advantages	Disadvantages
Available to general public	Expensive compared to 1080 and cyanide
Can rapidly reduce possum numbers (an acute toxin)	Not registered for aerial application
Low risk of secondary poisoning	Treatment for accidental poisoning of pets is available, but is complex—use of secure bait stations is essential
Less toxic to birds than 1080	
A useful single-dose alternative to 1080	
No long-term residue risks in sub-lethally exposed animals	

- The active ingredient of cholecalciferol is vitamin D_3.
- Cholecalciferol occurs in fish, liver, eggs, and milk.
- Cholecalciferol is practically insoluble in water.
- Possums and rodents that receive a lethal dose of cholecalciferol usually die within 4–7 days after ingestion.
- Possums, rats, and rabbits are particularly susceptible to cholecalciferol; however, cholecalciferol will be toxic to all mammals that eat baits intended to kill possums or rodents. Post-mortem pathological changes in possums are consistent with heart failure. In other species kidney damage and gastrointestinal haemorrhage are more prominent.
- After ingestion, cholecalciferol is converted to 25-hydroxycholecalciferol (25OHD), which acts to increase serum calcium concentrations by multiple

mechanisms. The persistence of the active metabolite increases with increasing dose levels. For example, in humans the half-life of 25OHD is normally 15–36 days, but this increases to 25–68 days in humans during vitamin D toxicity. Elevated levels of 25OHD are likely in possum carcasses. Cholecalciferol poisoning can be diagnosed by elevated blood 25OHD and calcium concentration, and at post-mortem by evidence of calcification.

- The risk of secondary poisoning would appear to be low; however, poisoned carcasses are likely to contain active metabolites of cholecalciferol. These metabolites will be partially degraded in the intestine of an animal eating poisoned possums. Domestic pets and farm dogs should always be discouraged from eating poisoned carcasses.

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