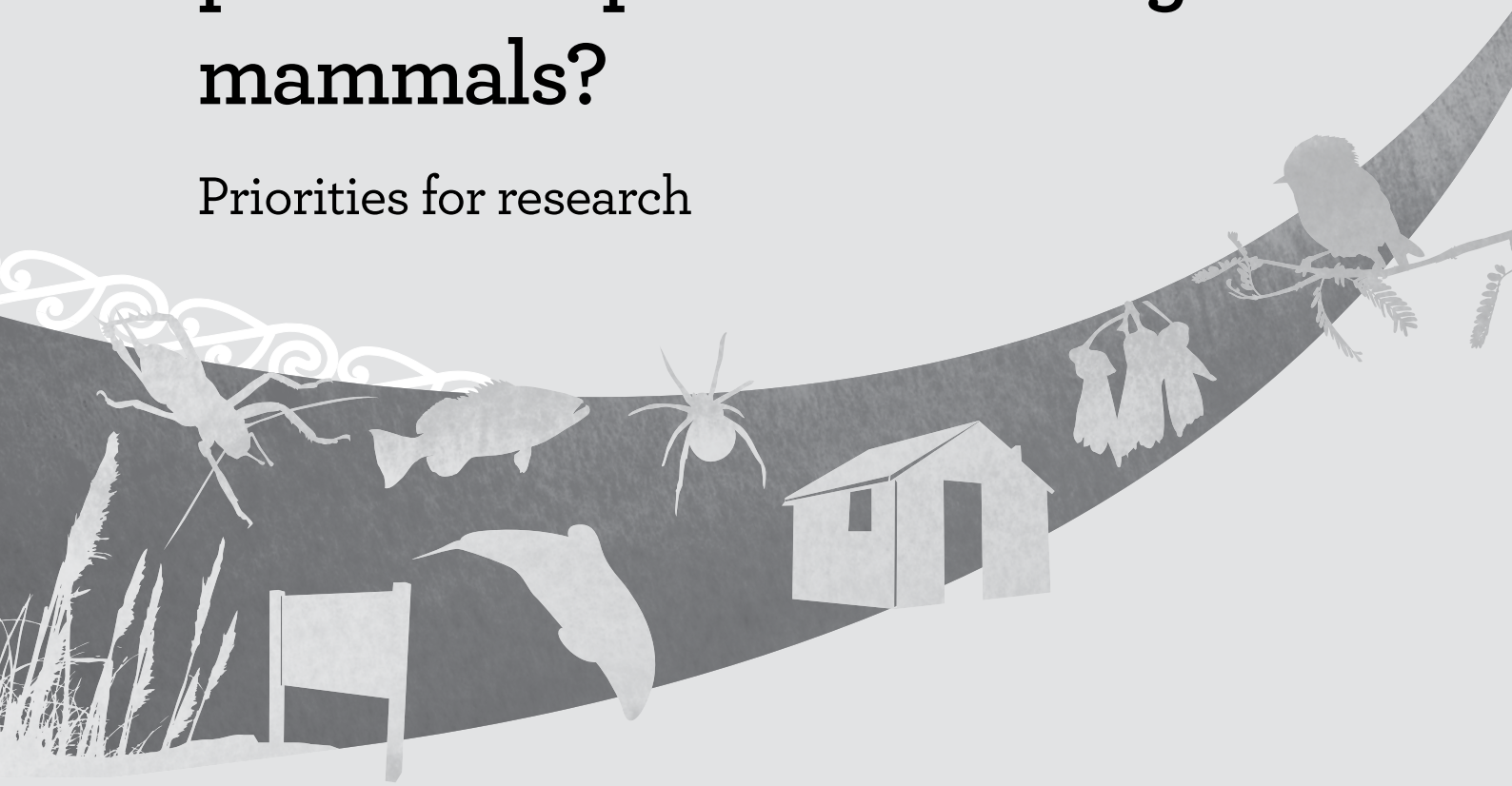
How long do vertebrate pesticides persist in living mammals?

Priorities for research



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CONTENTS

Abstract 1

1. Introduction 2

2. Pharmacokinetics of vertebrate pesticides 4

2.1 Fast excretion 5
2.1.1 Cyanide 5
2.1.2 Zinc phosphide 5
2.1.3 Sodium nitrite 5
2.1.4 Para-aminopropiophenone (PAPP) 6
2.1.5 Sodium monofluoroacetate (1080) 6

2.2 Moderate to slow excretion 7
2.2.1 Phosphorus 7
2.2.2 Pindone 8
2.2.3 Diphacinone 8
2.2.4 Coumatetralyl 9
2.2.5 Cholecalciferol 10

2.3 Very slow excretion 11
2.3.1 Brodifacoum 11
2.3.2 Bromadiolone 12

3. Discussion 12

4. Acknowledgements 16

5. References 16

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Abstract

We review the pharmacokinetic literature for 12 vertebrate pesticides available (or in the registration process) for broad-scale use in New Zealand and summarise their likely persistence in sublethally exposed animals. Vertebrate pesticides differ in the way they are absorbed, metabolised, distributed and excreted, as well as the length of time that these processes take in different animals. Understanding persistence times helps to manage two sources of contamination risk to the human food chain relating to wild and farmed animals, both of which have implications for food safety and trade. Wild animals such as deer (*Cervus* spp.) and pigs (*Sus scrofa*) may be hunted for food and caution periods are set in areas where pesticide operations have been carried out to inform hunters that residues may be present. Livestock do not normally have access to vertebrate pesticides but may be accidentally exposed; withholding periods are required to ensure residues are excreted prior to slaughter. Sublethal persistence time is the focus of this review, but it is not the only determinant of food safety risks. The period of risk to the human food chain also includes how long pesticide baits and lethally poisoned carcasses remain toxic in the field. This review classifies vertebrate pesticides of similar half-life and/or persistence time into three groups: fast—cyanide, zinc phosphide, sodium nitrite, para-aminopropiophenone (PAPP), and sodium monofluoroacetate (1080); moderate to slow—phosphorus, pindone, diphacinone, coumatetralyl and cholecalciferol; and very slow—brodifacoum and bromadiolone. Gaps in the literature are identified, the most important of which relate to pindone and PAPP.

Keywords: persistence, residues, pharmacokinetics, vertebrate pesticides, pest control, New Zealand

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1. Introduction

We review the pharmacokinetic literature for 12 vertebrate pesticides available (or in the registration process[1]) for broad-scale use in New Zealand (Table 1) and summarise their likely persistence in sublethally exposed animals.

Vertebrate pesticides differ in the way they are absorbed, metabolised, distributed and excreted, as well as the length of time that these processes take in different animals. For example, persistence in the liver is a major focus for investigating anticoagulant residues, whereas a wider range of metabolic and excretion pathways occur for the other vertebrate pesticides.

Understanding persistence times helps to manage two sources of contamination risk to the human food chain, both of which have implications for food safety and trade. The sources of risk relate to consumption of meat from wild animals and domestic livestock that may have been exposed to toxic baits and/or the carcasses of animals killed by them.

Wild animals such as deer (*Cervus* spp.) and pigs (*Sus scrofa*) are often hunted for food in New Zealand and there are minimum legal time limits after a vertebrate pesticide operation when warning signs must remain in place[2] and other minimum legal timeframes when wild animals cannot be hunted for processing and sale[3]. Caution periods are set and publicised to inform hunters and other people (such as owners of dogs (*Canus lupus familiaris*)) that residues may be present at places where vertebrate pesticides targeting other animals have been laid.

On land managed by the Department of Conservation (DOC), DOC managers set and manage the caution period for any vertebrate pesticide operation in their area. DOC defines the caution period as the timeframe from the last date of bait application (or bait removal) after which DOC expects that pesticide residues will no longer pose a risk to the public. The caution period must meet or exceed regulatory minimum timeframes. Local managers estimate caution periods using a technical resource called the caution period calculator[4], which makes a recommendation based on basic climate and operational variables selected by the manager. A specialist group (DOC Pesticides Advisory Group or PAG) evaluates current data and populates the calculator with recommendations for all possible variables and all vertebrate pesticides registered for broad-scale use in New Zealand, based on the following equation:

Recommended caution period = Time residues are expected to persist in **baits** + Time residues are expected to persist in **carcasses** or Time residues are expected to persist in **living animals** (whichever is longest)

Good estimates of the likely persistence time in sublethally exposed animals are required for the last component of this equation. Estimates are also required for persistence in baits and carcasses, although this is not the subject of this review. One vertebrate pesticide where bait and carcass persistence is important is sodium monofluoroacetate (1080). 1080 can persist in cereal pellets on the ground for weeks after the last date of application (e.g. Wright 2004), during which time it forms an exposure risk to any wild game. It can also persist in carcasses for weeks or months (Meenken & Booth 1997), creating a potential for secondary poisoning of wild pigs and any other scavengers (e.g. dogs).

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[1] Products including sodium nitrite are in the registration process, as are products including a combination of cholecalciferol and coumatetralyl.

[2] Set as controls under the Hazardous Substances and New Organisms Act 1996 and as conditions of registration under the Agricultural Compounds and Veterinary Medicines Act 1991.

[3] Animal Products (Specifications for Products Intended for Human Consumption) Notice 2004.

[4] www.doc.govt.nz/publications/science-and-technical/doc-procedures-and-sops/managing-animal-pests/other-technical-documents/.

Table 1. Twelve vertebrate pesticides available (or in the registration process) for broad-scale use in New Zealand. Details include the target pest, bait types and methods permitted under the hazardous substance legislation and the conditions of registration for relevant trade name products. Not all bait types can be used with all methods or to target all pests.

VERTEBRATE PESTICIDE	TARGET PEST	BAIT TYPE	METHODS	OTHER DETAILS
Sodium cyanide Potassium cyanide	Bennett's wallaby (*Macropus rufogriseus rufogriseus*) Dama wallaby (*Macropus eugenii eugenii*) Possum (*Trichosurus vulpecula*)	Encapsulated pellet Micro-encapsulated paste Paste	Bait bags Bait stations Handlaying	Grouped together as 'cyanide' in this review
Zinc phosphide	Possum	Micro-encapsulated paste	Bait bags Bait stations	
Sodium nitrite	Pig (*Sus scrofa*) Possum	Block	Bait stations	In the registration process at the time of publication
Para-aminopropiophenone (PAPP)	Feral cat (*Felis catus*) Stoat (*Mustela erminea*)	Paste (inside a meat bolus)	Bait stations	
Sodium monofluoroacetate (1080)	Deer (*Cervus* sp.) Feral cat Goat (*Capra hircus*) Mouse (*Mus musculus*) Possum Rabbit (*Oryctolagus cuniculus cuniculus*) Rat (*Rattus* sp.) Wallaby Wasp (*Vespula germanica*, *V. vulgaris*)	Apple Block Carrot Cereal pellet Fish meal pellet Grain Paste	Aerial Bait bags Bait stations Handlaying	
Phosphorus	Possum Rabbit	Paste	Handlaying	Also known as white phosphorus or yellow phosphorus
Pindone	Possum Rabbit Rat	Carrot Cereal pellet Grain	Aerial Bait stations Handlaying	First generation anticoagulant
Diphacinone	Ferret (*Mustela furo*) Mouse Rat	Block Cereal pellet Grain Paste	Bait bags Bait stations Handlaying	First generation anticoagulant
Cholecalciferol	Possum Rat	Block Cereal pellet Paste	Bait bags Bait stations	Occurs naturally as Vitamin D_3
Coumatetralyl	Mouse Rat	Block	Bait stations	First generation anticoagulant
Brodifacoum	Mouse Possum Rat	Block Cereal pellet	Aerial* Bait stations Handlaying	Second generation anticoagulant
Bromadiolone	Mouse Possum Rat	Block Grain Paste	Bait stations	Second generation anticoagulant

* For the control of rodents on non-stocked off-shore islands or for rodent control carried out in accordance with the Code of Practice Aerial and Hand Broadcast Application of Pestoff® Rodent Bait 20R for the Intended Eradication of Rodents from Specified Areas of New Zealand approved for this product.

The actual food safety risk from eating hunted animals depends on where and how the pesticide is used; in other words, the use pattern. For example, brodifacoum and bromadiolone products play a critical role in eradications (on offshore islands and the mainland) and biosecurity (incursion responses) (Broome 2009). In these applications, the pesticides are laid over a very short timeframe, usually as a one-off operation, and the potential benefit to wildlife is generally very high (Towns et al. 2009; Bellingham et al. 2010). In contrast, repeated field use of brodifacoum and bromadiolone for sustained pest management can and does present a risk of bioaccumulation in sublethally exposed animals. In 2000, DOC put in place a policy to reduce the sustained use of these vertebrate pesticides on land it manages because of concerns relating to their persistence in the living tissue of birds and game (DOC 2000).

Domestic livestock do not normally have access to vertebrate pesticides but may be accidentally exposed. When this happens, exposed animals should be withheld from slaughter for the period over which we expect all residues to be metabolised and excreted. Of most relevance to calculating the time period to withhold stock from slaughter is the pharmacokinetic literature relating to livestock such as sheep (*Ovis aries*), cattle (*Bos taurus*), pigs and deer.

2. Pharmacokinetics of vertebrate pesticides

This review classifies vertebrate pesticides into three groups of similar elimination half-life and/or persistence time:

- Fast (hours to days): cyanide, zinc phosphide, sodium nitrite, para-aminopropiophenone (PAPP), and sodium monofluoroacetate (1080)
- Moderate to slow (weeks to months): phosphorus, pindone, diphacinone, coumatetralyl and cholecalciferol
- Very slow (years): brodifacoum and bromadiolone

The elimination half-life is an estimate of how long it might take for a specific dose to decline by half (50%) in blood plasma or a specific organ (usually the liver for anticoagulants). Persistence time is defined in this review as the time after dosing when we expect residues would no longer be detected. A minority of studies track residue depletion to this point, and there is variation in the minimum detection limit (MDL) used.

The classification makes it easier to identify which results and information gaps are most relevant to managing the risk to the human food chain becoming contaminated. Erickson & Urban (2002) reviewed rodenticides registered in the United States as part of a risk assessment for birds and non-target mammals. This review complements Erickson & Urban (2002) in that it has a different scope (vertebrate pesticides registered in New Zealand), a different focus (sublethal persistence as a food contaminant) and includes more-recent studies. Importantly, Erickson & Urban (2002) included birds, whereas the current review does not.

The published scientific literature on the pharmacokinetics and metabolism of vertebrate pesticides is extensive and complex to summarise. For example, studies use a range of different animal species, dosing approaches, and analytical techniques with different limits of detection. Accuracy of methods and mathematical techniques has improved over time. This complexity needs to be remembered as a caveat to the simple classification into three groups used in this report.

2.1 Fast excretion

This group includes cyanide, zinc phosphide, sodium nitrite, PAPP, and 1080. All of these vertebrate pesticides are metabolised within hours or days. The slowest excretion time is for PAPP, which takes about 5 days.

2.1.1 Cyanide

Cyanide is readily absorbed into the bloodstream and (based on all studies to date) distributed to all organs and body fluids, often within minutes of exposure (PSD 1996; Taylor et al. 2006; US EPA 2010). Cyanide detoxification occurs mainly in the livers of sublethally exposed animals, where 60–80% is converted to the less acutely toxic metabolite thiocyanate (US EPA 2010).

The elimination half-life of cyanide in the blood plasma of humans has been estimated as 20 minutes to 1 hour (Taylor et al. 2006). Sousa et al. (2003) compared cyanide kinetics in laboratory rats (*Rattus norvegicus* Wistar), landrace large White pigs (*Sus scrofa domesticus*) and goats (*Capra hircus*) orally dosed with 3 mg/kg potassium cyanide; the plasma elimination half-lives were estimated at 0.64 hours, 0.54 hours and 1.28 hours respectively.

No studies were found where depletion of cyanide was monitored to the point where it could no longer be detected. Based on the available plasma elimination half-life estimates, we would expect the persistence time to be less than one day.

2.1.2 Zinc phosphide

Zinc phosphide reacts with acids in the gastrointestinal tract to produce phosphine and other breakdown products (Eason et al. 2012). Phosphine is the compound that causes its high toxicity and is absorbed through the gastrointestinal tract.

In a study by Andreev et al. (1959), grey rats (*Rattus norvegicus* Berk) were given a lethal oral dose of 40 mg/kg of radio-labelled zinc phosphide and the organs of sacrificed animals were analysed at short intervals afterwards. Within one hour, radio-labelled phosphorus (phosphorus-32) was detected in all organs except brains, bone and muscles. At death (within 6 to 8 hours), phosphorus-32 was present in all organs and a considerable accumulation in the rats' livers was noted.

Excretion occurs as exhaled phosphine from the lungs, and as other metabolites, including phosphoric acid and phosphate, in urine and faeces (WHO 1976). In a study by Meredith (1981, reported in WHO 1988), laboratory rats were orally dosed with zinc phosphide and their exhaled air was monitored. Virtually all the phosphine had disappeared from exhaled air within 12 hours. However, given the observations of Andreev et al. (1959), residues would be expected to persist in the rats' livers, even though phosphine had disappeared from their exhaled air.

The US EPA (1998) concluded that the risk of secondary poisoning with zinc phosphide was low, noting that it did not accumulate in tissues and that the primary risk stemmed from zinc phosphide remaining in the gastrointestinal tract of poisoned animals.

No estimates of plasma or hepatic elimination half-life were found in the literature. The paucity of data makes it difficult to estimate persistence time, but it seems unlikely to be more than several days.

2.1.3 Sodium nitrite

Sodium nitrite is absorbed in the upper part of the gastrointestinal tract and transferred to the blood. Schneider & Yeary (1975) reported plasma elimination half-life values of 29.0, 30.0 and 34.0 minutes in sheep, dogs and ponies (*Equus caballus*), respectively. Dejam et al. (2007) calculated a plasma elimination half-life of 42 minutes for humans. In research to develop a mathematical model, peak plasma levels of nitrite were observed for laboratory rats approximately 30 minutes after oral dosing (Kohn et al. 2002). Reanalysis of the Kohn et al. (2002) data by Lapidge & Eason (2010) provided estimates for the plasma elimination half-life for sodium nitrite in laboratory rats of 42.0 minutes (male) to 62.5 minutes (female).

No studies were found where depletion of sodium nitrite was monitored to the point where it could no longer be detected. Based on the available plasma elimination half-life estimates, we would expect the persistence time to be less than 1 day (24 hours).

2.1.4 Para-aminopropiophenone (PAPP)

PAPP is metabolised by the liver, which produces N-hydroxylaminopropiophenone (PHAPP), the compound that causes the toxic effect (methaemoglobinemia). Wood et al. (1991) investigated the metabolism and excretion of radio-labelled PAPP in Sprague-Dawley rats (*Rattus norvegicus*), dogs and cynomolgus monkeys (*Macaca fascicularis*) given oral doses of PAPP (5 mg/kg for rats, 0.5 mg/kg for dogs and 25 mg/kg for monkeys). They found that PAPP was rapidly absorbed by all three species, with peak plasma concentrations at 15 minutes (male rats), 1 hour (female rats), 30 minutes to 1 hour (beagles) and 1 to 1.5 hours (monkeys) after oral ingestion. Rapid excretion via urine and faeces was observed in all three species, with the majority of PAPP and its metabolites recovered within 24 hours (93–96% in rats, 84% in dogs, and 84–95% in monkeys). Excretion of trace amounts was detected in urine and faeces for all species at 120 hours (5 days).

No estimates of plasma elimination half-life were found in the literature. No studies were found where depletion of PAPP was monitored to the point where it could no longer be detected. Based on the excretion study, it would appear that PAPP is eliminated in about 5 days.

2.1.5 Sodium monofluoroacetate (1080)

1080 is metabolised in the mitochondria of cells, where it enters the tricarboxylic acid (Krebs) cycle to produce the toxic metabolite fluorocitrate (Egeheze & Oehme 1979; Eason et al. 2011). Other metabolites include fluoride, fatty acids, cholesterol, carbon dioxide and other unidentified non-toxic compounds (Eason et al. 2011). Following oral or intravenous dosing, 1080 was found to be rapidly absorbed into the blood and distributed through the soft tissues and organs of laboratory rats (Hagan et al. 1950). Highest concentrations of 1080 occur in the blood of dosed animals (Hagan et al. 1950; Gooneratne et al. 2008).

Sykes et al. (1987) intravenously dosed mice (*Mus musculus*) with approximately 0.4 mg/kg of radio-labelled fluoroacetate and sacrificed animals at 0.25, 1.0, 2.0 and 4.0 hours after injection. Elimination half-lives of 1.6–2.0 hours were estimated for all organs studied (including liver, muscle, heart, and kidneys) and 1.6 hours for blood plasma. Accumulation of radioactivity in bone was evident over the first 2 hours after injection, declining slightly after 4 hours. Fluoroacetate is known to degrade to fluoride (F^-) and this anion has a high affinity for bone and teeth. It may be that accumulation is as fluoride rather than fluoroacetate.

In another study, rats dosed with 0.25 mg/kg carbon-14-labelled fluoroacetate and were sacrificed 72 hours after dosing. Various organs each contained between 0.5% and 1% of the total carbon-14 dose (Tecle & Casida 1989).

Eason et al. (1994) dosed sheep and goats via a gastric cannula with 0.1 mg/kg 1080 and estimated the elimination half-life of 1080 in blood plasma as 10.8 hours in sheep and 5.4 hours in goats. The concentration of 1080 was higher in blood plasma than in kidney, muscle and liver tissue of sheep 2.5 hours after an oral dose of 0.1 mg/kg. Only traces of 1080 were found in blood plasma and organs of sheep 96 hours after dosing (MDL = 0.010 µg/g in plasma and MDL = 0.002 µg/g in organs). In goats, only traces of 1080 were present after 18 hours (Eason et al. 1994).

Gooneratne et al. (2008) gave ewes a relatively high oral dose of 0.30 mg/kg and monitored 1080 in blood serum for up to 14 days in surviving sheep. After animals died or were killed, muscle, kidney and liver samples were analysed for 1080. 1080 peaked in blood serum 2 to 4 hours after dosing, declined to one-third of peak level by 24 hours and was not detected 3 days after dosing (MDL = 0.0015 µg/g). No 1080 was detected in the skeletal muscle, kidneys or liver of three sheep 14 days after dosing. 1080 was detected in the heart, muscle and liver of three animals that died 22–25 hours after dosing, whereas it was detected only in muscle (not in heart or liver) of animals that died 43–52 hours after dosing.

1080 was administered orally to six possums (*Trichosurus vulpecula*) at 0.1 mg/kg and its persistence was assessed in blood plasma at intervals up to 96 hours after dosing (Eason et al. 1993, 1996b). A mean plasma elimination half-life of 9.1 hours was estimated. Trace amounts of 1080 were detected at 48 hours and none was detected at 96 hours (MDL not stated).

Rabbits (*Oryctolagus cuniculus*) were given an oral dose of 0.1 mg/kg 1080 and individuals were killed at intervals from 0.25 to 72 hours after dosing (Gooneratne et al. 1995). 1080 residues were highest in blood and a plasma elimination half-life was estimated at 1.1 hours (MDL = 0.010 µg/g). Very little 1080 was detected in blood plasma at 6 hours and none was detected 9 hours after dosing. 1080 concentrations were detected in muscle, kidney and liver in decreasing quantities (MDL = 0.002 µg/g in tissues).

Studies across a number of species suggest that 1080 is rapidly metabolised and is unlikely to persist beyond about 4 days.

2.2 Moderate to slow excretion

This group includes phosphorus, pindone, diphacinone, coumatetralyl and cholecalciferol. There is a lot of variation in what is known about the pharmacokinetics of these vertebrate pesticides, with the least known about phosphorus. The likely persistence time is in the range of 2 weeks (diphacinone and pindone in laboratory rats) to 5 months (diphacinone in cattle).

2.2.1 Phosphorus

Phosphorus is readily absorbed from the gastrointestinal tract and is excreted in urine and exhaled air (Shlosburg & Booth 2004). The pharmacokinetics of phosphorus are not well understood, principally because methods for quantifying phosphorus in body tissues have not been developed (Duerksen-Hughes et al. 1997). In addition, organic and inorganic phosphorus occurs in cells throughout animals' bodies, making it more complicated to track ingested phosphorus. It is not clear when phosphorus is converted to metabolites (in the gut or after absorption into blood) or whether enzymes are involved. Duerksen-Hughes et al. (1997) suggest that it is likely that the main end product of phosphorus metabolism is orthophosphate (produced either in the gut or after absorption into the blood) and that it is incorporated into phosphorus-containing molecules throughout the body.

Duerksen-Hughes et al. (1997) summarised several studies where laboratory rats were dosed with radio-labelled phosphorus. These studies indicated that phosphorus is absorbed into the liver and other organs within hours and persists for at least 5 days. For example, radioactivity was detected 15 minutes after dosing in blood and livers of laboratory rats given an oral 'toxic dose' of phosphorus and 82–87% of the dose could be recovered from organs and blood within 2 to 3 hours of dosing, of which 65–70% was recovered from the liver (Goshal et al. 1971 in Duerksen-Hughes et al. 1997). Lee et al. (1975) completed a similar study where the distribution of an unspecified radio-labelled oral dose of phosphorus given to laboratory rats was monitored 4 hours, 1 day and 5 days after dosing (summarised in Duerksen-Hughes et al. 1997). The highest proportion of the administered dose was recovered from the rats' livers, with 16.1%, 16.9% and 6.3% of the total dose recovered at 4 hours, 1 day and 5 days, respectively, after dosing. At 5 days after dosing, the concentration of radio-labelled phosphorus was more than 100 times higher in liver tissue than in blood plasma.

No estimates of elimination half-life were found in the literature. No studies were found where depletion of phosphorus was monitored to the point where it could no longer be detected. Based on the radioactive tracing studies, it would appear that phosphorus takes much longer than 5 days to be eliminated from mammals' livers.

2.2.2 Pindone

Pindone concentration seems to remain higher in blood plasma for longer and be distributed more evenly between the liver and kidneys, relative to the other anticoagulants. Nine dogs were dosed either orally or intravenously with either 3 mg/kg or 5 mg/kg pindone and blood samples were taken at intervals up to 182 hours after dosing (Fitzek 1978). The plasma elimination half-life was estimated as 109–118 hours (MDL not stated, Fitzek 1978). The organs of three dogs that died or were sacrificed were analysed at 72 hours, 132 hours and 182 hours after dosing. Residues were consistently highest in blood and at similar concentrations in the kidneys and liver for all three dogs.

Sixteen sheep were dosed orally with 10 mg/kg and pairs were sacrificed at 2, 4, 8, 16, 32, 64, 128 and 256 days after dosing (Nelson & Hickling 1994). Pindone was detected in the livers of these sheep up to 8 days after dosing and not detected at 16 days (MDL = 0.09 fi/g). A further five sheep were dosed orally with 30 ml of a pindone suspension containing 2 mg/ml active ingredient, and individuals were sacrificed 1, 2, 4, 8 and 16 days after dosing. Pindone was detected in fat from these sheep on all but the last day that samples were taken.

Robinson et al. (2005) administered either a single 3-day oral dose (i.e. 10, 3, and 2 mg/kg on three consecutive days) of pindone to merino ewes or a double 3-day oral dose (i.e. regime repeated after 8 days) of pindone to merino wethers. Pindone was at very low levels in blood within 7 (single dose) to 14 (double dose) days of the last dose, and no pindone was detected at 29 days (single dose) to 26 days (double dose) after the last dose (MDL= 0.02 mg/ml). Sheep were sacrificed 25 days after the single dose or 19 days after the double dose regime and no pindone residues were detected in muscle, brain, fat, liver and heart tissues (MDL = 0.1 mg/kg). An elimination half-life in blood was estimated (based on prothrombin time) as 4.9 days for the single dose ewes and 5.4 days for the double dose wethers.

Martin et al. (1991) estimated the blood elimination half-life at 3.1 days for cattle, 2.8 days for goats, 1.9 days for horses (*Equus caballus*) and dogs and less than 1 day for cats (*Felis catus*). Animals were given an oral dose of pindone daily for 5 days, with the daily dose ranging from 0.3 mg/kg for dogs to 2.0 mg/kg for cattle. Extension of prothrombin time was monitored as an index of poisoning.

In a comparative study of rodenticides by Fisher et al. (2003), laboratory rats (*Rattus norvegicus* Wistar) were given an oral dose of 35 mg/kg pindone and the hepatic elimination half-life was estimated at 2 days (MDL = 0.2 µg/g). Residues were present 1 week after dosing but were not detected 2 weeks after dosing.

Studies across a number of species suggest that pindone is unlikely to persist in the liver beyond 14 days after dosing, although hepatic persistence in cattle has not been studied and may be different (see section 2.2.3).

2.2.3 Diphacinone

Yu et al. (1982) investigated the metabolism and excretion of radio-labelled diphacinone in laboratory rats. Eight days after female laboratory rats were administered a single oral dose of 0.4 mg/kg diphacinone, the highest concentration of the toxin was found in their livers, significant residues were found in their kidneys, lungs, and brains, and the lowest residues were measured in fat and muscles. By 8 days after dosing, 80% of the administered dose was eliminated in faeces and about 10% in urine.

Cahill and Crowder (1979) found the highest concentrations of diphacinone in livers and the lowest concentration in fat tissue in mice given an oral dose of 4.14 mg/kg radio-labelled diphacinone, when tissues were analysed at time intervals up to 192 hours after dosing. Within 48 hours after dosing, 76% and 67% of diphacinone was excreted in faeces by male and female mice respectively.

In a comparative study of rodenticides by Fisher et al. (2003), laboratory rats were given an oral dose of 1.5 mg/kg diphacinone and the hepatic elimination half-life was estimated at 3 days (MDL = 0.1 µg/g). Residues were present 1 week after dosing but were not detected 2 weeks after dosing.

In a trial with ten pigs dosed at 1.5 mg/kg, Crowell et al. (2013) estimated a mean hepatic elimination half-life of 12.4 days for diphacinone. Diphacinone residues in the liver were near or below the method detection limit (MDL = 0.05 µg/g) for a pair of pigs that were euthanised 28 days after dosing, and not detected at 43 days after dosing. In pigs dosed at 12.5 mg/kg, Fisher (2006) calculated an initial and terminal hepatic elimination half-life in recognition that elimination of anticoagulants from the liver is often biphasic (i.e. an initial rapid phase followed by a slower terminal phase, Parmar et al. 1987). The initial elimination half-life in liver was estimated as 1.30 days and the terminal hepatic elimination half-life in liver was estimated as 14.1 days. Diphacinone was not cleared from the livers of three pigs that were sampled at 15 days after dosing (MDL = 0.02 µg/g).

Three red deer (*Cervus elaphus scoticus*) were dosed at 1.5 mg/kg diphacinone and biopsied periodically by Crowell et al. (2013). A mean hepatic elimination half-life of 6.0 days was estimated, and diphacinone residues in the liver were below the method detection limit (MDL = 0.10–0.20 µg/g) in two of three deer sampled at 12 days after dosing. The liver sample taken from the third deer at 29 days was below the MDL (0.10 µg/g).

Studies on cattle suggest that they may excrete diphacinone significantly more slowly than other species. Bullard et al. (1976) dosed six Hereford cows with 1 mg/kg diphacinone by injecting it into the rumen, and found that liver residues were almost identical when analysed at 30, 60 and 90 days after treatment (0.14–0.15 µg/g). Crowell et al. (2013) carried out two trials in which cattle were dosed orally at 1.5 mg/kg. In both trials, the maximum diphacinone concentration in the liver was much higher than that recorded in pigs and deer that had been given the same dose. A rapid initial decline in hepatic concentration was observed before it increased on either day 43 (first trial) or day 29 (second trial), and so initial elimination half-lives (day 0 to day 30) and terminal elimination half-lives (from day 30 onwards) were calculated for these trials. The mean terminal elimination half-lives were 25 days and 35 days for the first and second trials respectively. Diphacinone residues in the liver were below the method detection limit for all animals by 155 days after dosing in the first trial (MDL = 0.10 µg/g) and 125 days after dosing in the second trial (MDL = 0.10–0.20 µg/g).

Based on studies where residues were tracked until no longer detected in liver, we would expect diphacinone to be no longer detected at about 40 days after dosing. The exception to this is in cattle, where it may be detected at least 3 times longer.

2.2.4 Coumatetralyl

Coumatetralyl is absorbed rapidly from the gastro-intestinal tract to blood. Following a single oral dose of 0.1 mg/kg given to laboratory rats, coumatetralyl concentration peaked in blood plasma after 3 hours in male rats and after 8 hours in female rats (Danish EPA 2005). At 7 days after dosing, the liver retained the highest proportion of ingested coumatetralyl in rats (21–25% of a single dose or 7% after repeat dosing) followed by skin (7–16% of a single dose or 4% after repeat dosing). The gastrointestinal tract contained 1.5–4.6% and all other organs contained <1% of the administered dose.

In a comparative study of anticoagulant retention in liver, 24 male laboratory rats were given a single oral dose of 20.55 µmol/kg coumatetralyl and 3 animals were killed at intervals up to 182 days after dosing (Parmar et al. 1987). Elimination was described by the authors as biphasic and the hepatic elimination half-life was estimated at 55 days.

In a trial with 24 mice dosed at 250 mg/kg coumatetralyl, the plasma elimination half-life was estimated at 0.52 days (MDL = 0.005 µg/g) and the hepatic elimination half-life was estimated at 15.8 days (MDL = 0.25 µg/g, Vandenbroucke et al. 2008). No coumatetralyl was detected in the plasma of 4 mice killed on day 7 or in 4 mice killed on day 21 of the trial.

In a trial with three red deer dosed at 8.25 mg/kg coumatetralyl, a mean hepatic elimination half-life of 18.9 days was estimated, and coumatetralyl residues in the liver were below the method detection limit (MDL = 0.05–0.20 µg/g) in two of three deer sampled at 50 days after dosing and below the MDL in the third deer sampled at 85 days (Crowell et al. 2013).

Crowell et al. (2013) is the only study we know of where residues were tracked until no longer detected in liver, which leads us to expect coumatetralyl to be no longer detected sometime between 50 and 85 days after dosing. Hepatic persistence in cattle has not been studied and may be different (see section 2.2.3).

2.2.5 Cholecalciferol

Cholecalciferol (Vitamin D_3) is metabolised to 25-hydroxycholecalciferol (25-OHD or calcidiol) in the liver, with any surplus cholecalciferol either further metabolised and excreted in bile or stored in fat and muscle tissue (Parfitt et al. 1982; Holick 2003; Heaney et al. 2009). Further metabolism of 25-OHD in the kidneys produces 24,25- dihydroxycholecaliferol or 1,25-dihydroxycholecaliferol (1,25-OHD or calcitriol). 25-OHD circulates in the blood and is the metabolite generally monitored to determine whether an animal has consumed cholecalciferol, as it is more stable and its concentration is more strongly correlated with cholecalciferol intake or synthesis than other metabolites (Fairweather et al. 2013). Because 25-OHD occurs naturally in animals, Fairweather et al. (2013) recommend excessive cholecalciferol consumption is indicated where 25-OHD residues in plasma or liver are at least four times as high as defined reference levels for particular species.

Persistence studies in possums orally dosed with 20 mg/kg cholecalciferol showed elevated concentrations of 25-OHD are likely to persist in plasma, heart, liver, kidney and fat for at least 29 days. 25-OHD levels declined in all tissues except fat between sampling on 3 days and 29 days after dosing (Eason et al. 1996b). The authors had measured a concentration of 25-OHD in plasma prior to dosing, and residues were 15 times higher than this reference level by 29 days after dosing.

Brouwer et al (1998) administered an oral dose of 37.5 µg cholecalciferol (0.20–0.25 mg/kg) daily for 14 days (days 0 to 13) to 90 female rats. Groups of six rats were sacrificed at day 0 (before treatment), days 3, 6, 9 and 12 (during treatment) and days 14, 15, 16, 17, 40, 76, 98, 99, 100 and 101, and the concentration of cholecalciferol and 25-OHD in tissue and blood was measured. The half-lives of cholecalciferol in plasma, perirenal and subcutaneous adipose tissue were 1.4, 97.3 and 80.9 days, respectively. The half-life of 25-OHD in plasma was calculated as 22.5 days. 25-OHD in plasma was still elevated 27 days after the final dose (i.e. on day 40), but by 63 days after the final dose, the 25-OHD concentration had returned to normal (Brouwer et al. 1998).

Cattle had raised 25-OHD levels 42 days after being injected intramuscularly with 375 mg of cholecalciferol (Hollis et al. 1977).

In humans, the plasma elimination half-life for cholecalciferol is 19–25 hours (Marcus 1996). Estimates of the mean plasma elimination half-life of 25-OHD range from 13.5 days to 27.5 days in normal human subjects (Mawer et al. 1971; Batchelor et al. 1982; Davie et al. 1982). The wide range in 25-OHD half-life values has been attributed to factors including the vitamin D status of the subjects, the small sample sizes in the studies, and the slow release of cholecalciferol from fat tissue (Batchelor et al. 1982; Hidiroglou 1987; Brouwer et al. 1998).

Brouwer et al. (1998) is the only study where depletion of 25-OHD was monitored until the level could be described as normal. This result is consistent with observations from other studies; we would expect elevated concentrations of 25-OHD to persist in mammals for about 63 days after dosing.

2.3 Very slow excretion

Brodifacoum and bromadiolone are second-generation anticoagulants and have a strong affinity to receptors (vitamin K-epoxide reductase) found in the liver, kidney and pancreas (Parmar et al. 1987).

2.3.1 Brodifacoum

Once absorbed through the gastrointestinal tract, brodifacoum accumulates in the liver and levels remain relatively constant. Bachmann & Sullivan (1983) gave a single oral dose of 0.2 mg/kg brodifacoum to Sprague-Dawley laboratory rats and monitored residues in serum, liver and small intestines at intervals up to 120 hours. In serum, brodifacoum declined slowly, with an elimination half-life estimate of 156 hours. Brodifacoum concentration declined rapidly in the small intestine for the first 24 hours, although there was an increase from 24 to 72 hours after dosing. They found that liver concentration was twenty-fold higher than in serum, with a maximum of 5.0 mg/kg after 50 hours, and that liver concentration remained high when analysed for the last time at 96 hours after dosing.

In a comparative study of anticoagulant retention in livers, 24 male laboratory rats were given a single oral dose of 0.67 µmol/kg brodifacoum and three animals were killed at intervals up to 182 days after dosing (Parmar et al. 1987). The hepatic elimination half-life was estimated at 130 days.

New Zealand white rabbits were dosed intravenously with 20 µmoL/kg brodifacoum and blood samples were taken at periods up to 340 hours after dosing (Breckenridge et al 1985). Brodifacoum concentration in plasma was described as biphasic, with a terminal elimination half-life of 60.8 hours in plasma.

Laas et al (1985) evaluated brodifacoum persistence in sheep given an oral dose of either 0.2 mg/kg or 2.0 mg/kg, with individuals slaughtered at intervals up to 128 days after dosing. Brodifacoum was not detected (MDL = 0.05 mg/kg) in omental fat from 8 days after dosing at either level; however, it was still detected in liver tissue at 128 days after dosing (0.64 mg/kg for the high-dose group and 1.07 mg/kg for the low-dose group).

Brodifacoum was administered orally to possums at 0.1 mg/kg and its persistence was assessed in blood and in muscle and liver tissue (Eason et al. 1996a, b). Brodifacoum was detected (MDL not stated) in blood up to 32 days after dosing and it was detected at a high level (0.085 µg/g) in liver and at a lower level (0.007 µg/g) in muscle 256 days (over 8 months) after dosing.

Eason et al. (1999) determined the concentration of brodifacoum in muscle and liver tissue after primary and secondary poisoning of pigs. Brodifacoum concentration was up to 20-fold higher in liver than in muscle in pigs killed 5 days after they started eating brodifacoum baits or brodifacoum-contaminated possum carcasses.

Vandenbroucke et al. (2008) estimated a plasma elimination half-life of 91.7 days (MDL = 0.005 µg/g) and a hepatic elimination half-life of 307.4 days (MDL = 0.10 µg/g) in mice that had been given a single oral dose of 6.44 µg brodifacoum.

All of the elimination half-life estimates and monitoring of depletion in liver tissue suggest that brodifacoum persists for more than a year in mammals. No studies were found where depletion of brodifacoum was monitored to the point where it could no longer be detected. Without information on final elimination times (or, at least, a better range of hepatic elimination half-life estimates), it is difficult to say how much longer than a year brodifacoum might persist in the livers of exposed mammals.

2.3.2 Bromadiolone

In a comparative study of anticoagulant retention in their livers, 24 male laboratory rats were given a single oral dose of 1.76 µmol/kg bromadiolone and 3 animals were killed at intervals up to 182 days after dosing (Parmar et al. 1987). The hepatic elimination half-life was estimated at 170 days.

Wild-caught Norway rats (*Rattus norvegicus*) were dosed orally with bromadiolone at either 0.8 mg/kg or 3 mg/kg and groups of four rats were killed at intervals up to 97 hours after dosing (Kamil 1987). The plasma elimination half-life was estimated at 25.7 hours for the low dose and 57.5 hours for the high dose. In rats dosed at 3 mg/kg, liver concentrations of bromadiolone ranged from 14 to 46 times higher than the plasma concentration at specific sampling times and bromadiolone was detected in the final sample 97 hours after dosing. Bromadiolone was also detected in kidney tissues throughout the study.

Vandenbroucke et al. (2008) estimated a plasma elimination half-life of 33.3 days (MDL = 0.005 µg/g) and a hepatic elimination half-life of 28.1 days (MDL = 0.10 µg/g) in mice that had been given a single oral dose of 28.18 µg bromadiolone.

Sixteen sheep were dosed orally with 2 mg/kg bromadiolone and pairs were sacrificed at 2, 4, 8, 16, 32, 64, 128 and 256 days after dosing (Nelson & Hickling 1994). Bromadiolone was detected in the livers of all sheep except one of the pair sacrificed 256 days after dosing (MDL = 0.09 fi/g). Bromadiolone was detected at 0.8 mg/kg in the other sheep sacrificed 256 days after dosing.

Elimination half-life estimates are limited to rodents and there is wide variance between the two available studies, one focussing on rats and the other focussing on mice. The hepatic elimination half-life estimate for rats is similar to the estimate for brodifacoum. The paucity of data makes it difficult to estimate persistence time, but we would guess that it would be longer than a year.

3. Discussion

Table 2 summarises the studies described in section 2 in the New Zealand context, by listing for each vertebrate pesticide:

- All elimination half-life estimates available for target pest species and for non-target domestic and wild mammals
- All persistence times estimated for target pest species and for non-target domestic and wild mammals

It is evident from the table that the coverage of pharmacokinetic data is far from comprehensive, but not all combinations of species and vertebrate pesticides are important in the New Zealand context. Furthermore, there may be other unpublished data not available to this review.

There is reasonable coverage of elimination half-life estimates for rats; completing studies of persistence in rats for the remaining vertebrate pesticides would be valuable. There are very few studies in group 1 (fast excretion) that track residue depletion to the point where residues are no longer detected. This means that we are dependent on the elimination half-life estimates to gauge how long residues may persist.

Based on the information obtained during this review, seven questions stand out as a priority for research. These are listed below in order of importance:

1. How long does pindone persist in the livers of sublethally poisoned rabbits? Pindone is broadcast widely to target rabbits, including from the air, yet there is no information on hepatic half-life or persistence in this species.

2. Does pindone behave in the same way as diphacinone in the livers of cattle? Diphacinone persisted for much longer in cattle than it did in deer or pigs in the same study. Is this is also true for pindone? It is important to have this information because of the possibility of cattle having accidental access to pindone (for example, following a rabbit control operation in farm paddocks).
3. What is the plasma elimination half-life for PAPP in rats? PAPP is one of four vertebrate pesticides where there is no elimination half-life estimate for rats. Having half-life estimates for most vertebrate pesticides in rats provides a baseline for comparing relative persistence.
4. What is the plasma elimination half-life for 1080 in rats? There is a plasma elimination half-life estimate for mice, which makes this a lower priority compared with PAPP.
5. What is the hepatic elimination half-life for brodifacoum in pig liver? We know from work with other species that brodifacoum persists for a long time. No studies have observed the point where hepatic residues are no longer detected. This is not surprising, given the husbandry costs of supporting animals for many months. Having a hepatic elimination half-life estimate in pigs would improve our understanding of the potential food safety risks of wild pork.
6. How long does pindone persist in the livers of sublethally poisoned pigs? Farmed and wild pigs may be present in the vicinity of rabbit control operations. Observations of the persistence time would help to inform caution periods for hunted wild pigs and to inform a withholding period for any farmed pigs that gain accidental access to pindone baits or carcasses of poisoned rabbits.
7. What is the hepatic elimination half-life for coumatetralyl in rats? The hepatic elimination half-life estimated by Parmar et al. (1987) of 55 days seems anomalous compared with the other first-generation anticoagulants and the study was published as an abstract without supporting data.

Some uncertainty is raised by Sykes et al. (1987) over potential 1080 accumulation in bone, as they detected progressive uptake of radio labelled F^- over the first 2 hours of the study. This radioactivity could stem from both 1080 and the metabolite fluoride, as the latter has a high affinity for bone. It would be valuable to ascertain whether the accumulation is from fluoroacetate or fluoride and how long it persists, as there are potential safety implications for dogs that scavenge in pest control areas after the caution periods for the pesticide operations have concluded.

Table 2. Synthesis of the elimination half-lives and persistence times estimated in studies summarised in this review. All estimates are stated in days. Elimination half-lives are for blood (usually plasma) unless specified. Empty cells indicate that no data is available. Shaded cells with bold numbers relate to the list of priority research questions explained in Section 3 of the review.

TOXIN	ELIMINATION HALF-LIFE ESTIMATES (DAYS)										PERSISTENCE TIME (DAYS)									
	TARGET PEST SPECIES				NON-TARGET DOMESTIC AND WILD ANIMALS						TARGET PEST SPECIES				NON-TARGET DOMESTIC AND WILD ANIMALS					
	RAT	POSSUM	RABBIT	OTHER	DOG	SHEEP	CATTLE	DEER	PIG	OTHER	RAT	POSSUM	RABBIT	OTHER	DOG	SHEEP	CATTLE	DEER	PIG	OTHER
Group 1																				
Cyanide	0.0[a]								0.02[a]	0.05[a]										
Zinc phosphide											0.5[b]									
Sodium nitrite	0.04[c]				0.02[d]	0.02[d]				0.02[d]										
PAPP	**#3**																			
1080	**#4**	0.38[e]	0.05[f]	0.08[g]		0.45[h]				0.23[h]	>3[i]	4[e]	>0.25 <0.38[f]			4[h]				0.75[b]
Group 2																				
Phosphorus																				
Pindone	2[j]		**#1**		4.9[k]	5.4[l]	3.1[m]			2.8[m]	>7 <14[j]				>7.58[k]	>8 <16[n]	**#2**		**#6**	
Diphacinone	3[j]						25–35[o]	6.0[o]	12.4[o]		>7 <14[j]						125–155[o]	>12 <29[o]	>28 <43[o]	
Coumatetralyl	55[p] **#7**			15.8[q]				18.9[o]										>50 <85[o]		
Cholecalciferol	22.5[r]									13.5–27.5[s]	63[r]	>29[t]					>42[u]			
Group 3																				
Brodifacoum	130[p]		2.5[v]	307.4[q]					**#5**			>256[w]				>128[x]				
Bromadiolone	170[p]			28.1[q]												>256[u]				

See next page for Table 2 footnotes.

Table 2 footnotes

[a] Section 2.1.1 Sousa et al. (2003)

[b] Section 2.1.2 Meredith (1981) in WHO (1988)

[c] Section 2.1.3 Lapidge & Eason (2010)

[d] Section 2.1.3 Schneider & Yeary (1975)

[e] Section 2.1.4 Eason et al. (1996b)

[f] Section 2.1.4 Gooneratne et al. (1995)

[g] Section 2.1.4 Sykes et al. (1987), in mice

[h] Section 2.1.4 Eason et al. (1994); the other domestic animal is goat

[i] Section 2.1.4 Tecle & Casida (1989)

[j] Sections 2.2.2 and 2.2.3 Fisher et al. (2003), in liver

[k] Section 2.2.2 Fitzek (1978)

[l] Section 2.2.2 Robinson et al (2005)

[m] Martin et al. (1991); the other domestic animal is goat

[n] Sections 2.2.2 and 2.3.2 Nelson & Hickling (1994)

[o] Sections 2.2.3 and 2.2.4 Crowell et al. (2013), in liver

[p] Sections 2.2.4, 2.3.1, 2.3.2 Parmar et al. (1987), in liver

[q] Sections 2.2.4, 2.3.1, 2.3.2 Vandenbroucke et al. (2008), in mouse liver

[r] Section 2.2.5 Brouwer et al. (1998), 25–OHD in plasma; plasma elimination half-life of cholecalciferol was 1.4 days

[s] Section 2.2.5 Mawer et al. 1971; Batchelor et al. 1982; Davie et al. 1982, 25–OHD in human plasma; plasma elimination half-life of cholecalciferol was about 1 day in humans

[t] Section 2.2.5 Eason et al. (1996b), 25–OHD in plasma, heart, liver, kidney, fat

[u] Section 2.2.5 Hollis et al. (1977), 25–OHD in plasma

[v] Section 2.3.1 Breckenbridge et al. (1985)

[w] Section 2.3.1 Eason et al. (1996a,b), in liver and muscle

[x] Section 2.3.1 Laas et al. (1995), in liver

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