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Connections between rodenticides and drugs: a review of natural compounds with ecological, biocidal and medical applications

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ABSTRACT

Natural products have inspired over 60% of today's drugs and biocides, including rodenticides, with examples such as warfarin, fluoroacetate and cholecalciferol. Fluoroacetate is a toxic component of poisonous plants found in Australia, Africa, South America and India and is thought to deter herbivores. Together with other rodenticides it has medical applications. In relation to its use for the control of unwanted introduced animals in New Zealand, research has focused on mode of action, sub-lethal effects, welfare, reducing its risk to non-target species, and fate in the environment following use in baits. Less attention has been placed on its role in nature. In this paper the natural occurrence of bioactives that have stimulated the development of rodenticides are reviewed and links between biocidal and medical applications are explored.

Introduction

The use of rodenticides for conservation and in agriculture remains important, but there are safety, toxicity and ethical concerns (Hansford 2016), which include special concerns as chemicals are viewed as unnatural. Ironically, compounds or chemicals derived from natural sources have inspired many of today's medicines as well as biocides, including rodenticides and vertebrate pesticides. The chemical structures of natural compounds have evolved over millennia for specific biochemical purposes and they remain a platform for developing new drugs and biocides. There is a surprising ignorance, or lack of recognition, of the existence of xenobiotics and natural compounds and that all living organisms are rich in biochemical reactions and chemistry. A second irony is that it has been known for centuries, highlighted in Europe by Paracelsus, that it is the dose that distinguishes between a drug and a poison, regardless of whether the substance is a xenobiotic or naturally derived. Even today, discussions relating to risk or relative toxicity frequently ignore dose–response principles, regardless of whether the compounds in question are natural compounds or xenobiotics. Paracelsus, in the fourteenth century, expounded the concept of dose–response, stating that 'Solely the dose determines that a thing is or is

not a poison.' He used this to defend the use of substances in medicine that some considered too toxic to be used as therapeutic agents (Borzelleca 2000).

The importance of natural compounds is exemplified by the observation that over 60% of drugs are classified as naturally derived (i.e. modified natural product, unmodified natural product or synthetic compound with a natural product as pharmacophore) (Cragg et al. 2009). For example, covering the period from 1981 to 2008, around 68% of all the drugs used to curb infection (including antibacterial, antiviral, antiparasitic and antifungal compounds) and 63% of anti-cancer drugs were naturally derived (Cragg et al. 2009). Compounds used to control animal pests linked directly or indirectly to natural products include anticoagulants such as warfarin and brodifacoum, older poisons such as cyanide, strychnine and red squill, and also cholecalciferol and sodium fluoroacetate. Before 1950, rodenticides were acute or quick-acting. After the introduction of warfarin, the importance of these non-anticoagulants was reduced, at least for rodent control. The history and links between natural compounds, drugs and rodenticides are reviewed in the sections that follow.

Anticoagulant rodenticides, their discovery and development

Warfarin was one of the earliest anticoagulant rodenticides and was inspired by naturally occurring coumarins in nature. It has been used in a range of rodent baits since it was first introduced in 1947 (Link 1959). Like the other anticoagulants, it inhibits the synthesis of vitamin K, and several days elapse following ingestion before anticoagulant effects occur. It has been estimated in the past that at least 1% of the population and 8% of the over-80s are taking warfarin regularly (Pirmohamed 2006). Even with the development of newer synthetic direct oral anticoagulants (e.g. dabigatran, rivaroxaban, apixaban and edoxaban), which have been brought into market sequentially since 2010, warfarin continues to play a role in clinical practice (Barnes et al. 2015).

Brodifacoum, a more potent rodenticide, was developed three decades later (Hadler and Shadbolt 1975). Both are structurally related to a naturally occurring coumarin that causes haemorrhagic syndrome in cattle eating improperly cured or mouldy sweet clover. Warfarin was, and brodifacoum is now, the most widely used rodenticide worldwide.

The development of warfarin and related compounds is based on observations nearly 100 years ago that linked haemorrhagic disease in cattle and sheep with grazing on sweet clover hay (*Melilotus alba* and *Melilotus officinalis*) in the USA. The incidence of bleeding occurred most frequently when damp hay became infected by moulds such as *Penicillium nigricans* and *Penicillium jensi*. The resultant bleeding disorder, which was known as 'sweet clover disease', became manifest within 15 days of ingestion and killed the animal within 30–50 days (Duxbury and Poller 2001). After intensive research in the 1930s the causative agent was isolated and identified. It was found that a natural coumarin became oxidised in mouldy hay, to form 3,3-methylene-bis[4-hydroxycoumarin] commonly known as dicoumarol (Campbell and Link 1941). Research funded by the Wisconsin Alumni Research Foundation (i.e. WARF), led to exploration of dicoumarol and coumarin derivatives between 1946 and 1948. Warfarin, number 42 out of a total of 150 synthesised analogues, was particularly active and became a successful rodenticide.

After its success as a rodenticide, the transition of warfarin to clinical application was made originally under the name 'Coumadin'. The principal advantages of warfarin were its high water solubility and high oral bioavailability. It was more potent than dicoumarol but retained the ability to have its effect reversed by vitamin K (Link 1959) another natural compound that might, in nature, have protected animals from mild coumarin toxicity. When it was first proposed that warfarin should undergo clinical trials, fear of using a poison as a medicine caused some concerns (Link 1959), echoing the challenges faced by Paracelsus over 400 years earlier. Despite this, warfarin was successfully developed and has now been used as a medicine for over 70 years. Early recipients of warfarin treatment included US President Eisenhower following a myocardial infarction (Duxbury and Poller 2001).

As mentioned above, brodifacoum, which is also structurally related to a naturally occurring coumarin, is now the most commonly used rodenticide worldwide, and has largely replaced warfarin for rodenticide applications. It is a very potent anticoagulant, active against rodents, including strains resistant to warfarin and other anticoagulants (Hadler and Shadbolt 1975). A single ingestion of 1 mg/kg is usually sufficient to kill rodents. In New Zealand it is used principally to control possums and rats. Brodifacoum and related second-generation anticoagulants have unusual pharmacokinetics, namely a hepatic half-life of 150–300 days, which causes concerns relating to bioaccumulation of brodifacoum in birds and other non-target species (Eason et al. 1999) and makes these more potent anticoagulants unsuitable for medical use. Hence, medical practice continues to use warfarin today.

Vitamin D-related compounds

Cholecalciferol, (vitamin D_3), 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, milk fat and plants (Zucker et al. 1980). 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. To gain biological and toxicological activity, they must undergo metabolic conversion to 25-hydroxycholecalciferol ($25OHD_3$). Large differences in normal background concentrations of $25OHD_3$ are reported between species of mammals and are thought to be due to diet, calcium requirements, skin exposure, excretion rates and storage capability (Fairweather et al. 2013).

Cholecalciferol deficiency is associated with ill-health. As a supplement it is taken orally to treat and prevent vitamin D deficiency including rickets (Coulston et al. 2013). It is also used for familial hypophosphataemia, hypoparathyroidism, causing low blood calcium. Cholecalciferol supplements are also a common treatment for osteoporosis and are most effective in patients identified as being cholecalciferol deficient (Delmas 2002). It is toxic when consumed in large doses and cholecalciferol (vitamin D_3) was developed in the 1980s as a rodenticide (Marshall 1984). It is used in the USA as a rodenticide and in Europe has been added to baits to overcome anticoagulant resistance in rats and mice (Pospischil and Schnorbach 1994). It is registered for possum and rodent control in New Zealand. At toxic doses, this active metabolite mobilises calcium stores from

bones into the bloodstream, and decreases calcium excretion by the kidneys to such an extent that rodents receiving a lethal dose usually die within 4–7 days as a result of hypercalcaemia, tissue calcification, and renal or cardiac failure.

Because vitamin D_3 is naturally occurring and is involved in normal calcium homeostasis, there has, on occasion, been a tendency to consider baits containing cholecalciferol as safe to non-target species, ignoring the dose–response principles of toxicology highlighted by Paracelsus. 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 a subsequent backlash against its use. Target species for cholecalciferol are among the most sensitive, but 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. Nevertheless, cholecalciferol is an example of a naturally occurring chemical that, like warfarin, can be used as a rodenticide in higher doses, and as a therapeutic agent in lower doses, on a mg/kg basis. In addition, it does have interesting properties that improve its utility as a rodenticide. For example, cholecalciferol is far less toxic to birds than rodents (Eason et al. 2000).

Fluoroacetate and 1080

Fluorinated organic compounds are rare in nature. Among plants only eight of these fluorinated organic compounds, all derived from fluoroacetate, have been identified in tropical and sub-tropical plants (Meyer and O'Hagan 1992). Marais (1944) identified fluoroacetate in the South African plant gifblaar (*Dichapetalum cymosum*). Fluoroacetate has also been identified as the toxic agent in many other poisonous plants native to South America (de Oliveira 1963; de Moraes-Moreau et al. 1995), as well as Africa (Steyn 1934; Atzert 1971; Marais 1944; Meyer and O'Hagan 1992; Meyer 1994) and some 40

Table 1. Fluoroacetate content in Australian plants (derived from Oelrichs and McEwan 1961; Aplin 1971; Meyer 1994; Twigg et al. 1999).

Location	Species	Plant part	1080 µg/g maximum measured or average with SD
Central Australia	Gastrolobium brevipes	Leaves	52/9 (± 34.7)
	Acacia georginae	Leaves	25
		Seeds	32.4 (± 52.7)
Northern Australia	Gastrolobium grandiflorum	Leaves	185
South-west Australia	G. villosum		100
	G. stenophyllum		90
	G. velutinum		300
	G. spinosum		400
	G. microcarpum		600
	G. callistachys		1000
	G. calycinum		2500
	G. graniticum		1250
	G. bennettsianum		1300
	G. parviflorum		2500
	G. bilobum		500–3500
	G. graniticum	Flowers	1240
	G. parviflorum	Young leaves	2500
	G. racemosum	Leaves	1500
	G. spectibile	Leaves	400
	G. tetragonophyllum	Leaves	750

Table 2. Fluoroacetate content in plants from Africa and South America (derived from Marais 1944, de Oliviera 1963; O'Hagan et al. 1993; Meyer 1994).

Location	Species	Plant part	1080 µg/g maximum measured
East Africa	*Dichapetalum braunii*	Seeds	8000
South Africa	*Dichapetalum cymosum*	Seeds, leaves	6000
Brazil	*Palicourea marcgravii*	Leaves	455

plant species in Australia (Twigg 1994; Twigg et al. 1996a, 1996b, 1999) (see Tables 1 and 2). The highest fluoroacetate concentration so far reported from a living source is 8.0 mg/g in the seeds of the African plant *Dichapetalum braunii* (O'Hagan et al. 1993) (Table 3).

As well as being a natural toxin it has been extensively researched and used to control introduced pests in New Zealand. In relation to sodium fluoroacetate (1080) use for the control of unwanted introduced animals in New Zealand, research has focused on mode of action, sub-lethal effects, welfare, reducing its risk to non-target species, and fate in the environment following use in baits (Seawright and Eason 1994; Eason et al. 2011). Toxicology studies have determined that the mechanism of toxicity for naturally occurring fluoroacetate and for 1080 in bait is the same. Both forms are equally poisonous (de Moraes-Moreau et al. 1995) and poisonous plants have been recognised as hazardous to livestock (Steyn 1934; Quin and Clark 1947; Whittem and Murray 1963; Meyer 1994; de Moraes-Moreau et al. 1995). Fluoroacetate like cyanide (see below) 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 (King et al. 1981). The ability of plants to synthesise fluoroacetate may be more widespread than generally supposed, as fluoroacetate occurs at extremely low concentrations in some Finnish plants (Vartiainen and Kauranen 1980), in tea leaves (Vartiainen and Kauranen 1984; Twigg et al. 1996b), and guar gum (*Cyamopsis tetragonolobus*) (Vartiainen and Gynther 1984; Twigg et al. 1996b). Research testing 10 common varieties of tea available in New Zealand showed fluoroacetate concentrations of 0.4–2.4 ng/cup (Twigg et al. 1996b). Fluoroacetate biosynthesis can also occur in some bacteria, notably *Streptomyces cattleya* (O'Hagan and Harper 1999; O'Hagan 2006).

Table 3. Examples of plants with cyanogenic potential (derived from 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

The primary mode of action of 1080 is mediated through its toxic metabolite fluorocitrate, which inhibits the energy production in the tricarboxylic acid (Krebs) cycle (Peters 1952, 1957; Peters et al. 1953; Hayes and Laws 1991). Synthesis of fluorocitrate, termed 'lethal synthesis' (Peters 1952), occurs in the mitochondria. Several studies have revealed that animals that forage in areas where fluoroacetate-producing plants are common have evolved to try and overcome the plants' defence mechanism and have resistance to fluoroacetate. 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 (Twigg 1994). For example, the emu (*Dromaius novaehollandiae*) is the oldest seed-eating bird species in Australia, and has a very high level of resistance to fluoroacetate with a median lethal dose (LD$_{50}$) of 100–200 mg/kg (Twigg et al. 1988) 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. Therefore, where fluoroacetate is widely distributed in terrestrial ecosystems it appears to play a role in the chemical ecology of plant–herbivore relationships and drives evolutionary selection of fluoroacetate tolerance in species ranging from insects to possums (Mead et al. 1979; McIlroy 1981, 1982; Twigg 1994) in the same way that other potent marine toxins, such as tetrodotoxin, do in predator–prey relationships (Moczydlowski 2013). Interestingly, the caterpillar moth, *Sindrus albimaculatus*, which feeds on fluoroacetate-containing *Dichapetalum cymosum*, can not only detoxify fluoroacetate, but also accumulate it (probably in vacuoles) and uses fluoroacetate as a defence against predation (Meyer and O'Hagan 1992).

In biomedical research the positive inotropic action of sodium fluoroacetate has been explored (Korth et al. 1978). Inotropic agents are used to treat congestive heart failure and an understanding of their mode of action is needed to improve therapies. Fluorouracil is an anti-cancer agent that is partially metabolised to fluoroacetate (Arellano et al. 1998). Researchers have investigated the cause of cardiotoxicity associated with fluorouracil treatment (Matsubara et al. 1980); fluoroacetate has been implicated. What has not been explored is whether fluoroacetate is formed in sufficient amounts to contribute to the anti-cancer effects of fluorouracil by selectively having most effect on highly active tissue (Ataria et al. 2000), which might possibly include rapidly dividing cancer cells.

Recently, sodium fluoroacetate has been explored for experimental use in radiology and metabolic/molecular imaging using positron emission tomography emitters (Matthies et al. 2004; Nishii et al. 2012), which is a growth area in radiology for cancer imaging. As has occurred in the past with warfarin. (Link 1959), Nishii et al. (2012) noted that although the use of a compound that is known to be extremely toxic could be a cause for concern, the amounts required for diagnostic imaging are extremely small and similar to those that might be ingested in tea (Nishii et al. 2012).

In accordance with the principles of toxicology highlighted by Paracelsus and through this review it is important that users of 1080 do not underplay its risks when used in pest control operations versus the extremely small amount in tea leaves or those amounts proposed for use in radiology.

Older poisons

Older compounds used as poisons that occur in nature include strychnine, red squill and cyanide. Strychnine is found in the seeds of the tree *Strychnos nux-vomica* and is used in

extremely low doses in homeopathy (Pelletier and Caventou 1819). Strychnine was popularly used as an athletic performance enhancer and recreational stimulant in the late nineteenthth century, (http://io9.gizmodo.com/why-strychnine-was-an-early-performance-enhancing-drug-512532345?IR=T2017) and in the early twentieth century in low doses as a tonic. It has been used, at higher doses, for rodent and vertebrate pest control since the mid-1800s (Schwartze 1922). Strychnine is a fast-acting compound and poisoned animals often die in less than 1 hour, or occasionally in 24 hours or longer, as a result of respiratory failure (asphyxia). The typical signs of strychnine poisoning are restlessness and muscular twitching, which progress to convulsive seizures and violent muscular spasms before death (Osweiler et al. 1985). Strychnine was used in New Zealand but has been deliberately phased out because of being inhuman and its persistence.

Red squill, another very old poison, was extracted from the bulbs of the Mediterranean plant *Urginea maritima* and has been used as a rodenticide and medicine (Gentry et al. 1987). It has been used as a medicinal plant since ancient times and is noted in the Ebers Papyrus of the sixteenth century BC, one of the oldest medical texts of ancient Egypt (Gentry et al. 1987). The bioactive substance in red squill is the cardiac glycoside, scilliroside. Its rodenticidal uses are summarised in earlier reviews (Hone and Mulligan 1982; Meehan 1984). When used as a rodenticide, symptoms of poisoning include hind limb paralysis, convulsions, emesis (except in rodents) and diarrhoea. Red squill is considered inhumane and has not been pursued in New Zealand.

At therapeutic doses *Urginea maritima* has been used as a medicinal plant since ancient times. Its primary medicinal use was as a treatment for oedema linked to cardiac failure (Hollman 1992).

Cyanide has been used in New Zealand for several decades for killing possums, but has limited use in other countries. Cyanogenic (cyanide-containing) compounds occur in plants (see Table 2) and also in some fungi and bacteria. More than 2000 plants are known to be cyanogenic, including food plants and forage crops. There are reports from overseas that yields of hydrogen cyanide from common food and feed sources range from 0 to 912 mg/100 g (Hayes 1994). There are also numerous overseas reports of livestock that have been acutely poisoned by young sorghum and sugar gums (Webber et al. 1984). Young bamboo shoots and peach leaf 'tea' are examples of dietary sources of hydrogen cyanide poisoning in children (Hayes 1994).

Like fluoroacetate, cyanogenic compounds in plants 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 the release of cyanide from the glycoside are kept spatially separated from the glycoside in intact plant cells. Upon damage to leaves, free hydrogen cyanide may be released as cellular damage allows enzymatic degradation of the glycoside.

Medical uses include the cyanide compound sodium nitroprusside applied to measure urine ketone bodies mainly for diabetic patients. Nitroprusside is a complex anion surrounded by five tightly bound cyanide ligands. It has a number of medical applications including treatment of severe hypertension (Friederich and Butterworth 1995). Early in the twentieth century, a copper cyanide compound was briefly used by Japanese physicians for the treatment of tuberculosis and leprosy (Takano 1916).

Conclusion

Chemical structures that have evolved naturally over millennia remain a platform for developing new drugs and have inspired over 60% of today's drugs as well as biocides, including rodenticides and vertebrate pesticides. Compounds used to control animal pests linked directly or indirectly to natural products include cyanide, cholecalciferol, sodium fluoroacetate and anticoagulants such as warfarin and brodifacoum. This review has highlighted the link between their biocidal and medical applications, and that it is the dose that distinguishes between a drug and a poison. This is most clearly illustrated by the importance of anticoagulants for the treatment of clotting disorders, cholecalciferol for maintenance of calcium homeostasis, and fluoroacetate as a potential diagnostic tool in radiology.

Research in the field of natural compounds as medicines and biocides continues. Not surprisingly there is a renewed focus on bioactives from marine sources because of their antibiotic, antiparasitic, antiviral, anti-inflammatory, antifibrotic, analgesic and anticancer activities. Marine life constitutes almost 80% of the world biota with thousands of bioactive compounds and secondary metabolites derived from marine organisms such as tunicates, sponges, molluscs, bryozoans, sea slugs and algae (Suleria et al. 2015). Some compounds are extremely toxic and yet when administered at the appropriate dose and route offer opportunities for a step change in treatment of acute and chronic conditions (Lagos et al. 2004; Chau et al. 2011; Moczydlowski 2013), further illustrating the principles of toxicology expounded by Paracelsus.

At the Cawthron Institute, in Nelson, New Zealand, natural compounds are being evaluated from marine organisms, including shellfish and seaweeds and a unique collection of over 300 micro-algae, and while some of these compounds have medical applications some are potential biocides and vertebrate pesticides of the future. Portimine is one example of a natural marine compound that has unique anticancer properties (Selwood et al. 2013) and is also being explored as a biocide.

Some could be candidate rodenticides given their reported LD_{50} of < 100 ng/kg (Munday et al. 2013, Munday 2014). Their potency means that very small amounts would be used in baits; hence taste avoidance and bait shyness, which occur with many rodenticides, would be unlikely. This could be particularly helpful when developing rodenticides effective for the control of mice, which are easily deterred from eating baits, and compared with rats are more susceptible to anticoagulants.

Some naturally produced chemicals that have been reviewed in this paper have interesting properties that improve their utility as rodenticides. For example, cholecalciferol is far less toxic to birds than rodents (Eason et al. 2000) and further exploration of potent naturally occurring compounds from marine sources could yield useful new rodenticides with improved efficacy and safety profiles. At present the only truly species-specific rodenticide undergoing development is the xenobiotic norbormide (Jay-Smith et al. 2016). Research to enable the wide-scale use of norbormide in targeted conservation programmes continues, and further evaluation of natural compounds from marine and other sources is warranted for their biocidal and medical potential.

Acknowledgements

References

Aplin TEH. 1971. Poison plants of Western Australia: the toxic species of Gastrolobium and Oxylobium. Western Australian Department of Agriculture Bulletin. 3772(8): 1–66.

Arellano M, Malet-Martino M, Martinol R, Gires P. 1998. The anti-cancer drug 5-fluorouracil is metabolized by the isolated perfused rat liver and in rats into highly toxic fluoroacetate. British Journal of Cancer. 77(1):79–86.

Ataria JM, Wickstrom M, Arthur D, Eason CT. 2000. Biochemical and histopathological changes induced by sodium monofluoroacetate (1080) in adult male mallard ducks (Anas platyr-hynchos). Proceedings of the 53rd New Zealand Plant Protection Conference. p. 293–298.

Atzert SP. 1971. A review of sodium monofluoroacetate (Compound 1080), its properties, toxicology, and use in predator and rodent control. United States Department of the Interior Fish and Wildlife Services Special Scientific Report. Wildlife No. 146. 34 p.

Barnes GD, Lucas E, Alexander GC, Goldberger ZD. 2015. National trends in ambulatory oral anticoagulant use. The American Journal of Medicine. 128:1300–1305.

Borzelleca JF. 2000. Paracelsus: herald of modern toxicology. Toxicological Sciences. 53(1):2–4.

Campbell HA, Link KP. 1941. Studies on the hemorrhagic sweet clover disease. IV. The isolation and crystallization of the hemorrhagic agent. Journal of Biological Chemistry. 138:21–33.

Chau R, Kalaitzis JA, Neilan BA. 2011. On the origins and biosynthesis of tetrodotoxin. Aquatic Toxicology. 104:61–72.

Coulston AM, Boushey C, Ferruzzi M. 2013. Nutrition in the prevention and treatment of disease. San Diego: Academic Press. p. 818.

Cragg GM, Grothaus PG, Newman DJ. 2009. Impact of natural products on developing new anti-cancer agents. Chemical Reviews. 109:3012–3043.

de Moraes-Moreau RL, Harguich M, Harasuchi M, Morita H, Palermo-Yeto J. 1995. Chemical and biological demonstration of the presence of monofluoroacetate in the leaves of Palicourea marc-gravii. Brazilian Journal of Medical and Biological Research. 28:685–692.

de Oliveira MM. 1963. Chromatographic isolation of monofluoroacetic acid from Palicourea marc-gravii. Experientia. 19:586–587.

Delmas PD. 2002. Treatment of postmenopausal osteoporosis. The Lancet 359:2018–2026.

Duxbury BM, Poller L. 2001. State-of-the-art review: the oral anticoagulant saga: past, present, and future. Clinical and Applied Thrombosis and Hemostasis. 7:269–275.

Eason CT, Miller A, Ogilvie S, Fairweather A. 2011. An updated review of the toxicology and eco-toxicology of 1080 in relation to its use as a pest control tool in New Zealand. New Zealand Journal of Ecology. 35(1):1–20.

Eason CT, Milne L, Potts M, Morriss G, Wright GRG, Sutherland ORW. 1999. Secondary and tertiary poisoning risks associated with brodifacoum. New Zealand Journal of Ecology. 23:219–224.

Eason CT, Wickstrom ML, Henderson R, Milne L, Arthur D. 2000. Non-target and secondary poisoning risks associated with cholecalciferol. Proceedings New Zealand Plant Protection Conference. 53:299–304.

Fairweather AAC, Eason CT, Elder PA, Eason CMF, Arthur D. 2013. Reference concentrations of cholecalciferol in animals: a basis for establishing non-target exposure. New Zealand Journal of Zoology. 40(4):280–289.

Friederich JA, Butterworth JF. 1995. Sodium nitropusside: twenty years and counting. Anesthesia and Analgesia. 81(1):152–162.

Gentry HS, Verbiscar AJ, Banigan TF. 1987. Red squill (Urginea maritima, Liliaceae). Economic Botany. 41(2):267–282.

Hadler MR, Shadbolt RS. 1975. Novel 4-hydroxycoumarin anticoagulants active against resistant rats. Nature. 253:275–277.

Hansford D. 2016. Protecting paradise 1080 and the fight to save New Zealand's wildlife. Nelson, New Zealand: Potton and Burton. 318 p.

Hayes AW. 1994. Principals and methods in toxicology. 3rd ed. Philadephia: Ravens Press. 1468 p.

Hayes WJ, Laws ER, eds. 1991. Handbook of pesticide toxicology. Vol. 3. Classes of pesticides. San Diego: Academic Press. 949 p.

Hollman A. 1992. Plants in cardiology: medicinal plant discovery. British Heart Journal. 67(6):506.

Hone J, Mulligan H. 1982. Vertebrate pesticides. Science Bulletin 89. Sydney: Department of Agriculture.

Jay-Smith M, Murphy EC, Shapiro L, Eason CT, Brimble MA, Rennison D. 2016. Stereoselective synthesis of the rat selective toxicant norbormide. Tetrahedron. 72:5331–5342.

King DR, Oliver AJ, Mead RJ. 1981. Bettongia and fluoroacetate: a role for 1080 in fauna management. Australian Wildlife Research. 8:521–536.

Korth M, Weger N, Reiter M. 1978. The positive inotropic action of sodium fluoroacetate on guinea-pig ventricular myocardium. Naunyn-Schmiedeberg's Archives of Pharmacology. 303:7–14.

Lagos NC, García C, Lattes K, Azolas R, Bocic G, Cuneo A, Chiong H, Jensen C, Henriquez A. 2004. Paralytic shellfish poison: toxins that can kill and heal. In: Proceedings Chemical and Biological Medical Treatment Symposium; April 25–30, Switzerland: Spiez Laboratory. p. 197–202.

Link KP. 1959. The discovery of dicumarol and its sequels. Circulation. 19:97–107.

Marais JS. 1944. Monofluoroacetic acid, the toxic principle of "gifblaar" Dichapetalum cymosum. Onderspoort Journal of Veterinary Science. 20:67–73.

Marshall EF. 1984. Cholecalciferol: a unique toxicant for rodent control. Proceedings of 11th vertebrate pest conference, Davis: University of California. p. 95–98.

Matsubara I, Kamiya J, Imai S. 1980. Cardiotoxic effects of 5-fluorouracil in the guinea pig.. The Japanese Journal of Pharmacology. 30:871–879.

Matthies A, Ezziddin S, Ulrich EM, Palmedo H, Biersack H-J, Bender H, Guhlke S. 2004. Imaging of prostate cancer metastases with 18 F-fluoroacetate using PET/CT. European Journal of Nuclear Medicine and Molecular Imaging. 31:797.

McIlroy JC. 1981. The sensitivity of Australian animals to 1080 poison. I. Intraspecific variation and factors affecting acute toxicity. Australian Wildlife Research. 8:369–383.

McIlroy JC. 1982. The sensitivity of Australian animals to 1080 poison. II. Marsupial and eutherian carnivores. Australian Wildlife Research. 8:385–399.

Mead RJ, Oliver AJ, King DR. 1979. Metabolism and defluorination of fluoroacetate in the brush-tailed possum (Trichosurus vulpecula). Australian Journal of Biological Sciences. 32(1):15–26.

Meehan AP. 1984. Rats and mice. Their biology and control. Horsham: Rentokil Ltd.

Meyer JJM. 1994. Fluoroacetate metabolism of Pseudodomonas cepacia. In: Seawright A, Eason CT, editors. Proceedings of the International Science Workshop on 1080; The Royal Society of New Zealand, SIR Publishing Wellington Miscellaneous Series 28. P. 54–58.

Meyer M, O'Hagan D. 1992. Rare fluorinated natural products. Chemistry in Britain. 28:785–788.

Moczydlowski EG. 2013. The molecular mystique of tetrodotoxin. Toxicon. 63:165–183.

Munday R. 2014. Toxicology of seafood toxins: a critical review in seafood and freshwater toxins. In: Botana LM, editor. Seafood and freshwater toxins, pharmacology, physiology, and detection. 3rd ed. Boca Raton, FL: CRC Press, Taylor and Francis Group; Chapter 7, p. 197–290.

Munday R, Thomas K, Gibbs R, Murphy C, Quilliam MA. 2013. Acute toxicities of saxitoxin, neosaxitoxin, decarbamyl saxitoxin and gonyaytoxins 1&4 and 2&3 to mice by various routes of administration. Toxicon. 76:77–83.

Nishii R, Tong W, Wend R, Soghomonyan S, Mukhopadhyay U, Balatoni J, Mawlawi O, Bidaut L, Tinkey P, Borne A, et al. 2012. Pharmacokinetics, metabolism, biodistribution, radiation dosimetry, and toxicology of 18f-fluoroacetate (18F-FACE) in non-human primates. Molecular Imaging and Biology. 14:213–224.

Oelrichs PB, McEwan T. 1961. The toxic principles of Acacia georginae. Queensland Journal of Agricultural Science. 19:1–16.

O'Hagan D. 2006. Recent developments on the fluorinase from Streptomyces cattleya. Journal of Fluorine Chemistry. 127(11):1479–1483.

O'Hagan D, Harper DB. 1999. Fluorine-containing natural products. Journal of Fluorine Chemistry. 100:127–133.

O'Hagan D, Perry R, Lock JM, Meyer JJM, Dasaradhi L, Hamilton JTG, Harper DB. 1993. High levels of monofluoroacetate in Dichapetalum braunii. Phytochemistry. 33:1043–1045.

Osweiler GD, Carson TL, Buck WB, Van Gelder GA. 1985. Chemical and diagnostic veterinary toxicology. Dubuque, IA: Kendall Hunt. 494 p.

Pelletier and Caventou. 1819. Mémoire sur un nouvel alcali vegetal (la strychnine) trouvé dans la feve de Saint-Ignace, la noix vomique. Annales de Chimie et de Physique. 10:142–176.

Peters RA. 1952. The puzzle for therapy in fluoroacetate poisoning. British Medical Journal. 2:1165–1170.

Peters RA. 1957. Mechanism of the toxicity of the active constituent of Dichapetalum cymosum and related compounds. Advances in Enzymology and Related Subjects of Biochemistry. 18:113–159.

Peters RA, Wakelin RW, Rivett DEA, Thomas LC. 1953. Fluoroacetate poisoning: comparison of synthetic fluorocitric acid with the enzymically synthesized fluorotricarboxylic acid. Nature (Lond.). 171:1111–1112.

Pirmohamed M. 2006. Warfarin: almost 60 years old and still causing problems. British Journal of Clinical Pharmacology. 62:509–511.

Pospischil R, Schnorbach HJ. 1994. Racumin plus, a new promising rodenticide against rats and mice. Proceedings: Sixteenth Vertebrate Pest Conference; Davis: University of California. p. 180–187.

Quin JI, Clark R. 1947. Studies on the action of potassium monofluoroacetate (CH2FCOOK) [Dichapetalum cymosum (Hook) Engl.] toxin on animals. Onderstepoort Journal of Veterinary Science and Animal Industry. 22:77–82.

Schwartze EW. 1922. The relative toxicity of strychnine to the rat. Washington, DC: US Department of Agriculture.

Seawright A, Eason CT. 1994. Proceedings of the international science workshop on 1080. The Royal Society of New Zealand, Miscellaneous Series 28: 173 p.

Selwood AI, Wilkins AL, Munday R, Shia F, Rhodes LL, Holland PT. 2013. Portimine: a bioactive metabolite from the benthic dinoflagellate Vulcanodinium rugosum. Tetrahedron Letters. 54 (35):4705–4707.

Steyn DG. 1934. Plant poisoning in stock and the development of tolerance. Onderstepoort Journal of Veterinary Science. 3:119–123.

Suleria HAR, Osborne S, Masci P, Gobe G. 2015. Marine-based nutraceuticals: an innovative trend in the food and supplement industries. Marine Drugs. 13:6336–6351.

Takano R. 1916. The treatment of leprosy with Cyanocuprol. The Journal of Experimental Medicine. 24(2):207–211.

Twigg LE. 1994. Occurrence of fluoroacetate in Australian plants and tolerance to 1080 in indigenous Australian animals. In: Seawright AA, Eason CT, editors. Proceedings of the science workshop on 1080. The Royal Society of New Zealand Miscellaneous Series 28. Wellington: SIR Publishing. p. 97–115.

Twigg LE, King DR, Bowen LH, Wright GR, Eason CT. 1996a. Fluoroacetate found in Nemcia spathulata. Australian Journal of Botany. 44:411–412.

Twigg LE, King DR, Bowen LH, Wright GR, Eason CT. 1996b. Fluoroacetate content of some species of the toxic Australian plant genus, Gastrolobium and its environmental persistence. Natural Toxins. 4:122–127.

Twigg LE, King DR, Davis H, Saunders D, Mead RJ. 1988. Tolerance to, and metabolism of, fluoroacetate in the emu. Australian Wildlife Research. 15:239–247.

Twigg LE, Wright GR, Potts MD. 1999. Fluoroacetate content of Gastrolobium brevipes in Central Australia. Australian Journal of Botany. 47:877–880.

Vartiainen T, Gynther J. 1984. Fluoroacetic acid in guar gum. Food and Chemical Toxicology. 22:307–308.

Vartiainen T, Kauranen P. 1980. Determination of fluoroacetic acid by capillary column-mass spectrometry and occurrence of fluoroacetate in plants. Kernia-Kami. 12:760.

Vartiainen T, Kauranen P. 1984. The determination of traces of fluoroacetic acid by extractive alkylation, pentafluorobenzylation and capillary gas chromatography-mass spectrometry. Mass Spectrometry Analytica Chemica Act. 157:91–97.

Webber JJ, Roycroft CR, Callinan JD. 1984. Cyanide poisoning of goats from sugar gums (*Eucalyptus cladocalyx*). Australian Veterinary Journal. 62:84.

Whitten JH, Murray LR. 1963. The chemistry and pathology of Georgina River poisoning. Australian Veterinary Journal. 39:168–173.

Zucker H, Stark H, Rambeck WA. 1980. Light-dependent synthesis of cholecalciferol in a green plant. Nature. 283:68–69.