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SODIUM FLUOROACETATE (1080) IN RELATION TO ITS USE IN NEW ZEALAND REVISITED: A 2021 REVIEW

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Abstract: Traps, poisons and hunting are pest control tools used internationally for crop protection and to restore ecosystems, particularly on islands and continents where introduced mammals endanger native species. Sodium fluoroacetate (1080) is a vertebrate pesticide, initially developed in the 1940s, principally used to control unwanted introduced mammals in New Zealand and Australia. During the last ten years, there have been over 260 new research and review publications, specifically on 1080 in scientific journals. These publications supplement a body of scientific information regarding mode of action, natural occurrence, toxicology, including poisoning incidents and antidotes, metabolism and fate in the environment and risk to non-target species. Multi-year studies now go beyond immediate non-target impacts and explore ecosystem-level outcomes, including population-level changes for multiple native bird species following the sustained removal of predators. Numerous review publications on community attitudes to pest control and the merits of different tools and techniques have been stimulated, in part by the Predator Free NZ 2050 campaign, and these are summarised. Many sectors of our communities would prefer not to use poisons for pest control, particularly if applied aerially. If 1080 is to continue to be used in New Zealand, research still needs to focus on additional improvements in target specificity, particularly concerning the interactions of kea and game species with bait, and address any new questions raised by regulatory agencies such as the Environmental Protection Agency (EPA; formally ERMA), communities, and iwi. Additionally, there is a need to innovate how different pest control tools are used and advance close-to-market tools with the highest public acceptance, such as species-specific poisons and more targeted bait delivery or trapping systems. Community engagement should continue to be open and transparent, highlight risks and benefits, and seek consensus. In most cases, consensus will involve an

integrated approach to pest control using acceptable levels of both aerial and ground-based tools. Greater acceptance of any pest control tool occurs when use is discussed within the context of long-term goals for saving endangered species and ecosystem recovery, with communities that treasure the restoration of their landscapes. However, values are changing, such that no (or minimal) pesticide use is a theme that is increasingly mainstream. In this changing environment, strategies that rely on 1080 or other toxins as *one-off treatments* for eradicating pests or disease versus continued application for maintenance control are likely to be more and more important.

Keywords: Sodium fluoroacetate, 1080, fate, pest control, non-target responses, toxicology, ecosystem changes, community engagement.

INTRODUCTION

1080 baits have been used for decades to protect biodiversity in New Zealand (NZ), targeting introduced pests such as rodents (*Rattus* spp.), stoats *(Mustela erminea)* and the brushtail possum *(Trichosurus Vulpecula)*. Possums are still a resource to those involved in the fur recovery but unfortunately more often considered NZ's number one vertebrate pest species having a deleterious effect on native flora and depredating native species. Possums also spread Tb to cattle (*Bos* spp.), a key driver for their control with 1080 baits (Pracy & Kean 1949; Batcheler et al. 1967; Hutchings et al. 2013; Byrom et al. 2016; van Vianen et al. 2018). Aerial distribution of 1080 baits is a globally unique practice, restricted to NZ and Australia (Doherty et al. 2020). It continues, despite sometimes fierce opposition from some sections of society (Hansford 2016), simply because aerial 1080 baiting is still considered to be the only practical and affordable approach to address the threats to conservation and agricultural production, particularly in inaccessible areas (PCE 2011, 2013; Warburton et al. In press)

In part fuelled by the controversy, but also by scientific uncertainties and the desire to protect endangered native species better, there have been over 260 publications on 1080 and pest control technology in scientific journals, book chapters and books published since the last review in 2011. Some of these publications are linked to aspects of NZ's predator-free strategy with the ambitious goal of eradicating predators from mainland areas by the year 2050 (Owens 2017; DoC 2018; Ross et al. 2020). Other publications highlight expanded or increased frequency of 1080 use on the conservation estate with the instigation of the *Battle for the Birds* (BfB; later renamed Protect the Birds Tiakina Ngā Manu) campaign in 2014, focusing on rodent control following beech (*Fuscopora* and *Lophozonia* spp.) masting events. The BfB campaign can trace its origins to the initial recommendations of the Parliamentary Commissioner for the Environment in 2013 (PCE 2013) and again in 2017 (PCE 2017).

Both the continued use of 1080 and the development of new pest-control tools in NZ are fuelled by significant biodiversity declines (Simberloff 2019) and the continued effort by many to reverse these. Globally, these declines are prevalent on isolated islands, including NZ and Australia, and Pacifica where unique fauna and flora have evolved in the absence of exotic mammals, or at least in the absence of mammals of European origin (Glen & Hoshino 2020). NZers have led the way internationally with toxic baiting strategies, using both 1080 and brodifacoum to enable ecosystem recovery and translocations of endangered species to newly secure islands and mainland sanctuaries (Bellingham et al. 2009; Broome et al. 2010; Russell et al. 2015; Veitch et al. 2019; Glen & Hoshino 2020; Ross et al. 2020). Managing the impacts of invasive species is a priority for conserving global biodiversity, and NZ conservationists are part of a global network working to preserve iconic species and ecosystems (Campbell et al. 2015; Byrom et al. 2016; Binny et al. 2020; Campbell et al. 2019). Island conservation strategies seek to completely remove rodents and other unwanted mammals, allowing native species to recover or be reintroduced. Unlike the mainland, the likelihood of reinvasion is relatively small and controllable (Veitch et al. 2019). As such, the use of toxins for island conservation may be more acceptable, where one-off use of a toxin achieves pest eradication goals versus repeated use of 1080 to suppress pest populations on the NZ mainland.

The last major journal review focused on 1080 was undertaken nearly a decade ago and detailed 1080 mode of action, acute toxicity, fate in the environment (water, soil, animals) and non-target risks for birds, invertebrates, deer, and domestic animals (Eason et al. 2011). This current review advances and updates these areas and has incorporated several new sections. For example, a new section summarises all significant international 1080 review documents spanning from the 1960s to today. These reviews cover many diverse areas relevant to 1080 use in NZ, including social license, alternatives to 1080, early research on toxicology and assessments of the cost-benefits of continued 1080 use. There are also new sections on antidotes and treatments, short-to-medium term benefits of 1080 use for native bird species using meta-analysis techniques, and a final section on the politics and social pressure associated with 1080 use.

1080 In Context

Baits containing 1080 were first registered for aerial application in 1964 (Green 2003) under the Agricultural Chemicals Act. Not surprising, the data that supported this registration was outdated by the 1990s and did not meet the needs of pest control practitioners, communities, or the standard expected for pesticide registration in the 21st Century (Seawright & Eason 1994). Hence there is an ongoing requirement for newer regulatory toxicology studies and generation of new data on the fate of 1080 in the environment, non-target effects, and health and safety (Eason et al. 2011). This type of research data was also a pre-requisite for the reregistration of 1080 by Environmental Risk Management Authority (ERMA) in 2011 (see: ww.epa.govt.nz).

A basic outline of the history and the genesis of rodenticides and vertebrate pesticides, which includes 1080 (Eason 2017), provides further context to this review paper and additional analyses of new information on 1080. For example, some natural pesticides, such as cyanide and strychnine, have been used worldwide for hundreds, possibly thousands of years. Then, between 1940 and 1990, there was prolific international research and the introduction of new rodenticides and vertebrate pesticides. 1080 was developed during this period along with the first-generation anticoagulant rodenticides in the 1940s, 50s and 60s. Cholecalciferol and second-generation anticoagulant rodenticides were developed in the 70s and 80s (Eason & Wickstrom 2001). In contrast to global trends, NZ has retained essential toxins and traps, refined how they are used, and developed the capability to explore and register new mammalian toxins. Some of these are target specific, selected on welfare grounds, or have favourable breakdown characteristics such that they are unlikely to bioaccumulate (Beausoleil et al. 2016; Eason 2017; Chand & Cridge 2020).

Regardless of how or where they were developed, rodenticide and vertebrate pesticides are generally classified as slow-acting anticoagulant toxins or acute-acting non-anticoagulants.

First-generation and second-generation anticoagulant rodenticides are all slow acting. They have the same mode of action, namely interference with the synthesis of blood clotting factors, which results in haemorrhaging and death. Over ten anticoagulant agents have been synthesized, and their principal use worldwide in pest control has been against commensal rodents, primarily Norway rats (*Rattus norvegicus*), but also ship rats (*Rattus rattus*) for conservation purposes. Warfarin was one of the earliest first-generation anticoagulant rodenticides introduced in 1947. Second-generation anticoagulants were developed in the 1970s, such as brodifacoum used to target rodents and possums. In NZ, seven poisons are currently registered for possum control: 1080, cyanide, cholecalciferol (Vitamin D3), brodifacoum, pindone, sodium nitrite and a combination of diphacinone and cholecalciferol (Eason et al. 2017; Eason et al. 2019). Acute toxins such as 1080 and cyanide are still considered essential tools as the excessive field use of brodifacoum, which is popular globally for commensal rodent control, will lead to bioaccumulation in wildlife following repeated use.

Despite advances with new toxins and safer combinations (Eason et al. 2019), and the registration of more humane toxins such as para-amino-propiophenone (PAPP) and sodium nitrite (Shapiro et al. 2015), 1080 is more widely used as these other toxins are not yet registered for aerial control. Hence, the perceived importance of 1080 (Warburton et al. In press) and the rationale for this updated 2021 review, synthesising recently published material on 1080, building on the review published in 2011 (Eason et al. 2011).

History and Properties of 1080

The toxic nature of 1080 and fluoroacetate in different forms has been studied intensively for approximately 80 years. Research in the 1940s led to its development as a potential rodenticide before the Second World War (Peters 1963; Keiner 2005). Its mode of action was first studied in detail by Sir Rudolf Peters at Oxford University and then US researchers (Peters 1963; Atzert 1971). There are at least ten major review publications, books, and book chapters published on 1080, summarised in Table 1:

Table 1 Major review publications on 1080

(Peters 1963)	Book Chapter in "*Lethal synthesis*" Pergamon Press, Oxford.	Lethal synthesis and carbon-fluorine compounds.	Focus on mode of action and toxicology of fluoroacetate, included the conversion to fluorocitrate termed *lethal synthesis*
(Atzert 1971)	Review publication USA Department of Interior Fish and Wildlife Service.	A review of sodium fluoroacetate (compound 1080) its properties, toxicology, and role in predator and rodent controls.	A comprehensive review of history, chemistry and toxicology, treatment metabolism, fate in the environment up to 1971.
(Rammell & Fleming 1978)	Book published by Ministry of Agriculture and Fisheries, Wellington, NZ.	Compound 1080: properties and use of sodium fluoroacetate in NZ.	Similar to the Atzert review above: a review of history, chemistry and toxicology, treatment metabolism, fate in the environment, but updated and focused on NZ use patterns.
(Seawright & Eason 1994)	Conference proceedings publication. The Royal Society of NZ, Wellington.	The science workshop on 1080.	Updated information on 1080 use, natural occurrence and fate in the environment, metabolism in animals, non-target impacts and effectiveness, from NZ and international researchers.
(PCE 1994)	Parliamentary Commissioner for the Environment Report, Wellington.	Possum management in NZ.	Review of 1080 non-target effects, fate in the environment and effectiveness alongside other tools. Recommendations for improved usage and not to maintain overreliance on a single tool.
(Watts 1994)	Book Chapter Auckland Institute of Technology Press, Auckland.	1080 -Unacceptable risks.	Highlight's data gaps on fate in the environment and non-target effects.
(Eisler 1995)	Review publication US Department of Interior National Biological Service.	Sodium fluoroacetate (1080) hazards to fish, wildlife, and invertebrates: a synoptic review.	Updated review on use of 1080, environmental fate, lethal and sublethal effects and antidotes.
(Eason 2002)	A review paper in the Journal Toxicology 181: 523-530.	Sodium fluoroacetate (1080) risk assessment and risk communication.	Updated NZ data on fate in the environment and toxicology. Recommendation that risk communicators must not trivialise toxicity but discuss risk alongside measures to mitigate adverse effects.
(Green 2003)	Review document published by Animal Health Board and Department of Conservation, Wellington.	The use of 1080 to control possums and other pests: a resource document.	Focuses on the rationale for use, key information about 1080 and outcomes from using 1080.
(ERMA 2007)	ERMA report, Wellington, NZ.	ERMA Decision. Application for the reassessment of a hazardous substance under	Reassessment of 1080. Allowed the continued use of 1080 but placed

		section 63 of the HSNO act 1996: sodium fluoroacetate (1080) and formulated substances containing 1080.	additional controls on aerial application to mitigate risks.
(Ogilvie et al. 2010a)	Book chapter in Maori and the environment: Kaitiaki, Huia Publishers, Wellington.	There's a rumble in the jungle -1080 poisoning our forests or necessary tool?	Highlights Maori concerns, accepts use of 1080 reluctantly and looks to a future where more culturally acceptable tools are used.
(Eason et al. 2011)	A review article in NZ Journal of Ecology 35 (1): 1-20.	An Updated Review of The Toxicology And Ecotoxicology Of Sodium Fluoroacetate (1080). Concerning its use as a pest control tool in NZ.	A comprehensive update of toxicology and fate data building on the 2002 review above.
(PCE 2011)	Parliamentary Commissioner for the Environment Report, Wellington.	Evaluating the use of 1080: Predators, poisons and silent forests.	Review of 1080 non-target effects, fate in the environment and effectiveness. Recommendations for improved transparency, continued use of 1080 and scaling up control efforts, and not maintaining overreliance on a single tool.
(Hansford 2016)	Book Published by Potton and Burton, Nelson, NZ.	Protecting paradise.	Review of the politics and science regarding 1080.

Most of these reviews, book chapters and books are technical, with some focusing on social, political, and controversial aspects of 1080 use (Watts 1994; Ogilvie et al. 2010b; Ogilvie et al. 2010a; Hansford 2016). Several hundred peer-reviewed publications cover the period 1940 to 2021 on all aspects of 1080, with over 260 of these in the last decade, spanning topics ranging from the experimental use of 1080 in radiology (Nishii et al. 2012) to its toxicology, environmental fate (Northcott et al. 2014; Liu et al.), and the short- and long-term population responses in native species following 1080 bait applications for predator control (Byrom et al. 2016).

1080 was first applied in bait to rodents and other pests in the United States (Delfın-Alfonso et al. 2012; Ripple et al. 2013) and has been used in NZ for pest control since the 1950s (Rammell & Fleming 1978). Baits containing 1080 were first developed for aerial application in the 1950s and 1960s (Green 2003), and it is the only poison that is registered for aerial control of possums, and the aerial application of this toxin the most contentious (Green & Rohan 2012; Warburton et al. In press). The first aerial 1080 baiting operation specifically targeting ship rats was carried out in 1989 (Innes et al. 1995). In Australia, 1080 is used for the protection of native animals from introduced species such as foxes (*Vulpes vulpes*) (Marlow et al. 2015a) (Berry et al. 2012), feral cats (*Felis catus*) (Algar et al. 2010), feral dogs (*Canis lupus familiaris*) (Allen 2014), feral pigs (*Sus scofra*) (Bengsen et al. 2011; Bengsen et al. 2014), and dingoes (*Canis familiaris dingo*) (Allen 2010; Allen 2015).

It is noteworthy that the most extensive use of 1080 occurs in NZ, increasingly followed by Australia, and most international research comes from these two countries (PCE 1994; Marks et al. 2009; PCE 2011; Woodford et al. 2012; Dundas et al. 2014; Marlow et al. 2015a; Marlow et al. 2015b; Mallick et al. 2016; Kinnear et al. 2017), and more recently Israel (Glausiusz 2018). In some countries where it is not currently registered, such as China, research papers report human exposure, poisoning and fatalities (Liu et al. 2020), which are probably linked to poor handling and inadequate safety procedures associated with its unregulated or illegal use. In the USA, research now focuses on antidotes in response to concerns regarding the misuse of 1080 and other poisons (DeLey Cox et al. 2020), which we witnessed this first- hand in 2014 with a threat to poison infant milk powder with 1080 (Cooney et al. 2016). In countries where 1080 is still legally used, there continues to be a focus on improving the targeting and the precision of pest control. This focus has been a prerequisite for the EPA when deciding that 1080 use should continue to be permitted in NZ.

Before further reviewing new information material previously reported in 2011 (Eason et al. 2011), key physicochemical features of 1080 are briefly summarised. The structural formula for 1080 is FCH2COONa (empirical formula C2H2FNaO2). It forms an odourless, white, non-volatile powder that decomposes at about 200º C. Sodium fluoroacetate (1080) is very water-soluble but has low solubility in organic solvents such as ethanol and oils. Carbon-fluorine compounds are distinguished very clearly from fluorides (Peters 1963). Fluorides present in soil and water in excessive amounts can induce fluorotic teeth and other disorders in cattle (Peters 1963). The chemistry of carbon-fluorine compounds, including 1080, really started with a researcher in Belgium in 1896 who was interested in the synthesis of these compounds (Swarts 1896). Later their toxicity became apparent, but no one suspected that fluoroacetate had been in existence in nature before Swarts' synthesis of 1080 when he was pursuing his interests in F-C chemistry (Peters 1963).

1080 and Natural Toxins

Potent natural chemical structures have evolved in plants and animals over millennia for specific biochemical purposes. While their role in nature is not always fully understood, they remain a platform for developing new drugs and biocides. Compounds used to control animal pests linked or inspired by natural products include anticoagulants, cyanide, strychnine, red squill, and 1080 (Eason 2017). For example, the development of anticoagulants was linked to haemorrhagic disease in livestock after grazing on sweet clover hay (*Melilotus alba* and *Melilotus officinalis*) by moulds such as *Penicillium nigricans* and *Penicillium jensi.* Dicoumarol was formed under these conditions, (Campbell & Link 1941) which inspired the development of warfarin and related compounds. Strychnine is found in the seeds of the tree *Strychnos nux-vomica* and has been used for pest control since the mid-1800s (Schwartze 1922). Red squill, another very old poison, was extracted from bulbs of the Mediterranean plant *Urginea maritima* and used as a rodenticide. Cyanide has been used for several decades for killing possums (Rammell & Fleming 1978) and is also found in cyanogenic (cyanide containing) plants (Hayes 1994). Cyanogenic compounds in plants are considered a chemical plant defence to deter browsing animals (Eason 2017). Fluoroacetate also appears to be one of the many secondary plant compounds that have evolved at high concentrations as a defence mechanism against browsing animals (King et al. 1981; Lee et al. 2014; Leong et al. 2017; Pessoa et al. 2018).

Fluorinated organic compounds are rare in nature, and up to 1940, no one suspected that fluoroacetate existed in plants even though it had been synthesized in the laboratory (Swarts 1896). In the typical sequence of events, compounds derived from natural sources inspire the development and synthesis of new drugs and biocides (Eason 2017). In the case of fluoroacetate, it was synthesized by an academic chemist nearly 50 years before its toxic properties were understood, and its role in protecting plants from browsing herbivores was elucidated (Marais 1944; Lee et al. 2014). As pointed out in earlier work by Eason et al.(2011), the caterpillar moth (*Sindrus albimaculatus*), which feeds on *Dichapetalum cymosum*, is unique in that it can accumulate fluoroacetate (probably in vacuoles) and uses fluoroacetate as a defence against predation (Meyer & O’Hagan 1992).

As noted in numerous reviews and research papers, manufactured 1080 for toxic baits is chemically and toxicologically identical to the fluoroacetate found in poisonous plants. The mechanism of toxicity for naturally occurring fluoroacetate and 1080 in a bait is the same. Both forms are equally poisonous (de Moraes-Moreau et al. 1995), and fluoroacetate containing plants have been recognised as hazardous to livestock. Research and review papers on the plants worldwide that contain fluoroacetate and cause sudden death in livestock span 60 years (Steyn 1934; Marais 1944; Quin & Clark 1947; Oelrichs & McEwan 1961; Whitten & Murray 1963; Aplin 1971; Meyer 1994; de Moraes-Moreau et al. 1995; Twigg et al. 1999; Lee et al. 2014), and include recent publications (Lee et al. 2014; Leong et al. 2017; Pessoa et al. 2018). The research papers and reviews focus on the toxic plants found in the southern continents of Africa, Australia, and South America, which belong to the *Fabaceae, Rubiaceae, Bignoniaceae, Malpighiaceae*, and *Dichapetalaceae* families (Lee et al. 2014). They have negatively affected livestock production in these regions throughout recorded history (Quin & Clark 1947; Whitten & Murray 1963; Aplin 1971; Meyer 1994; de Moraes-Moreau et al. 1995; Deakin et al. 2013; Lee et al. 2014; Leong et al. 2017). For example, early settlers of Western Australia experienced heavy livestock losses due to animal consumption of *Gastrolobium spp*., which resulted in the colloquial term for the plants as *poison peas*. In Brazil, plants that cause sudden death (*Palicourea, Arrabidaea*, and *Amorimia* spp.) are responsible for half of all cattle deaths attributed to poisonous plants, which amount to hundreds of thousands annually (Pessoa et al. 2018).

In South Africa, *Dichapetalum cymosum* is the third most important poisonous plant and causes livestock death losses, particularly during spring and drought episodes (Lee et al. 2014). Fluoroacetate occurs naturally in some 40 plant species in Australia (Twigg 1994; Twigg et al. 1996a, b; Twigg et al. 1999). Early settlers in Western Australia were misled about the safety of these plants for their livestock because they observed native animals grazing *Gastrolobium spp*. with impunity (Lee et al. 2014).

Concentrations of fluoroacetate can reach very high levels in these plants. For example, concentrations of 8.8 mg/g in young *Palicourea marcgravii* leaves have been reported (O'Hagan et al. 1993; Lee et al. 2014), and 7.2 mg/g fluoroacetate in young *D. Braunii* leaves. Air-dried leaves of *Gastrolobium bilobum* (heart-leaf poison) and *G. parviflorum* (box poison), two Australian plants, can contain up to 2.6 mg/kg (ppm), and seeds of *G. bilobum* can have more than 6.5 mg/kg (Twigg et al. 1999).

These high concentrations of fluoroacetate in many plant species seem excessive when it is recognized that most unadapted mammals are fatally poisoned by <2 mg/kg. However, it was not until the late 1970s that tolerance to fluoroacetate was demonstrated in some species of native mammals in Western Australia. It is believed that these very high concentrations in plants are the result of a co-evolutionary event in which the plants produced fluoroacetate as protection against herbivory at the same time as the herbivores developed a resistance to the poison to use these plants in their diet (Lee et al. 2014). Whilst the genetic basis for differences in tolerance remains elusive (Deakin et al. 2013), it is apparent that the degree to which the population of any species of animal is tolerant depends on their diet and habitat specialization, the size of their home range, and the length of their evolutionary exposure to the toxic vegetation (Lee et al. 2014). For example, the emu (*Dromaius novaehollandiae*) is the oldest seed-eating bird species in Australia and has a very high resistance to fluoroacetate 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 range of 0.2 to 20 mg/kg (Twigg et al. 1988). 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 the evolutionary selection of fluoroacetate tolerance (McIlroy 1981, 1982; Twigg 1994) in the same way that other potent toxins, such as tetrodotoxin, do in predator-prey relationships (Moczydlowski 2013). Paracelsus, in the C15th, 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). In the case of 1080, it is not just the dose that determines its poisonous effect but whether animal, insects or birds have co-evolved with fluoroacetate containing plants or not (Lee et al. 2014).

Most attempts to protect against plant induced fluoroacetate toxicity in livestock have been unsuccessful except for physically preventing access to toxic plants. Genetically modified bacteria capable of degrading fluoroacetate have been researched in Australia to protect ruminants from fluoroacetate toxicity under experimental conditions. Still, concerns over the release of these microbes into the environment have prevented the application of this technology. Bacterium from the rumen of cattle have been isolated, which can degrade fluoroacetate (Leong et al. 2017). Further surveys for the presence of other fluoroacetate degrading rumen bacteria and studies on the genes responsible for degrading the toxin have been suggested as a logical *rumen detoxification* approach for developing a practical strategy to protect livestock from fluoroacetate plant poisoning (Leong et al. 2017). *Amorimia septentrionalis* is one of several plant species containing fluoroacetate, responsible for the sudden death of ruminants in northeast Brazil (Pessoa et al. 2018). Proof of concept for a similar approach has been achieved by Brazilian researchers protecting goats (*Capra aegagrus hircus*) from intoxication by pre-treating with fluoroacetate degrading bacteria before exposure to *A.septentrionalis* in their diet.

Most studies assessing fluoroacetate concentrations in plants have focused on those species that are overtly toxic to mammals. However, as pointed out in earlier work by (Eason et al. 2011), the ability of plants to synthesise fluoroacetate may be more widespread than generally supposed since fluoroacetate occurs at extremely low concentrations in some Finnish plants (Vartiainen & Kauranen 1980), in tea leaves (Vartiainen & Gynther 1984), and guar gum (Cyamopsis tetragonolobus) (Vartiainen & Gynther 1984; Twigg et al. 1996b). Also, some plants, when exposed to fluoride ions, can biosynthesise fluoroacetate, albeit at very low levels (Cheng et al. 1968). Fluorocitrate, the toxic metabolite of fluoroacetate, has also been detected in tea leaves (Peters et al. 1972). Fluoroacetate biosynthesis can occur in some bacteria, notably *Streptomyces cattleya* (O'Hagan & Harper 1999). NZ research has shown fluoroacetate to be present at extremely low concentrations in native NZ plants such as puha (*Sonchus spp.*), both naturally and by uptake when exposed to 1080 baits in the environment (Ogilvie et al. 2006) but is not considered hazardous due to the negligible 1080 concentrations present (Ogilvie et al. 2010b). Nevertheless, again following the principles of toxicology highlighted by Paracelsus (Borzelleca 2000) and through this review, advocates for 1080 use should not underplay the risks of 1080 used in pest control operations versus the extremely small amount in tea leaves or trace amounts in other environmental samples.

Mode of Action and Toxicology

Over the last decade, there have been many review publications, which include details on the mode of action and toxicology of 1080 and other poisons concerning their use in wildlife management (McLeod & Saunders 2013; Eason et al. 2017; Fairweather & Broome 2018; Chand & Cridge 2020; Warburton et al. In press). In the case of 1080, toxicology research and review papers have provided other strategies for mitigating poisoning in livestock (Pessoa et al. 2013; Leong et al. 2017; Pessoa et al. 2018), and toxicology research has been linked to poisoning incidents or a resurgence of interests in the development of antidotes (McCranor et al. 2019; DeLey Cox et al. 2020; Liu et al. 2020). This interest in the development of antidotes by the US Army Medical Research Institute of Chemical Defence is driven by 1080 being identified as a potential chemical weapon that assassins or terrorists may use (CIA 2004; Holstege et al. 2007; Hume 2015; Cooney et al. 2016; DeLey Cox et al. 2020).

Despite some new insights and advances with regards to protecting livestock and an increased understanding of the progression of 1080 toxicity (Leong et al. 2017; Pessoa et al. 2018; McCranor et al. 2019; DeLey Cox et al. 2020; Liu et al. 2020), most of these publications essentially reproduced what has been reported earlier (see Table 1). This is the case regarding the mode of action of 1080, where the most insightful research by Peters (1963) was completed approximately 60 years ago. Similarly, extensive acute toxicity studies defining LD 50's in target and hundreds of non-target species were undertaken mainly between 1940 - 2000, with no new publications defining LD 50's in the last two decades. LD 50 data exists for many laboratory and wildlife species, including native species in Australia and NZ (Atzert 1971; McIlroy 1981, 1982; Eisler 1995; Fairweather & Broome 2018). This data obviates the need for further acute toxicity testing of 1080. Additionally, LD 50 tests have, for some time, been considered to be unethical and to be avoided unless absolutely necessary (IRAC 1993), and future risk-assessment extrapolations should be possible based on existing data versus further testing of this type. As indicated above, the relatively small number of recent toxicology publications do not involve acute toxicity testing but instead report on incidents of poisoning (Giannitti et al. 2013; Brower et al. 2017; Liu et al. 2020), or animal research to further understanding of 1080 toxicity to mitigate poisoning in livestock or develop treatments and antidotes (Pessoa et al. 2018; McCranor et al. 2019; DeLey Cox et al. 2020). The review by Liu et al. (2020) is unusual in that it reports on 68 human patients with characteristics of fluoroacetate poisoning from the Habin Medical University in China that were poisoned (over a two-year period) and correlated plasma 1080 concentrations and haematological and biochemical changes in those who survived with those that did not, as a basis for improved prognosis and treatment. Patients with fluoroacetate intoxication were treated with the following therapies: gastric lavage, electrolyte correction with Na, K, Cl, and Ca and acetamide. No indication of how so many individuals were poisoned is provided in the publication, although the authors note that the illegal use of 1080 occurs in poorer countries.

Mode of Action

Eason et al. (2011) summarised research and review papers describing the mode of action, acute toxicity, toxicokinetic welfare, and sublethal effects of 1080. For completeness, brief details of these aspects' of 1080 toxicology are provided below, supplemented by new information derived from a small number of recent publications.

The tricarboxylic acid cycle (TCA) is central to cellular energy production, and 1080 disrupts the TCA cycle. Following ingestion, 1080 is distributed through the body. At a cellular level, 1080 is converted within the mitochondria to fluorocitrate (Peters 1963; Peters et al. 1972; Buffa et al. 1973). Fluorocitrate competitively inhibits the TCA enzyme, aconitase hydratase (Morrison & Peters 1954; Buffa et al. 1973), which prevents the conversion of citrate to aconitate (Fanshier et al. 1964). It also inhibits citrate transport into and out of mitochondria (Kirsten et al. 1978; Kun 1982). The inhibition of this metabolic pathway results in the accumulation of citrate in the tissues and blood. At high concentrations, this accumulation causes various disturbances, including acidosis, citrate binds serum calcium, resulting in hypocalcemia and ultimately heart failure (Roy et al. 1980; Omara & Sisodia 1990; Parton 2001; Goh et al. 2005), when sufficiently high doses of fluoroacetate are ingested (Peters 1957; Buffa et al. 1973). Central nervous system effects also occur in many species (Buffa et al. 1973; Kirsten et al. 1978; Kun 1982). Death may result from: a) gradual cardiac failure or ventricular fibrillation; or b) progressive depression of the central nervous system (CNS) with either cardiac or respiratory failure as the terminal event; or c) respiratory arrest following severe convulsions (Atzert 1971; Chi et al. 1996). Despite a common mechanism of poisoning, the symptoms of 1080 toxicity show much species variation (Leong et al. 2017). Death in herbivores results from cardiac disorders, with little or no CNS signs, and in carnivores resulting from CNS disorders. Death in omnivores tends to result from both cardiac and CNS disorders (Chenoweth 1949). Species differences in elevation of citrate concentrations in different organs and tissues may, in part, explain species variation in response to 1080 (Bowsakowski & Levin 1986).

Recent studies in rats report impaired organ function, consistent with previous publications, with increased concentrations of aspartate transaminase and alanine aminotransferase in blood reflecting impaired liver function, while elevated blood urea nitrogen concentrations are associated with renal damage and cardiac dysfunction (DeLey Cox et al. 2020). As highly metabolically active cells, hepatocytes may be especially susceptible to 1080-induced toxicity. Cardiomyocytes may also be particularly sensitive to mitochondrial dysfunction as cardiac cells have a high number of mitochondria to fulfil the energy demands of the heart muscle (DeLey Cox et al. 2020). More sophisticated measurement of the effects of 1080 on cardiopulmonary function has utilised whole-body plethymography and telemeterised rats, allowing for real-time measurement of respiratory and cardiac function (McCranor et al. 2019). Approaches such as these may assist in the future development of countermeasures to poisoning (McCranor et al. 2019). Conventional diagnosis is still generally based on exposure, clinical signs, necropsy findings, chemical analyses of vomitus, stomach or rumen contents, or analyses of plasma samples.

Antidotes and Treatment

Several research groups have previously focused on antidotes or treatments (Wickstrom et al. 1999; Norris et al. 2000; Cook et al. 2001; Robinson et al. 2002; Goh et al. 2005; Collicchio-Zuanaze et al. 2006; Goncharov et al. 2006). For example, glycerol monoacetate and related compounds have been found to double the survival in cats *(Felis catus)* lethally dosed with 1080 (Collicchio-Zuanaze et al. 2006). 1080 is thought to induce seizures through alterations to neurotransmitter concentrations within the brain (Wickstrom et al. 1998). The administration of neurotransmitter modulating agents (e.g., glutamate inhibitors, GABA and serotonergic antagonists) reduced the toxic effects of 1080 (Cook et al. 2001; Goh et al. 2005).

Calcium replacement may also have a role in offsetting fluoroacetate induced hypocalcemia (Robinson et al. 2002; Collicchio-Zuanaze et al. 2006). In more recent research by DeLey Cox et al. (2020), a combined treatment of methylene blue, an antioxidant, and monosodium glutamate, a precursor of the citric acid cycle substrate alpha-ketoglutarate, was explored as an effective countermeasure to 1080 poisoning. While these treatments resolved some signs of intoxication, ultimately methylene blue and monosodium glutamate could not significantly reduce lethality in this study for laboratory rats.

Despite these earlier and recent endeavours, no effective new antidote has been produced; hence ethanol, administered immediately to reduce fluorocitrate synthesis, is likely to remain an accepted antidote for 1080 poisoning, as it has for the last six or more decades (Goncharov et al. 2006). As mentioned earlier, Liu et al. (2020) treated patients with gastric lavage; electrolyte correction with Na, K, Cl, and Ca and acetamide. Veterinary treatment of poisoned dogs (*Canis lupis familiaris*) relies on symptomatic and supportive care (Norris et al. 2000; Goh et al. 2005; Parton et al. 2018). For example, poisoned dogs are heavily sedated to reduce the possibility of tremors, and fluid levels are maintained to offset electrolyte imbalances (Parton 2001; Goh et al. 2005). Pursuing a completely different approach, as described in a previous section, pre-treating and protecting livestock with fluoroacetate degrading bacteria before exposure to fluoroacetate in plant material has been shown to have a protective effect in sheep (*Ovis aries*) and goats (Leong et al. 2017; Pessoa et al. 2018); however, this proactive approach is intended for areas of the world where grazing livestock eat poisonous plants and is not an antidote. In conclusion to this section, whilst the mode of action and toxicology of 1080 is well understood, there is still no effective antidote, and further research is warranted, which could involve combining some of the most promising treatments from earlier studies, coupled with a better understanding of the link between plasma concentrations and toxicity (Liu et al. 2020) to improve prognosis and targeted treatment or antidote development. This research could be coupled with real-time measurement techniques to understand better the effects of experimental treatments on the progression of 1080 effects (McCranor et al. 2019).

Acute Toxicity

As noted above, LD 50 data exists for a vast number of laboratory and wildlife species, and this includes birds, mammals, and reptiles cited in numerous earlier and recent review publications (Atzert 1971; Harrison 1978b; Rammell & Fleming 1978; McIlroy 1981, 1982; Eisler 1995; McLeod & Saunders 2013; Fairweather & Broome 2018). Unlike most other vertebrate pesticides, 1080 also has insecticidal properties (David & Gardiner 1950; Negherbon 1959; Notman 1989; Booth & Wickstrom 1999). In pest species, the LD 50 of sodium fluoroacetate is usually 1 mg/kg or less (Fairweather & Broome 2018). In humans, LD 50 doses have been estimated as 2-10 mg/kg (Nishii et al. 2012). Whilst fluoroacetate is a broad-spectrum toxin, there are some marked differences in susceptibility, with most carnivores being highly sensitive to poisoning and dogs are extremely susceptible, making them vulnerable to accidental poisoning or malicious poisoning (McLeod & Saunders 2013; Brower et al. 2017; Fairweather & Broome 2018). Most deaths in mammals generally occur 5–48 hours after ingestion of a lethal dose (McLeod & Saunders 2013). It appears that the acute toxicity of 1080 is increased at low temperatures (Veltman & Pinder 2001), which is important given the fact that control programmes are mostly conducted in months with the coldest average temperatures (Veltman & Pinder 2001). Research in Australia has indicated that resistance can develop after repeated use (Twigg et al. 2002).

Metabolism and Exposure Risk.

There have been only three new studies on the absorption, metabolism and excretion of 1080 reported in the last decade. One on the uptake and elimination of 1080 in rainbow trout (*Oncorhynchus mykiss*) (Champeau et al. 2014), and a second study on the pharmacokinetics of radio-labelled fluoroacetate in rhesus monkeys (*Macaca mulatta*) (Nishii et al. 2012). In trout dosed with a very high sub-lethal dose of 1080 (~6.4 mg/kg), the maximum concentrations measured in the tissue (up to 4.7 mg/kg) were recorded 24 hours and 48 hours after ingestion. The concentration of 1080 in the tissue decreased to approx. 2 mg/ kg after 48 hours (Champeau et al. 2014). MPI (2016) concluded that based on an exposure model, there was a small food safety risk to trout consumers, which can be avoided if anglers avoid waterways in areas where 1080 baits have been applied in the last seven days. In this study the trout doses used were many times those used in persistence studies for mammals, partly because of the tolerance of fish to 1080 and in part to mimic a worst-case scenario. When short- fined eels (*Anguilla* australis) were exposed to similar high doses, the residues could still be detected eight days later (Lyver et al. 2005), and sub-lethally poisoned koura (*Paranephrops* spp.) had residues of 1080 present for eight days, despite significant decreases between four and eight days (Suren & Bonnett 2006).

The metabolism study in rhesus monkeys, with radio-labelled fluoroacetate, had quite a different focus from most animal studies with 1080, and was part of a series of primate trials, evaluating the potential of radio-labelled fluoroacetate for use with positron emission tomography for improved diagnosis and staging of tumours in humans. The clearance of fluoroacetate from the blood showed bi-exponential kinetics with half-lives of four and 250 minutes after intravenous administration, and extensive metabolism occurred within three hours (Nishii et al. 2012).

In the recent publication on 1080 poisoning incidents in China, plasma fluoroacetate concentrations versus time curves are presented for 18 patients poisoned with 1080, showed clearance of 1080 within 2 to 10 days (Liu et al. 2020).

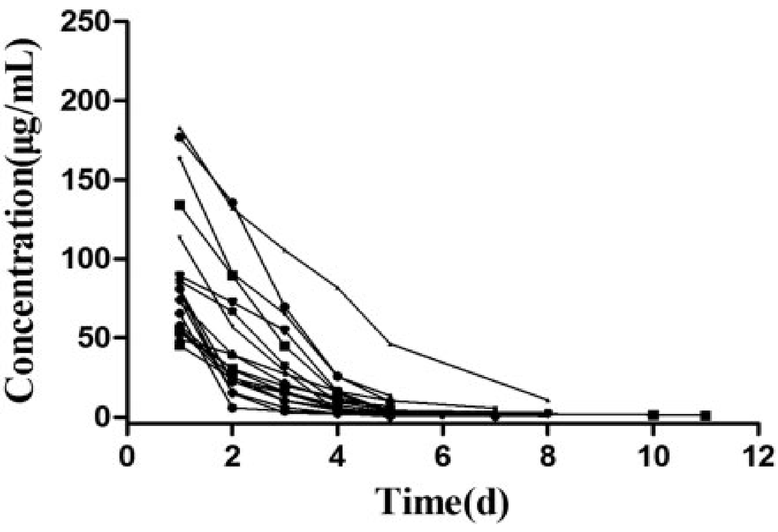

Fig. 1 Plasma fluoroacetate versus –time curves are presented for 18 patents poisoned with 1080 flowing its illegal use in China.

These results, particularly the plasma concentration results presented in Figure 1 (above), are consistent with previous research in the laboratory using larger animals (Gooneratne et al.

1994; Eason et al. 1994). The study in trout demonstrates that very high doses will be excreted more slowly than very small doses, which is not surprising. The very high doses administered to trout would be lethal to mammals and inappropriate for studies evaluating the persistence of 1080 in sub-lethal poisoned animals. As reported in an earlier review, 1080 is absorbed through the gastrointestinal tract or via the lungs if inhaled (Eason et al. 2011). 1080 is rapidly absorbed and distributed through the soft tissues and organs (Hagan et al. 1950; Egeheze & Oehme 1979; Sykes et al. 1987; Nishii et al. 2012). 1080 is excreted as unchanged fluoroacetate and a range of metabolites (Gal et al. 1961; Schaefer & Machleidt 1971).

Administration of ^{14}C-labelled fluoroacetate to rats showed that fluorocitrate, the toxic metabolite of 1080, accounted for only 3% of the radioactivity (Phillips & Langdon 1955; Gal et al. 1961) 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, and cleavage of the C-F bond is an effective detoxification process (Gal et al. 1961). In monkeys (Order *Simiiformes*), following administration of radio-labelled fluoroacetate, rapid initial uptake into major organs was followed by a rapid decline in tissue concentrations over 200 minutes, with 27.6% of the total radioactivity in the urine being radio-labelled fluoride and 72.4% unchanged fluoroacetate (Nishii et al. 2012).

Defluorination of 1080 or its metabolites, including fluorocitrate, has been demonstrated in several animal species and other living organisms (Kirk & Goldman 1970; Smith et al. 1977; Egeheze & Oehme 1979; Soifer & Kostyniak 1983, 1984; Twigg et al. 1986; Tecle & Casida 1989; Nishii et al. 2012). Although fluoride is also extensively excreted, primarily in urine, some deposition occurs in bone (Sykes et al. 1987). However, this was reported to be minimal in the more recent primate study (Nishii et al. 2012).

The earliest reports on rats suggested that some 1080 is retained for 1–4 days (Hagan et al. 1950; Gal et al. 1961). However, in a study using mice (*Mus musculus*), 1080 concentrations in plasma, muscle, and liver decreased by half in less than two hours (Sykes et al. 1987). Regardless of the variations, prolonged persistence of 1080 in animals after sub-lethal exposure seems unlikely, and this has been confirmed in studies for larger animals such as rabbits (*Oryctolagus cuniculus*), goats, possums, sheep, monkey, and recently in humans (Eason et al. 1994; Gooneratne et al. 1994; Nishii et al. 2012; Liu et al. 2020). In animal studies, 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 four days after dosing. The elimination half-life in blood is 11 hours or less in sheep, goat (5.5 hours), rabbit (1.1 hours), mouse (2.0 hours) and possums (9.0 hours) (Eason et al. 1994b). These results are consistent with the recent study in monkeys (Nishii et al. 2012) and the data derived in humans following a spate of poisoning in China (Liu et al. 2020). There is a marked contrast with the pharmacokinetics of commonly used anticoagulant rodenticides, such as brodifacoum, which preferentially bind to liver cells (Bachmann & Sullivan 1983) and has an extremely long elimination half-life in the liver (Eason et al. 2006; Crowell et al. 2013a; Horak et al. 2018), which continue to raise concerns regarding their bioaccumulation in wildlife (Alabau et al. 2020; Lettoof et al. 2020) and does not apply to 1080.

Minimal research has been conducted on the pharmacokinetics of rodenticides in invertebrates; however, in the case of 1080, information is available. In a laboratory study of tree and cave weta (e.g., Genus *Hemideina* and Subfamily *Rhaphidophoridae*) most of a 1080 dose was eliminated from 6–10 days after exposure, and all weta survived dose levels of 15 mg/kg (Eason et al. 1993). Similar results were obtained for a native ant (*Huberia brouni*) (Booth & Wickstrom 1999). Insects have been monitored in forests for 1080 residues after aerial sowing of toxic baits for possum control, and 1080 persistence in invertebrates appears short-lived hence the risk to insectivorous birds or other predators from this route of exposure is also confined to a short period after sowing baits. However, large invertebrates frequently eat bait (Spurr & Drew 1999) and, since species like weta can contain large amounts of bait, secondary poisoning via this route is possible. The toxicity and persistence of 1080 were assessed for land crab (*Gecarcinus lagostoma*) before eradicating feral cats on Ascension Island to help protect against the predation of resident breeding seabird populations. The authors reported most 1080 residues were eliminated rapidly from crab tissue (Pain et al. 2008), which is consistent with findings in other species.

Eason, (2011) and Crowell et al. (2013b) have classified compounds used for animal pest control into groups based on their persistence in sub-lethally exposed animals to help distinguish between the risks associated with different vertebrate pesticides. Sub-lethal doses of these poisons are likely to be substantially excreted within 24 hours (e.g., cyanide and 1080). For 1080, complete excretion of all residues may take up to 4-7 days, with some exceptions extending a little beyond this window. As noted earlier, like other compounds in this group, 1080 will not readily bioaccumulate. This contrasts markedly with residues resulting from sub-lethal doses of second-generation anticoagulants, which may not ever be completely cleared from the body (e.g., brodifacoum), and therefore bioaccumulate if there is repeated exposure.

If recommended practices are followed in pest control operations, 1080 is unlikely to be present in meat for human consumption and withholding periods have been established for livestock that may have come into contact with 1080. Whilst 1080 is comparatively rapidly eliminated from living animals, the slower breakdown of 1080 in poisoned carcasses means it can persist in for many months until the carcass is broken down and will pose a risk to scavenging dogs (Meenken & Booth 1997; Eason et al. 2012b). In possums that were sub-lethally poisoned, 1080 had a half-life of nine hours, suggesting no significant amount of 1080 would be expected in the tissue of live possums four days after exposure. In contrast, possum carcasses collected from the field were shown to pose a serious risk to dogs even up to 75 days after the poisoning operation (Meenken & Booth 1997). Lower, less hazardous concentrations have been found in deer bone marrow after 213 days (Ross & McCoskery 2012) and may pose some risk to dogs. When other species (e.g., insects or birds) come into contact with 1080 in carcasses, sublethal poisoning is more likely. In these cases, as with sub-lethal poisoning in any non-target animals, any 1080 ingested will be metabolised and excreted, and the trophic transfer will be minimal when compared to more persistent poisons.

Methods of analyses for 1080 in different tissue and environmental matrixes continue to be researched and improved. Several recent papers describe new analytical methods (Xu et al. 2016; Liu et al. 2018; Parry & Willison 2018), with some driven by food safety concerns following an extortion threat in NZ in 2014 and the need for rapid analytical techniques (Cooney et al. 2016).

Welfare

Welfare considerations were very extensively covered in the review by Eason et al. (2017) and hence will only be comparatively briefly outlined below. Animals receiving small sub-lethal doses of 1080 show mild signs of poisoning and then recover (Egeheze & Oehme 1979; Eason et al. 1997). However, animals receiving a lethal dose usually show more severe symptoms of poisoning in addition to non-specific clinical signs such as nausea and vomiting (Driesbach 1983; Leong et al. 2017).

Authors that report 1080 to be a humane poison in species, such as possums, do so in part based on observation of subdued behaviour in herbivores and death from cardiac failure (Batcheler 1978; Morgan 1990), and little or no CNS effects (Leong et al. 2017). In carnivores, CNS disturbances are marked, and poisoned dogs run uncontrollably, retch and vomit and appear distressed and agitated with convulsions and seizures before death from respiratory failure (Egeheze & Oehme 1979; Sherley 2007; Leong et al. 2017). Some authors suggest that, despite appearance to the contrary, 1080 is a humane poison in carnivores and primarily base their conclusions on the animals becoming unconscious in the final stages of 1080 toxicosis (Gregory 1996; Williams 1996). Other publications describe awareness during seizures or periodic lucidity that suggests CNS disruption cannot be assumed and conclude that 1080 should not be considered a humane poison (Cooper et al. 2007; Sherley 2004). People who have ingested 1080 by accident or as suicide attempts report abdominal pain, agitation, and vomiting (Chi et al. 1996; Liu et al. 2020).

Whilst the argument that 1080 induces a humane death in target species has been challenged (Sherley 2007, 2004), it is clear that the symptoms observed in possums (Morgan 1990; Littin et al. 2009) indicate considerably less severe distress than those reported in species such as dogs (Chenoweth & Gilman 1946; Leong et al. 2017) and possum bait formulations are optimized in NZ, containing 0.15% 1080 to induce as swift a death as possible (Henderson & Frampton 1999).

While 1080 is not as humane as cyanide, it would also appear preferable to compounds like brodifacoum for possum control (Littin et al. 2002; Littin et al. 2009). These earlier conclusions have been ratified by a recent systematic review evaluating and ranking the relative welfare impacts of control methods, including poisons (Beausoleil & Mellor 2015). Cyanide was assessed as having the lowest welfare impacts, and the overall impacts of 1080 were assessed at moderate (Beausoleil & Mellor 2015).

Sub-lethal Effects

Known target organs in animals include the heart, lungs, liver, kidney, testes, and foetus. Although 1080 itself is not cumulative (Rammell 1993; Eason et al. 1994; Eason et al. 2017), animal studies demonstrate that cumulative damage to the heart or other organs from repeated exposure to large sub-lethal doses of 1080 can occur (Annison et al. 1960; Whitten & Murray 1963; Schultz et al. 1982; Gooneratne et al. 2008). That single or repeated sub-lethal exposures to fluoroacetate can have toxic effects on the heart has been known for some time (Steyn 1934; Quin & Clark 1947; Hicks 1952). 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 other tissue.

Results of developmental toxicity studies in rats have shown that when female rats were exposed to relatively high doses (0.33 and 0.75 mg/kg) for about 30% of their gestation, mild skeletal effects were detected (Eason et al. 1999). The no observable effects level (NOEL) for developmental effects was 0.1 mg/kg/day based on observations of bent ribs at 0.33 mg/kg/day. The NOEL for rats administered 1080 via oral gavage for 90 days was 0.075 mg/kg/day, and microscopic changes in the testes and heart were seen in males dosed with 1080 at 0.25 mg/kg/day (Eason & Turck 2002).

The cancer-inducing potential of 1080 has been evaluated by in-vitro and in-vivo testing. Results of the Ames assay, the mouse lymphoma assay, and the mouse micronucleus assay (bone marrow assay to detect chromosome anomalies) indicate that 1080 is not mutagenic (Eason et al. 1999). In the mouse micronucleus assay, mice were given oral 1080 doses of 0.75, 1.5, 3.0, 6.0 and 7.5 mg/kg, and no mutagenicity was observed at any dose level.

Whilst 1080 is a male reproductive toxicant with effects on testes of mammals (Mazzanti et al. 1965; Sullivan et al. 1979; Hornshaw et al. 1986; Wolfe 1998; Shinoda et al. 2000; Eason & Turck 2002), and other species (Balcomb et al. 1983; Twigg et al. 1988), these effects on reproduction systems are not related to oestrogenic or anti-androgenic properties (Tremblay et al. 2004; Tremblay et al. 2005). Unlike well-known environmental EDCs like DDT or dioxins, 1080 and fluorocitrate are simple molecules which are water-soluble and do not persist in animals or the environment. In a 90-day toxicology study of 1080 in rats (Eason & Turck 2002), microscopic changes in males dosed with 1080 at 0.25 mg/kg/day included hypospermia in the epididymides, degeneration of the seminiferous tubules of the testes, and cardiomyopathy. The NOEL for rats administered 1080 via oral gavage for 90 days was 0.075 mg/kg/day. The lowest observable effects level (LOEL) dose was 0.25 mg/kg/day. Given that 1080 lacks EDC-like activity, these sub-lethal effects on testes are therefore distinct from those mediated by *classical* endocrine disruptors and are likely to occur through a direct intracellular effect on the mitochondria. No new regulatory toxicology studies of this type have been completed in mammals in the last decade.

The effects described above have mainly been observed in animal studies. Many cases of inadvertent human poisoning or exposure are described in the literature (Hayes & Laws 1991; Liu et al. 2020). In general, these cases are not relevant to the effects of low-level exposure to 1080. In several such cases, symptoms include vomiting, arrhythmia, tachycardia, cardiac dysfunction, convulsions, coma and death, or sometimes poisoning is associated with temporary or more prolonged brain damage in survivors. This information from poisoning cases is essential for reinforcing rigorous safety procedures and less relevant to 1080 risk assessments within the context of its use in NZ for pest control and potential exposure patterns, where the focus is on zero exposure. However, overseas experience (Liu et al. 2020) and continuing research on antidotes would be helpful to counter any cases of accidental poisoning.

In conclusion to this section, the known target organs for sub-lethal effects following 1080 exposure include the heart, lungs, liver, kidney, testes and foetus, and sub-lethal effects have been observed at doses in the range of 0.055 to 0.25 mg/kg (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; Twigg et al. 1988; Chi et al. 1996; Gregg et al. 1998; Eason et al. 1999; Eason & Turck 2002; Leong et al. 2017; McCranor et al. 2019; DeLey Cox et al. 2020). Concern regarding whether these effects are likely in people in NZ can be explored by examining the likelihood of exposure.

(Beasley 1996) pointed out that theoretical routes of human exposure to 1080 in NZ might be from drinking contaminated water, ingestion of toxic baits, consuming food contaminated by contact with the bait, or inhalation of bait dust or contact with 1080 solution. Bait consumption is unlikely, as is the contamination of meat and milk when 1080 is used with care and regulations are adhered to. Furthermore, environmental contamination from dust following aerial possum control is minimal and short-lived (Wright et al. 2002). Not surprising, the perceived most significant source of public exposure is considered to be contamination of surface water in public water supply catchments by aerially sown 1080 baits. In response, 1080 water monitoring programmes continue following numerous pest control operations using aerially sown 1080 baits. There has been no evidence of significant or prolonged 1080 contamination in surface waters (see below). Equally or probably more importantly in a practical sense, the use of 1080 must continue to include safeguards that focus on those individually handling 1080 or 1080 baits to ensure they do not ingest, inhale, or absorb 1080.

Fate in the Environment

There are only four significant NZ papers published in the last decade on the fate of 1080, and two are field trials relating to water conducted by a NIWA research team (Srinivasan et al. 2012; Srinivasan & Suren 2018) and two studies focused on biodegradation in soils (Northcott et al. 2014, Gentle & Cothier 2014). The NIWA studies investigated the fate of 1080 during rain events using modelling and field trials with lysimeters and tracking 1080 in surface and subsurface flows. These publications conclude that the potential for 1080 to contaminate receiving waters, including soil, ground, and surface water under normal operating conditions, is extremely small. This is consistent with decades of earlier research.

The 3rd study by Northcott et al. (2014) focused on 1080 degradation in a laboratory microcosm study incorporating three NZ soil types under different temperature (5, 10 or 20 °C) and soil moisture (35% or 60% water holding capacity) conditions using OECD Guideline 307. A combination of non-labelled and radio-labelled 1080 was added to soil microcosms, with sampling and analysis protocols for soil, soil extracts and evolved CO2 established using liquid scintillation counting and liquid chromatography-mass spectrometry. The major degradation pathway for 1080 was through microbial degradation to the hydroxyl metabolite, hydroxyacetic acid, and microbial mineralization to CO2, constituting the major transformation product. Temperature, rather than soil type or moisture content, was the dominant factor affecting the degradation rate. Soil treatments incubated at 20 °C displayed a more rapid loss of 1080 residues than lower-temperature treatments. The transformation half-life of 1080 in the three soils increased with decreasing temperature, varying from six to eight d at 20 °C, 10 to 21 d at 10 °C and 22 to 43 d at 5 °C. The recent Northcott study provided more robust information confirming aspects of earlier research which is summarised below.

After leaching from baits, 1080 can be metabolised (broken down) by soil micro-organisms such as *Pseudomonas* and *Fusarium* species (Bong et al. 1979; Walker & Bong 1981; King et al. 1994). Under favourable conditions, such as 11–20°C and 8–15% moisture, 1080 may be significantly defluorinated in 1–2 weeks. In less favourable conditions, the breakdown might take several weeks, and in extreme cold and drought, 1080 residues might persist in baits or the soil for several months (King et al. 1994; Weaver 2006). In the last ten years, an additional study has been completed in the field, and it focused on testing soils from South Eastern Australia for the presence of 1080 degrading microorganism (Gentle & Cother 2014). Defluorinating microorganisms were present, adding weight to the concept that defluorinating organisms are ubiquitous in a range of soil types. Enzymes capable of defluorinating fluoroacetate have been isolated from several such micro-organisms. The fluoride-carbon bond is cleaved, and ultimately, enzyme-bound intermediates form non-toxic metabolites such as glycolate ((O'Hagan & Harper 1999).

1080 derived from baits will also be dispersed by water since it is highly water-soluble and mobile (Parfitt et al. 1995). If heavy rainfall follows the use of 1080 baits, dilution to immeasurable concentrations (<0.0001 ppm) may precede biodegradation.

Studies on fate and ecotoxicology have focused on determining the actual concentrations of 1080 in soil and leaf litter and determining whether or not these concentrations would be likely to affect soil organisms. The highest concentrations of 1080 recorded in soil or leaf litter samples after aerial baiting was 0.19 mg/kg. Where other samples have contained 1080 with detectable residues, these were below 0.01 mg/kg (Wright et al. 2002). The toxicity of 1080 to earthworms (suborder *Lumbricina*) has been evaluated in separate laboratory studies. The lowest observable effect concentration (LOEC) of 90 mg/kg was determined based on reduced earthworm cocoon production (O'Halloran et al. 2005), which represents a very high concentration compared to that likely to occur in practice. No mortality was observed in worms exposed to a concentration of 1080 of 865 mg/kg (ppm), and concentrations of 1,000 mg/kg (ppm) in soil did not affect mineralisation of nitrogen by soil micro-organisms (O'Halloran et al. 2005). As reported in Eason et al. (2010), NZ research in plants has focused on determining whether 1080 residues might harm plant growth and whether uptake of 1080 in food plants could adversely affect animal or human health. Lettuce seedling emergence was adversely affected at 1080 concentrations in the soil of 7 mg/kg, which is significantly greater than the concentrations found in soil after aerial application of bait (O'Halloran et al. 2005). 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, supporting previous findings that plants can degrade 1080 (Preuss & Weinstein 1969; Ward & Huskisson 1969). The concentration achieved in broadleaf (family *Griseliniaceae*) and ryegrass would be most unlikely to cause poisoning (Ogilvie et al. 1998).

Research has been undertaken to determine if plants used by Māori for food and medicine would uptake 1080. Cereal baits containing 0.15% 1080 were placed at the base of naturally growing individual plants of two species, pikopiko (*Asplenium bulbiferum*) and karamuramu

(*Coprosma robusta*). Plants were sampled at various times up to 56 days and analysed for 1080 content. No 1080 was detected in any of the pikopiko samples, but it was detected in karamuramu at a maximum concentration of 5 ppb after seven days and 2.5 ppb after 14 days. This concentration decreased to zero at 28 days (Ogilvie et al. 2006). A similar study was carried out on two commonly eaten plant species, puha (*Sonchus asper*) and watercress (*Nasturtium microphyllum*), using methods comparable to Ogilvie et al. (2006). Samples of plant tissue were taken at various times up to 38 days for puha and up to 17 days for watercress. 1080 was detected at a maximum concentration of 15 ppb in a single puha sample after three days and at a maximum of 63 ppb from a single watercress sample on day eight. By day 38, all 1080 concentrations were below the method detection level for puha, and 1080 was not detected in watercress after day eight (Ogilvie et al. 2006). No further research has been undertaken in this field in the last decade.

Laboratory studies have shown that 1080 is biodegraded by aquatic plants and micro-organisms (Parfitt et al. 1995; Ogilvie et al. 1996; Ogilvie et al. 1998; Booth & Wickstrom 1999). Some of these studies' of 1080 breakdown in water and aquatic plants (Ogilvie et al. 1996; Booth & Wickstrom 1999) deliberately used solutions containing much higher concentrations of 1080 (0.12 to 5 ppm) than those that have been detected in streams during field monitoring (0.1 to 9 ppb), to simulate worst-case scenarios.

Water monitoring of streams and waterways after aerial application of 1080 baits has been undertaken since the early 1990s (Eason et al. 1992; Eason et al. 1993). It has continued to provide community reassurance and evolved into routine practice. The results of the initial research and subsequent monitoring demonstrate that there has been no evidence of 1080 presence in reticulated water and no evidence of significant or prolonged 1080 contamination in surface waters (Eason et al. 1992; Eason et al. 1993; Hamilton & Eason 1994; Meenken & Eason 1995; Parfitt et al. 1995; Booth et al. 1997; Eason et al. 1999; Eason & Wright 2001; Wright et al. 2002; Eason & Temple 2008; Eason et al. 2011). Between 1990 and the present time, several thousand water samples have been taken following pest control operations. Less than 5% have contained detectable 1080 residues, and most of these had 1080 concentrations of less than 1 µg/L (ppb). When 1080 was found in samples in monitoring programmes, it was at very low concentrations, typically in small streams in remote locations.

Often baits were seen near where samples were taken. The contamination was transient and not picked up in repeat samples. Suren's (2006) recommendation was that water samples should preferably be taken within 4-8 hours after streams are potentially contaminated with bait, suggesting that monitoring at subsequent time points after 1080 operations is likely to be of limited value. These findings are consistent with the research findings of Srinivasan et al. (2012) and Srinivasan & Suren (2018), who concluded that the potential for 1080 to contaminate receiving waters, including soil, ground and surface water, is extremely small. Suren's (2006) recommendations are relevant to sampling in streams where baits have been present. It would be sensible to extend these recommendations when sampling closer to reticulated supplies.

Eason et al. (2011) summarized research in this field as follows: there are two means by which any 1080 present in water will be reduced to undetectable and toxicologically insignificant amounts being: i) dilution; and ii) biodegradation. Even though substantial biodegradation can occur over the first 24 hours of 1080 entering the water, the effect of dilution will be immediate. Water monitoring since 1990, and research, has shown that significant water contamination is unlikely when safety procedures are followed. In the amounts used either in the ground or aerial application, exposure of individuals living near possum control areas is most unlikely to occur. If 1080 monitoring of small streams is to be undertaken, then water samples should be taken within 4-8 hours after the streams are potentially contaminated if the purpose is to detect transient contamination. However, when testing public water supply sources, water analyses need to demonstrate the absence of 1080; hence sampling within and at 24 hours will be necessary.

In terms of effects on aquatic organisms, the concentrations described above in *real-world* operation settings are consistently below those that impact aquatic organisms. This is most clearly demonstrated by assessing aquatic toxicology data, which has been previously summarized by Eason et al. (2017). In NZ, fingerling trout (species unspecified) 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).

In 1993, three aquatic toxicity tests were completed in the USA. Based on the results of this study and criteria established by the US EPA, 1080 would be classified as practically non-toxic to bluegill sunfish (*Lepomis macrochirus*). The second test on rainbow trout used the same test conditions as the bluegill sunfish studies. The No Observed Effect Concentration (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 freshwater invertebrate *Daphnia magna*. The EC 50 is defined as the concentration in water that immobilises 50% of the exposed daphnids. 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 *D. magna* by US EPA classification standards (Fagerstone et al. 1994). Since the concentrations of 1080 described above are many times higher than residue concentrations associated with 1080 use (<0.001 mg/L), adverse effects on aquatic animals are unlikely. 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.

In their field research of 1080 residue analyses in waterways, Suren (2006) not only studied the responses of an invertebrate community to 1080 contamination but also monitored longfin eels (*Anguilla dieffenbachiii*), koaro (*Galaxias brevipinnis*) and upland bullies (*Gobiomorphus breviceps*) after deliberately spiking small streams. Despite large numbers of toxic baits being placed in the study streams (maximum of 80 baits in the stream with greatest water discharge), 1080 was detected for less than 12 hours, and only at very low concentrations (0.2 µg/L). No effects were detected on any of the invertebrate species, including caddisflies (*Helicopsyche* spp., *Pycnocentrodes* spp., *Pycnocentria* spp.), orthoclad midges (family *Orthocladiinae*) and mayflies (*Deleatidium* spp.), or the three caged fish species from the 1080 concentrations detected here. This finding is consistent with the concentrations present being below those, which could have toxic effects in these species. Early *in-vitro* studies in cell lines from aquatic organism linking doses and effects reached similar conclusions (Zurita et al. 2007). Further work in eels (*Anguilla* spp.) and freshwater crayfish (*Paranephrops planifrons*.), where the animals were fed 1080 baits under experimental conditions designed to mimic real-site situations, also showed no effects (Lyver et al. 2005; Suren & Bonnett 2006).

Non-target Responses

Controlling pests using traps, hunting and poisons, including 1080 baits, is reported to have enhanced and restored ecosystems, and protected endangered native species on offshore islands, on mainland NZ, and on islands globally (Byrom et al. 2016; Binny et al. 2020). However, any control tool will have unwanted side effects, and careful monitoring is essential to ensure that non-target effects are minimised (Warburton et al. In press). The risk to non-target species following aerial application of 1080 baits has been a continued cause for special concern (Hansford 2009, 2016) since their early use in the 1950s and 1960s (Batcheler et al. 1967; Rammell & Fleming 1978) through to the present day. Non-target responses have now been studied during the last 40 to 50 years in NZ (Harrison 1978b; Spurr 1994; Eason et al. 1999; Innes & Barker 1999; Powlesland et al. 1999; Byrom et al. 2016; Binny et al. 2020) and more recently in Australia (Fenner et al. 2009; Hughes et al. 2011; Buckmaster et al. 2014; Gentle et al. 2014; Mallick et al. 2016; Heiniger et al. 2018). Previous research has focused on whether the use of 1080 causes, or does not cause, a short-term population decline in native species at sites where it is used to reduce or eliminate predator populations (Fairweather & Broome 2018; Dilks et al. 2020). Over the last decade, research has increasingly focused on deterring *high-risk* native bird species (i.e., kea *Nestor notabilis*) from baits and secondly monitoring (Veltman et al. 2014) longer-term benefits for bird populations (Binny et al. 2020), following the sustained removal of predators (Nugent et al. 2010; Robertson et al. 2010; Veltman & Westbrooke 2011; O'Donnell & Hoare 2012; Greene et al. 2013; Robertson et al. 2016). This research has also been complemented by refinements in baiting application strategies (Nugent & Morriss 2013).

Effects on Birds

Non-target bird deaths have been reported during pest control operations using 1080 almost from when they were first undertaken in NZ; however, the first formal monitoring of bird deaths did not occur until 1976-77 (Harrison 1978a). Early non-target research focused on minimizing the side effects of early baiting strategies to what ecologists, but not necessarily the wider community, deemed acceptable collateral effects (Eason et al. 2011).

During these early years of 1080 baiting, it was discovered that birds from a range of species were dying where undyed, raspberry-lured carrot bait was used (Harrison 1978b) and later apple baits were shown to be attractive to birds (Ross & Henderson 2003). In the 1990s, bait sowing application rates were reduced and there was increased use of the cereal-based baits, which fragmented less than carrot, incorporating green dye and cinnamon lure (Hickling 1997). As a direct result, pest species were still successfully targeted, and fewer bird species have been reported dead since these historical changes were made (Spurr 1994; Westbrooke & Powlesland 2005; Schadewinkel et al. 2014). As evidence of this, bird carcass searches following 15 aerial operations (2003-14) showed a minor risk to, small-sized, exotic bird species (particularly blackbirds) and lower risk for native bird species (Morriss et al. 2016). New bird monitoring techniques using automated sound recording devices (Bomans et al. 2021) have provided additional rigour. They have indicated no significant change in bird call frequency for nine, small-moderate sized, bird species recorded before-and-after 1080 aerial control (Cook 2017). Whilst this is reassuring, there does remain considerable concern regarding the vulnerability of larger-sized native birds, particularly kea (see the kea section below) (Kemp et al. 2019).

Other research has elucidated the *temporal* effects of single *one-off* 1080 possum-control operations, for three years post-control, at study sites on both the West and East Coasts of the South Island. This study indicated no negative impacts for 19 common native bird species with significant increases for tomtit (*Petroica macrocephala*), silvereye (*Zosterops lateralis*), and grey warbler (*Gerygone igata*) at 1080 control sites. At the non-treatment sites, higher possum densities were correlated with subsequence decreases in bird counts over time (van Vianen et al. 2018). Temporal benefits were also observed for mohua (*Mohoua ochrocephala*) populations following 1080 control in the Catlins, South Island (Katzenberger & Ross 2017). Research evaluating plant recovery indicated that lower pest numbers, following sustained 1080 use, correlates with more native pollinators and higher pollination rates for rare plant species such as *Fuchsia excorticata* (Iles & Kelly 2014).

Whilst the above research reports positive outcomes for many native birds, there has always been a major concern for the more highly *at-risk* bird species, as very low population numbers make any adult mortality significant. Given low population numbers, most studies focused on the survival of individually marked birds. For example, all 73 kaka (*Nestor meridionalis*), 19 blue duck (*Hymenolamus malacorhynchus*) and 15 kereru (*Hemiphaga novaeseelandiae*) monitored through aerial poisoning operations using radio transmitters survived unaffected (Broome et al. 2009). Other researchers observed 37 adult falcons (*Falco novaeseelandiae*) following aerial 1080 control with no observed adult mortality following either carrot or cereal 1080 aerial baiting (Horikoshi et al. 2018). Fifty-eight weka (*Gallirallus australis*) were monitored over two aerial operations, with only one death attributed to 1080 (Tinnemans et al. 2018), and three of 36 radio-tagged South Island fernbirds (*Bowdleria punctata punctata*) killed due to 1080 poisoning (van Klink et al. 2013). For other species, survival of individually marked bats was high at 99.1% following aerial 1080 control (Edmonds et al. 2017) and 1080 control improved prospects for endangered lizards (Reardon et al. 2012).

Perhaps the most significant research shift of the past decade has been meta-analysis using multi-year datasets. These key studies and results are detailed in Table 2:

Table 2: Key findings from multi-year bird studies.

Author	Bird Species	Number years	Key Findings
(Robertson et al. 2019)	North Island brown kiwi (NIBK)	22	100% survival for 142 monitored birds with improved prospects for kiwi (*Apteryx mantelli*) chick survival and NZ fantail (*Rhipidura fuliginosa*) nesting success in the first two breeding seasons following aerial application.
(Robertson et al. 2016).	NIBK	18	In the 1080 area - 62% chick survival compared with 20% in a trapped-only area nearby.
(Veltman & Westbrooke 2011)	Multiple	23	This analysis reported very low risk for kiwi, kaka, whio (*Hymenolaimus malacorhynchos*) and kokako (*Callaeas wilsoni*) with more risk for smaller birds when carrot baits were used. High kea mortality was observed in one operation at Franz Joseph.
(Fea et al. 2020)	Multiple	41	Larger endemic species such as kaka and NZ pigeon (*Hemiphaga novaeseelandiae*) respond positively to predator management, and deeply endemic birds, especially

			cavity nesters, are most at risk of further decline without predator control.
(Kemp et al. 2019)	Kea	9	24 out of 222 individually marked kea in 19 aerial 1080 operations either disappeared or were found dead after aerial 1080 control
(Byrom et al. 2016)	Multiple	25	Controlling both ship rats and possums using 1080 increased bird populations.
(Binny et al. 2020)	Multiple	17	Deeply endemic bird species had the strongest population recovery responses to pest control compared with recent native or introduced biota

Kea

While most of the research papers cited above report low bird mortality for vulnerable bird species, the Kemp et al. (2019) meta-analysis of nineteen aerial 1080 operations reported 24 kea deaths from 222 radio-tagged adult kea (~ 10% of their respective populations). This rate is higher than the desired, even with 13 out of 19 aerial operations reporting no mortality. Other research on kea has looked at reproductive success following aerial 1080 control over two nesting seasons (Before-After-Control-Impact design). This research indicated that nesting success for kea was only 12% in the untreated site, whereas nesting success increased to 84% for the site treated with 1080 to reduce predation (Kemp et al. 2018). Despite improved nesting success, the numbers of reported kea deaths is a concern, prompting intense research and management actions to ensure the overall effect on kea populations after 1080 control is positive and kea bait interactions are minimized (see below).

Previous kea research has identified that colour (Weser & Ross 2013; Cowan & Crowell 2017; Brunton-Martin et al. 2021) and a combination of a primary (d-pulegone) with a secondary (anthraquinone) repellent was effective at repelling captive kea from bait (Orr-Walker et al. 2012; Clapperton et al. 2013). Whilst promising, such techniques were not extended to the field due to concerns over bait stability (Crowell et al. 2016b) and potentially reduced consumption by target species (Clapperton et al. 2015; Crowell et al. 2016a). To circumvent target species being deterred by kea repellents, thar (*Hemitragus jemlahicus*) carcasses were placed above the tree line to lure kea to adjacent non-toxic bait containing anthraquinone.

The objective was to train kea to avoid such baits before 1080 control. (Nichols et al. 2021). (Nichols et al. 2020) and further work is now investigating the use of kea-specific bait feeders to train kea at lower altitudes. Whether these measures are effective, or can be applied at scale, remains to be determined. Collecting long-term census data on kea numbers in areas where 1080 has been used and in areas where there has been no predator control will be critical to determine ongoing population trends, like that currently occurring at Kahurangi National Park (DoC 2021b).

Effects on Invertebrates

Research assessing risk for invertebrates were first conducted in the late 1990s. These studies demonstrated no negative effects for weta populations 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 1994), following aerial 1080 control (Sherley et al. 1999; Spurr & Drew 1999). Research in the following decades using artificial refuges and mark-recapture techniques (Aspen et al. 1999; Spurr & Berben 2004) supported this early work, and recent research suggests that cinnamon oil to deter birds could also be repellent for tree weta (*Hemideina thoracica*) (Morgan et al. 2017). Additionally, monitoring of invertebrates in predator-fenced sanctuaries has demonstrated that most invertebrate species do better in the absence of mammal pests (Watts et al. 2011), particularly on predator-free offshore islands (Jones et al. 2016; Watts et al. 2020). This is also the case for mainland sites with sustained predator control (Barker 2016) and even on pastoral land (Glen et al. 2018).

Effects on Deer

Possum baits containing 1080 also kill deer with estimates widely ranging from 0 to >90% mortality (Pinney et al. 2020) but more commonly range from 30% to 60% (Fraser & Sweetapple 2000; Nugent et al. 2001; Nugent & Yockney 2004; Morriss et al. 2020). Previous research also highlighted a greater risk to deer from carrot bait like non-target native birds (Nugent et al. 2001; Nugent & Yockney 2004). Current best practice uses cereal bait with sowing rates of 2 kg/ha routinely applied (Nugent et al. 2012a). However, sowing rates have the potential to go even lower with cluster or strip sowing techniques achieving good kills of possums and rats at aerial sowing rates below 1 kg/ha (Nugent et al. 2012a; Nugent et al. 2012b; Nugent & Morriss 2013), and using ground sowing rates of 0.5 kg/ha (Morgan et al. 2015). As such, the continuing refinement of aerial sowing techniques could further reduce the risk for non-target game and native bird species.

Reducing deer by kill when targeting possums is important for recreational and subsistence hunters. In recognition of this, the first deer repellent (Green Epro Deer Repellent) was registered for use with 1080 bait in 2007. Early research, using the Epro deer repellent, indicated that that repellent reduces poisoning risk for fallow deer (*Dama dama*) (Morriss & Nugent 2008), red deer (*Cervus elaphus*) (Morriss 2007), and more recently has been confirmed for sika deer (*Cervus nippon*) (Morriss & Nugent 2017) and white-tail deer (*Odocoileus virginianus borealis*) (Pinney In press). The inclusion of deer repellent does not increase the risk of poisoning for native birds or invertebrates (Ross 2007; ERL 2008; Nugent et al. 2012a; Morgan et al. 2017), and possum mortality remains high (Morriss 2007). In the past two years, two new suppliers (Orillion and Pest Control Research Ltd) have developed alternative repellent formulations. This competition should help reduce the cost of using deer repellent and make these selective baits more readily available for routine possum control where game animals are a valued resource.

Risks to Domestic Animals

Dogs are extremely susceptible to 1080 (Rammel and Fleming 1978) and must be kept away from toxic baits, possum, and deer carcasses (Ross & McCoskery 2012). Livestock must also be kept well away from baits, and even partially degraded baits should be regarded as hazardous to sheep and cattle. Since 2008, there have been 27 documented farm animal deaths alleged to be from contact with 1080 bait. (Alexander 2019). These examples reinforce the need for extreme vigilance whenever 1080 is sown aerially, including using the most up to date GPS systems for targeting baits and sound fencing in areas adjacent to possum control operations to avoid such incidents.

The Predator Free 2050 Goal and 1080 Use

NZ conservationists have eradicated all introduced mammals (predators and herbivores) from over 100 offshore islands (Towns et al. 2013). Still, in 50 years of pioneering and persistent effort, this has only increased the pest-free island area from 0.5% to just over 10% (Russell et al. 2015). We also see growing numbers of community-led ecosanctuaries; however, the total area of ecosanctuaries on the NZ mainland, where pests are excluded or actively managed, is only 61,749 ha, covering 0.2% of the NZ land area (Innes et al. 2019). Recognition of these challenges (Elliott et al. 2010), was a catalyst for the development of the Department of Conservation (DoC) BfB programme starting in 2014, following recommendations from the Parliamentary Commissioner for the Environment (PCE 2013, 2017). Following on from this, the ambitious government goal of Predator Free 2050 (PF2050) was announced in 2016. Predator Free 2050 seeks to make NZ free of three introduced predators: possums, mustelids (ferrets, stoats, weasels) and rats by 2050. The Government has since shown its support for this goal by investing over $300 million in Predator Free initiatives, which bolsters other funding from local government, philanthropic organisations, and the time and effort invested by community groups (DoC 2021a).

An interim goal of PF2050 was to increase the area where pests are actively managed by one million ha before the end of 2025. To achieve this interim goal, several landscape-scale predator eradication projects have been established across the country (see PF2050 website). Initial attempts at the local elimination of pests involved closely timed, dual application of aerial 1080 combined with multiple non-toxic prefeeds. Dual application of 1080 (using a similar bait type) completely removed all rats but not all possums in four 100-ha study blocks (Nugent et al. 2019). A dual application of 1080 (changing the bait type see: Nugent et al. 2020) combined with multiple prefeeds removed >99% of possums and rats (Nichols et al. 2021) from a 2,240 ha block (ZIP 2017b), and this study also evaluated the use of rivers as reinvasion barriers (Cook et al. 2021). More recently, research teams have discussed adopting island eradication techniques on the NZ mainland using aerial brodifacoum. Island eradication techniques could have higher social acceptance if they are only applied once at a defendable site (Cowan & Warburton 2011; Fisher et al. 2019). In these situations, aerial 1080 is unlikely to be the main pest removal control tool for PF2050 projects; however, the use of aerial 1080 for BfB projects has increased and is discussed below.

Politics and Public Attitudes Towards 1080

The level of aerial 1080 control on conservation land has increased over the past decade. For example, in 2009, DoC completed active predator control over 1.3 million ha, with 174,000 ha being aerial 1080. The Animal health Board (AHB) undertook pest control over 3.4 million ha in the same year, with 400,000 ha being aerial 1080. In 2012/13, DoC invested more money on 1080 research ($2.9m) than it did on aerial 1080 pest operations. In 2019/20, OSPRI (formally the AHB) had reduced the area of its pest control operations to 2.4 million ha, with 130,000 ha being aerial 1080 control (EPA 2019). This reduction in control effort is expected to continue over time with a goal of TB freedom from possums likely to occur by 2040 (R. Curtis OSPRI pers. comm. 2020). In contrast under the BfB programme, DoC applied aerial 1080 over 694,000 ha in 2014/15, 894,000 ha in 2016/17, 531,789 ha in 2017/18 and 1,030,492 ha in 2019/20 (Elliott & Kemp 2016). Effectively, aerial control operations have doubled with control effort directly related to the numbers of rats following beech mast events. Those against 1080 use have certainly noted this increase in aerial operations, and there has been increasing resistance to pest control on public conservation land. Examples of this are a court injunction obtained in 2018 halting the proposed aerial 1080 operation in the Hunua Forest. This injunction was subsequently overturned in 2019, with the Environment Court awarding $40,000 in court costs to DoC and the Auckland Regional Council (Neilson 29 July 2019).

A magazine article in NZ Geographic back in 2009 stated that despite considerable research showing many benefits from using 1080 baits, there were still significant concerns regarding its ongoing use (Hansford 2009). Some of this is fuelled by misinformation, but there are equally many with valid concerns. Over the next decade, both supporters and opponents still see themselves in an ongoing *gallant battle* to protect NZ's *pristine* natural environment (Bidwell & Thompson 2015), and these polarized views create challenges. Hansford (2016) comprehensively addresses the politics and range of views surrounding 1080 in his book "*Protecting Paradise*". In this book, Hansford calls for more social research stating that "*we need to better understand why people chose not to trust science and why they chose instead to invest in mythology"*. Similarly, greater acknowledgement and understanding of the concerns could go some way to reduce the current polarization of views.

An indirect benefit of the PF2050 campaign has been an increase in surveys exploring attitudes towards pest control options, which enables comparative assessment over time. For example, a recent review of research (over the past 26 years) shows that support for aerial 1080 has varied markedly (Kannemeyer 2013). UMR omnibus surveys carried out in 2001 (Green & Rohan 2012), and repeated in 2007, found a rise from 32% to 43% in opposition to the use of aerial 1080. Similarly, in the 2012 survey, 40% of respondents believed aerial 1080 should not be used, approximately 9% more than an earlier 1994 survey (Russell 2014). Both surveys suggest an increase in opposition to 1080; however, Fraser (2006) suggests that much of this variation in public concern relates to the actual phrasings of the questions. For example, in a 2012 survey of Coromandel people, 78% of respondents supported 1080 if used in bait stations compared with 51% if aerially broadcast. Additionally, the same survey revealed 70% support for aerial 1080 if it was only used to control possums, rats, and stoats in "*remote or inaccessible areas*" and was the only cost-effective treatment to protect NZ's native species (Kannemeyer 2013).

Whilst some authors suggest that the acceptability of poisons may be declining, social attitudes to small herbivores such as possums and rabbits, and predators such as mustelids and rodents, remain mostly negative (Farnworth et al. 2014; Russell 2014). In contrast, urban cat management remains a contentious issue (Kikillus et al. 2017). Commonly used pest control methods such as shooting, trapping and poisons are generally preferred by the public over novel or new technologies (Kannemeyer 2017). Rationales for preferring existing methods include uncertainty or perceived risks associated with not knowing the future impacts of new tools. Other arguments driving the 1080 debate, and the development of new technologies, are place attachment (McSweeney 2011), uncertainty, controllability, and equity. Place attachment or a deep attachment to the natural environment is an argument identified by several researchers (Bidwell & Thompson 2015). In general, social attitudes to biological control and genetic approaches were characterised by high levels of uncertainty, unpredictability, and unintended consequences, frequently due to limited knowledge (MacDonald et al. 2021c) or understanding of how the new technology works (Wilkinson & Fitzgerald 2014).

In summary, social attitudes toward pest species remain mostly negative; however, attitudes regarding the use of 1080 remain contentious and polarized. It is difficult to determine whether opposition to 1080 has increased in the past decade, with survey responses dependent on how key questions are phrased. Hunting and trapping remain the most preferred control options; however, species-specific poisons have higher approval rates than multiple-species alternatives. Surveys also indicate that participants have concerns regarding genetic engineering or gene drive approaches (MacDonald et al. 2021b; MacDonald et al. 2020) as replacements for 1080. Many participants stated they are fearful of any new technology they do not entirely understand.

CONCLUSIONS

1080 Database of science

Ten years on from the previous review, our scientific understanding of 1080 continues to improve. There is an enhanced understanding of the toxic nature of 1080, as well as an up-to-date knowledge of global trends in the types of poisons available and their properties. This information is essential to inform debate and assist with the formulation of future wildlife management control strategies. Approval and continued registration of 1080 also requires continuous up-to-date technical and toxicological information (ERMA 2011, Eason et al. 2011), coupled with evidence of long-term ecosystem improvements and annual audits of operations by the EPA. As a result, 1080 continues to be one of the most closely monitored substances in NZ. A report on every aerial operation must be submitted to the EPA as soon as reasonably practicable. These are all documented by the EPA in an annual report (required after the Hazardous Substances New Organisms Act review in 2007). These reports cover public health protection measures, consultation with iwi and hunting groups, the outcome of some operations, and incidents and complaints. As such, these reports are designed to make the use and regulation of 1080 as transparent as possible.

Views on 1080

Over a decade ago, it was speculated whether completing more research on risks and benefits 1080 would reduce public concerns (Hansford 2009). This review indicates that over 260 new publications have been added to improve our understanding of 1080 use in NZ over the past decade. For pest control practitioners, and others involved in pest control, any new research on more targeted 1080 baiting is useful and will reduce non-target risk. Yet despite research showing many wildlife benefits resulting from aerial 1080 control (Forsyth et al. 2018; Binny et al. 2020), it seems that the concerns regarding the use of 1080 have not diminished, and likely no amount of additional research will change the views of those strongly opposed. This is perhaps partly due to social and mainstream media disseminating disparate points of view, but also because technical information detailing the positive or negative effects, for issues like kea and deer by-kill, remain confusing. As such, people find it increasingly more challenging to determine what is scientific opinion (Pike 2014) and what is "*fake news*" (Hansford 2016; Rosling 2018). As a result, court cases challenging pest control activity on conservation land are becoming more commonplace (Littlewood 2020) as different groups seek alternative approaches.

Desire for Change

Most researchers and pest control practitioners are empathic with the desire for change and would like to use non-lethal methods if they were available. However, this will not happen overnight, and it can be anticipated that toxins, including 1080, will continue to play a role in pest control over the next decade. When optimised innovations, such as resetting kill traps (Ross et al. 2020), could steadily reduce the need for 1080 (Eason et al. 2017) in more accessible terrain. Other ground-control options using poison dispensers have the potential to provide more targeted delivery systems (Blackie et al. 2014; Blackie et al. 2016), and could utilise alternative toxins (Eason et al. 2012a; Hix et al. 2012; Shapiro et al. 2016). There is also research looking drones, artificial intelligence, wireless communication (Jones et al. 2015), and biotechnology (Campbell et al. 2015; Russell & Broome 2016; Eason et al. 2017; Morley et al. 2017; Campbell et al. 2019). Whilst promising, many believe no new *game-changers* are on the immediate horizon, and for now, the focus is the sustained control of pests on the NZ mainland, with the aerial 1080 remaining an essential tool (PCE 2017; Warburton et al. In press).

Stock-take

So, in consideration of the above - where do we currently stand with the use of 1080 in NZ? *Silver-bullet* replacement tools, such as immunocontraceptive vaccines (McLeod et al. 2008), for 1080 have been promised for several decades without fruition. Some also remain sceptical of biotechnology (Kannemeyer 2017), such as gene drive, despite the possibility of non-lethal pest control (Gemmell et al. 2013; Campbell et al. 2019). In the interim, there is now a need to advocate for current close-to-market tools that have the highest social acceptance. For example, there is much higher social acceptance for species-specific poisons. As such, there has been significant research on norbormide for rats (Choi et al. 2016; Jay-Smith et al. 2016; Ma et al. 2018), and PAPP for predators (de Tores et al. 2011; Dilks et al. 2011; Blackie et al. 2012; Eason et al. 2014; de Burgh et al. 2021) with potential for aerial deployment (Brown et al. 2012).

For ground-based tools, there remains higher social acceptance of trapping. As such, there is a need for best-practice information for recently developed live-capture traps (ZIP 2017a)) and multi-kill traps (Gillies et al. 2012; Warburton & Gormley 2015; Carter et al. 2016; Murphy et al. 2019). Ground-control approaches are likely to improve with current research investigating social (Garvey et al. 2016), food-based (Waters et al. 2016; ZIP 2020) and audio-lure technologies (Kavermann et al. 2013).

1080 Research

Given that 1080 is likely to remain an essential control tool, there is always the need to reassess and refine best practice use. For example, there were some poor aerial 1080 results in the 2019/20 BfB campaign targeting rodents (DoC 2020). This could be a result of too frequent control (Allsop et al. 2017) or that higher rates of non-toxic prefeeding are necessary for rodents (Nugent et al. 2019). Multi-year studies of pest responses following control also document the competitive release of rodents with faster population recovery than possums (Ruscoe et al. 2011; Griffiths & Barron 2016). Additionally, high mice numbers can be detrimental for some beetle and weta communities (Watts et al. 2020), and 1080 is not always an effective tool when targeting mice (Fisher et al. 2009; Fisher & Airey 2009). As suggested by the PCE in 2017, research should look at methods of improving aerial 1080 efficacy for mice and develop of strategies to avoid rapid rodent recovery following 1080 control (PCE 2017).

SUMMARY

Up-to-date toxicological research and non-target population monitoring are necessary to refine the targeting of 1080 whilst its use continues. Other research needs to consider key social concerns being human health, non-targets, and animal welfare. Additionally, researchers will need to respond to any *unexpected* new questions raised by regulatory agencies such as the EPA. There is a need to further advance close-to-market tools with the highest public acceptance, such as species-specific poisons and trapping. For aerial 1080, advances in precision targeting (i.e., low sowing rates and targeted delivery systems) and the more widespread use of deer repellent could increase support.

More effective and empathic engagement with communities, iwi and hapu, is needed to discuss the goals of invasive species management and find common ground. As such, this engagement needs to be open, honest, highlight risks (MacDonald et al. 2021a) and benefits, and seek consensus with a long-term vision. In most cases, consensus will likely involve an *integrated* approach to pest control (Subroy et al. 2018) using the most socially acceptable tools. Greater acceptance of any pest control tool occurs when its use is discussed within the context of long-term goals for saving endangered species and ecosystem recovery, with communities that treasure the restoration of their landscapes. However, there is a broader context that cannot be ignored in national and global pest control trends. Values are changing, such that no (or minimal) pesticide use (Chamberlain 2016; Messenger-Sikes & Quinn 2020; Dayan et al. 2009) is a theme that is increasingly mainstream (MPI 2021). In this changing environment, strategies that rely on 1080 or other toxins as *one-off treatments* for eradicating pests or disease versus continued application for maintenance control are likely to be more and more important.

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