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Health Risk Assessment and Health Risk Management with Special Reference to Sodium Monofluoroacetate (1080) for Possum Control in New Zealand

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Abstract

The principal use of sodium monofluoroacetate (1080) in New Zealand is to control brushtail possums (*Trichosurus vulpecula*). Aerial application of baits containing 1080 is the most common method used for large-scale control of possums.

The use of 1080 attracts a great deal of controversy, in particular the effects on the environmental, non-target species, and the potential chronic effects in humans associated with environmental exposures. Although the nature of the acute toxicity of 1080 has been known for more than fifty years, little is known of its effects on humans, in particular its chronic effects to environmental exposures.

A benchmark dose (BMD) as an alternative to a no-observed-adverse-effect-level (NOAEL) approach was investigated as a means to improve current health risk assessment values of 1080. Both approaches were investigated for three critical toxicological end points, namely cardiomyopathy, testicular toxicity and teratogenic effects identified from the few available critical studies. The calculated BMDs and lower-bound confidence limits (BMDLs) for the three end points were estimated using the Weibull, probit and quanntal linear models. A benchmark response (BMR) of 10% (extra risk) was chosen and the Akaike's information criterion (AIC) was used in selecting the appropriate model. The BMDL estimates derived were generally slightly higher but comparable to the corresponding NOAEL for those same endpoints. The computed BMD_{10} and $BMDL_{10}$ for cardiomyopathy and testicular effects were 0.21 mg kg^{-1} bw^{-1} and 0.10 mg $kg^{-1}bw^{-1}$, respectively. Tolerable Daily Intakes (TDIs) were derived using the NOAEL approach and the BMD methodology and applying an uncertainty factor of 3000. The resulting TDI using the BMDL were generally consistently slightly higher than those derived using the NOAEL approach. Based on the best fit of modelled dose-response data, a TDI of 0.03 μg $kg^{-1}bw^{-1}day^{-1}$ is proposed for human health risk assessment.

Two sets of Provisional Maximum Acceptable Values (PMAV) were derived using the highest concentration of 4.0 μg L^{-1} 1080 found in water (N=1450), and using the maximum allowable concentration of 2.0 μg L^{-1} of 1080 in water for adults (0.58 μg L^{-}

^{1} and 0.94 μg L^{-1}, respectively) and children (0.23 μg L^{-1} and 0.4 μg L^{-1}, respectively). Parameters used in the derivation of PMAVs were average weight, average quantity of water consumed, and proportion of total intake allocated to drinking water. The derived adult PMAV of 0.60 μg L^{-1} is proposed in revising the PMAV for 1080 in the Drinking Water Standards New Zealand. This value is 6-fold lower than the current PMAV of 3.5 μg L^{-1}. Additional toxicology studies are recommended to meet the definition of a "complete database" and therefore estimating a more defensible TDI, and consequently a PMAV for 1080.

Risk management approaches are consistent with the Ministry of Health's current precautionary approach. A PMAV of 0.60 μgL^{-1} in drinking water is recommended to consider it suitable for human consumption and that continuous monitoring be carried if the level of 1080 exceeds 50% of the proposed PMAV as a requirement for Priority 2 determinands in the Drinking Water Standards. Precautionary approach appears to be warranted and this was supported by information provided by the Public Health Units (PHU) where 1080 was permitted to be dropped onto drinking water catchments. The PHUs exercised precautionary measures by imposing appropriate conditions to suit local circumstances. As 1080 may likely remain an essential tool to contain tuberculosis spread by possums and to reduce possum damage to forests and crops until better methods of control are developed, a number of recommendations were proposed to protect public health.

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List of Abbreviations

1080	sodium monofluoroacetate
ACVM	Agricultural Compounds and Veterinary Medicines Act 1996
ADI	acceptable daily intake
AHB	Animal Health Board
AIC	Akaike Information Criterion
ALARA	As low as reasonably achievable
ATP	Adenosine Triphosphate
ATSDR	Agency for Toxic Substances and Disease Registry
BEI	Biological Exposure Index
BMD	Benchmark Dose
BMDL	Benchmark Dose's lower bound confidence limit
BMR	Benchmark Response
C^{14}	carbon 14
CAAHEAP	Committee on Advances in Assessing Human Exposure to Airborne Pollutants
CAS	Chemical Abstract Service
C-F	carbon-fluorine
CNS	central nervous system
CoA	coenzyme A
DGPS	Digital Global Positioning System
DNA	deoxyribonucleic acid
DoC	Department of Conservation
DWS NZ	Drinking Water Standards New Zealand
EAF	European Aerosol Federation
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ERMA	Environmental Risk Management Authority
F	female
FDA	Food and Drug Administration
EPA	Environmental Protection Agency
FQPA	Food Quality Protection Act
GLP	Good Laboratory Practice

HSE	Health and Safety in Employment Act 1992
HSNO	Hazardous Substances and New Organisms Act 1996
HTn	4-hydroxy-trans-aconitate
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
LD_{50}	lethal dose, 50% kill
LD_{100}	lethal dose, 100% kill
LOAEL	lowest-observed-adverse-effect-level
LOEL	lowest-observed-effect-level
M	male
MAF	Ministry of Agriculture and Fisheries
MAV	maximum acceptable value
MfE	Ministry for the Environment
MLE	maximum likelihood estimate
MOE	Margin of Exposure
MoH	Ministry of Health
MRL	maximum residue limit
NAS	National Academy of Sciences
NF	Natalia Foronda
NIWA	National Institute of Water and Atmospheric Research Ltd.
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NPCA	National Pest Control Agencies
NRC	National Research Council
NZFSA	New Zealand Food Safety Authority
OECD	Organisation for Economic Co-operation and Development
OPP	Office of Pesticides Programs
PCE	Parliamentary Commissioner for the Environment
PHU	Public Health Unit
PMAV	provisional maximum acceptable value
RfC	reference concentration
RfD	reference dose
RMA	Resource Management Act 1991
TCA	tricarboxylic acid cycle

TDI	tolerable daily intake
TAD	tolerable absorbed dose
U_A	UF to take into account interspecies variation
UCL	upper confidence limit
U_D	database UF
UF	uncertainty factor
U_H	UF to take into account intraspecies variation
Us	UF to take into account the use of data from subchronic to chronic data
WCC	Wellington City Council
WHO	World Health Organization

bw	bodyweight
cm^2	centimetre square
g	gram
ha	hectare
kg	kilogram
L	litre
mg	milligram
mm	millimetre
$^{-1}$	per
ppb	parts per billion
ppm	parts per million
sp	species
µg	microgram
w	weight
v	volume
vs	versus
x^2	chi-square
*	multiplied by ("times" as in T * E)

Chapter 1

Introduction

1.1 Background

Sodium monofluoroacetate (commonly known as 1080) is a highly toxic vertebrate pesticide that has been proven to be effective in controlling possums, rabbits and wallabies (Eason 1996). However, despite its effectiveness, over several decades in New Zealand, its use continues to cause controversy to the general public because of its effects in non-target species, especially dogs, the fate of 1080 in water (Thomas 1994), and the uncertainty associated with its potential long-term effects on human health (S. Gilbert pers. comm. 2000).

In other countries, 1080 is also used, but in relatively small quantities compared with New Zealand. In Australia, 1080 is used in controlling the population of introduced European rabbits, foxes, pigs and mice, while it is used for the control of field rodents in Israel by aerial application or by hand. In the United States, most uses of 1080 were cancelled in 1972 because, in part, of deaths of non-target animals (Balcomb *et al.* 1983), including endangered species (Palmateer 1989, 1990). 1080 has a very limited use in the USA since it is only presently registered for use in a collar designed to protect sheep and cattle from coyotes (Morgan and Eason 2004; Eason 2002a). Likewise, 1080 is mainly used in livestock protection collars for predator control (e.g., wolves, coyotes, jackals) in South Africa (ERMA NZ 2006).

New Zealand is the largest user of 1080 in the world (Parliamentary Commissioner for the Environment (PCE) 1994), consuming approximately 80% of the world's production of 1080. To illustrate, a Department of Conservation (DoC) and Animal Health Board (AHB) report (2003) estimated the amount to be 3.2 tonnes of raw product in the period 1 July 2001 to 30 June 2002. The 1080 reassessment document prepared by Environmental Risk Management Authority New Zealand (ERMA NZ) (2006) suggested that DoC and AHB proposed an increase in quantity of 1080 use, i.e., from 1280 to 3000 kg per year and 600 to 1000 kg per year for AHB and DoC, respectively.

Although there is an extensive published database on 1080, some of the toxicological and metabolic data generated between 1950s and the 1970s are out of date and would not meet current standards. Before a new pesticide can be registered in New Zealand extensive toxicological data are required to meet worldwide standards (Seawright 1994). In view of this, DoC and the AHB commissioned Landcare Research Limited to carry out a number of toxicology studies on 1080 to comply with current regulatory requirements for pesticides in New Zealand in 1998-99. Studies carried out were:

- mutagenicity studies
- teratology study in rats
- 90-day feeding trial

The majority of public concerns about possum control operations relate to the possible contamination of drinking water supplies with 1080 resulting from aerially sown baits falling into streams (Hamilton and Eason 1994). This likely contamination fuels an ongoing debate concerning the potential toxicological effects of the use of this chemical in the environment (Thomas 1994; S. Gilbert pers. comm. 2000). Interest in the potential toxic effects of 1080 has **resurfaced** as a result of the latest findings from the animal studies commissioned by the DoC and AHB of rats with exposures to 1080. Compound 1080 was found to be teratogenic, a male reproductive toxin and a myocardial toxin (Eason *et al.* 1998, 1999, 2001; Eason and Turck 2002). Older studies carried out in England, such as McDowell (1972a, b) and Cater and Peters (1961) suggested that 1080 is also a nephrotoxin in rats.

From a public health point of view, the focus of concern recently has been the potential effects at low doses during long-term exposures. It should be noted that this study **excludes** exposures arising from places of work.

1.2 Aims of the Study

This study focuses on developing health risk assessment and health risk management methodologies using 1080 as the model. The aims of this study are to:

1) Review the adequacy of the available relevant toxicological data on 1080 and the outcomes of studies commissioned by the Department of Conservation and the Animal Health Board on 1080 and its relevance to the protocols used in New Zealand to control possums,

2) Investigate and carry out health risk assessment analyses of 1080 and its impact on public health,

3) Develop methodologies for the protection of sensitive segments of the population, specifically for children to ascertain their susceptibility to the adverse effects of 1080 and compare this finding with the data derived from adults,

4) To use a dose-response modelling approach in deriving the Tolerable Daily Intake and consequently the Provisional Maximum Acceptable Value (PMAV) on 1080, which will form the basis for revising the PMAV for 1080 in Drinking Water Standards New Zealand, and

5) Develop a risk management plan for 1080 that will:

   a) identify any problems and gaps (if any) on the current standard national application form and permit conditions used by the Medical Officers of Health,

   b) develop policy advice to assist the Medical Officers of Health in granting permit conditions for the use of 1080, and

   c) analyse the legal implications surrounding the use of 1080 as it affects public health, in particular the role of the Medical Officers of Health.

1.3 Scope of the study

Chapter 1 provides a brief introduction to the project, its background, the use of 1080 in New Zealand, natural occurrence, method of application, together with the aims and scope of the project.

Chapter 2 presents the biodegradation and human exposure pathways.

Chapter 3 discusses the identity, physical/chemical properties, stability of the C-F bond, toxicokinetics and metabolism in laboratory animals, and toxicodynamics.

Chapter 4 reviews information on the toxicological hazards of 1080.

Chapter 5 discusses the methodology and results to complete the health risk assessment process, which includes hazard identification, dose response assessment, exposure assessment, and risk characterisation used in the study.

Chapter 6 presents the general discussion and conclusions resulting from the health risk assessment process.

Chapter 7 discusses the health risk management framework, comprising the statutory framework of regulation of 1080, conclusions and recommendations, where appropriate.

1.4 The use of 1080 in New Zealand

Compound 1080 was first synthesised in Belgium in 1896, but its toxicity was not noted until 1934 (Atzert 1971). It is one of the most toxic vertebrate agents known. Compound 1080 was introduced into New Zealand in 1954 and its principal use has been to control possums (*Trichosurus vulpecula*), and to contain the spread of bovine tuberculosis to livestock such as cattle and deer herds.

New Zealand is the only country in the world with a "possum problem" (PCE 1994). Uncontrolled possum populations are a direct threat to vulnerable areas of the conservation estate and the diversity of New Zealand's flora and fauna (DoC and AHB 2003). In addition, possums are the major wildlife host of bovine tuberculosis which is New Zealand's main animal health problem (DoC, AHB and MAF 1994; DoC and AHB 2003). There is a potential risk that non-tariff trade barriers could be placed on New Zealand's exports of beef, dairy, and deer products if other countries perceived that they were contaminated with tuberculosis (PCE 1994).

A clear understanding of possible risks to the environment has been suggested by Parfitt *et al.* (1994) as being essential since more than 3.2 tonnes of 1080 are applied annually in New Zealand. Although 1080 has been used in New Zealand for a few decades now, Eason *et al.* (1993b) suggested that the long-term use of 1080 needs to be further studied because of the continuing controversy concerning its use, fate in water, and effects on non-target species, especially livestock and invertebrates. For instance, the Mangapeka Educational Trust and 1080 Action Group in Golden Bay have expressed concern about the teratogenic/reproductive effects of 1080. In addition, Takaka residents were angry and made their complaints to relevant regulatory authorities as 1080 was mistakenly dropped in an area where they obtain their drinking water and potentially contaminating their drinking water source.

An extensive published database on the fate of 1080 in the environment and effects on non-target species exists. However, one of the major gaps in knowledge surrounding 1080 is its potential long-term effects on human health.

1.5 Natural occurrence

Compound 1080 occurs naturally in certain plants in Western Australia and South Africa at concentrations similar to those used on bait for rabbit control (Twigg and King 1991). Approximately 40 species of plants in the genus *Glastrobium* occur in southwestern Australia and some species are abundant and contain high levels of fluoroacetate (Aplin 1971; Crisp and Weston 1987). Those species which occur in northern Australia are less toxic, i.e., *Acacia georgina* and *G. grandiflorum* (Twigg and King 1991).

Plant species of the genus *Glastrobium* can produce more than 2,000 mg kg^{-1} in leaves (Twigg 1994). The concentration of fluoroacetate in these plants varies between species, region, soil type, and season. As fluoroacetate had been an integral part of the Australian environment some animals have developed varying degrees of tolerance to fluoroacetate. This tolerance has not yet been quantified scientifically in New Zealand. The biochemical mechanism responsible for tolerance is poorly understood (Twigg 1994). Of the Australian seed-eating animals the emu *Dromaius novaehollandiae* has by far the greatest tolerance to fluoroacetate with an LD_{50} of 102-200 mg kg^{-1} (Twigg *et al.* 1988). This example illustrates that animals in areas where fluoroacetate has been part of their natural environment can tolerate high concentrations of the compound, compared with animals living in areas where fluoroacetate was not an integral component of their natural habitat. Such animals, e.g., dogs, with an LD_{50} of 0.06 mg kg^{-1} bw (body weight), are extremely sensitive to fluoroacetate.

The plant *Dichapetalum cymosum* (Gifblaar) was the first to be found to contain fluoroacetate in Africa. Several other species of *Dichapetalum* have also been shown to produce fluoroacetate (Vickery *et al.* 1973; Vickery and Vickery 1975). Fluoroacetate has also been isolated from *Palicourea marcgravii*, a South American species known to be poisonous (de Oliviera 1963). It has also been established that *Acacia georgina* contains fluoroacetate, producing a syndrome characterised by sudden death (Bell *et al.* 1955).

It can be assumed that because 1080 is not naturally present in the New Zealand environment, animals may be more susceptible to it as they would not have developed tolerance as opposed to their Australian counterparts. However, the tolerance exhibited by some Australian animals only relates to the lethal effects based on the fact that most publications in this field focussed on acute toxicity. However some studies have reported sub-lethal effects of 1080, such as elevation in blood/tissue citrate, such as that of Twigg *et al.* (1986) which may likely to precede pathological effects and it is also possible and likely that chronic toxicological effects might be less in resistant species (Twigg *et al.* 1994). Because of the widespread use and potential for long-term low-level exposure of sensitive species, it seems possible that chronic effects may

occur. Since the focus of this thesis is on the use of 1080 in New Zealand, i.e., synthetic 1080, no further work has been done on this topic. Naturally occurring 1080 was only mentioned in this thesis to put in context the toxicity of 1080.

1.6 Method of application

Compound 1080 is applied by aerial drops and ground-baiting operations, the latter utilising a range of control techniques including bait stations, bait on spits, and hand broadcasting. It may be applied using a variety of natural and manufactured baits. It is available as a 20% w/v stock solution for use on boiled oats, or for spraying onto diced carrots. It can be incorporated into manufactured cereal baits, apple based paste or a gel. Registered 1080 concentrations are available at 0.02, 0.04, 0.06, 0.08 and 0.15%.

In aerial poisoning for possum control, 1080 is coated on carrot baits or mixed into cereal baits. Aerial application of baits containing 1080 has been demonstrated to be very successful in controlling possums in up to 95% of the population. This method of application has eradicated possums over areas of up to 20,000 ha, as reported by Thomas (1994) and PCE (1994).

The Digital Global Positioning System (DGPS) uses satellites as reference points for establishing position and has been proven to be generally an effective tool in targeting the possum population (Morgan *et al.* 1996). DoC (1994) and DoC and AHB (2003) considered that aerial baiting of 1080 is the only available method of application that offers a cost effective eradication of possum populations in rugged, inaccessible terrain.

Chapter 2

Biological degradation and exposure pathways

2.1 Biodegradation

Biological degradation of 1080 may occur in the toxic bait, in the poisoned animal, and in the soil and waterways where it is finally deposited (Rammel and Flemming 1978). Environmental research shows biodegradation occurs in microbes, invertebrates, plants, and animals. Under wet mild conditions, 1080 residues will usually disappear within 1 to 2 weeks. However, 1080 may persist in bait, soil, or in carcasses for several weeks or even months in cold or dry conditions (Eason *et al.* 1993a; Parfitt e*t al.* 1994; Morgan and Eason 2004). A study carried out by Bowen *et al.* (1995) suggested that carrot baits were highly water resistant and showed no decline in 1080 concentration after 200 mm of rain while the pellet form was less resistant. Table 1 illustrates the time required for the biodegradation of 1080 in various conditions. In general, the bait may disintegrate during wet and warm conditions and takes longer under dry and cold conditions because there will be little biological activity to breakdown the structure of the bait. Bait breakdown is also dependent on the amount of rainfall and the nature of the bait.

Table 1

Time required for biodegradation of 1080 in various conditions

Source	Conditions	Change or effect measured	Time
Eason *et al.* 1993b	Laboratory, 20°C Field	1080 no longer detected - aquaria in water - plants in water elimination of 1080 traces in wetas and cockroaches	 After 2 days After 7 days 2-8 weeks
King *et al.* 1994	Laboratory, 15-28°C, 11% soil moisture	1080 reduction in soil –50% -up to 87%	6 days 23 days
Parfitt *et al.* 1994	Laboratory, 23°C At 10°C At 5°C Laboratory, 21° C	Time for 50% reduction of 1080 in soil (Kaitoke Silt Loam), and level remaining at end of experiment Elimination of 1080 in water	10 days (none after 27 days) 30 days (traces after 120 days) 80 days (traces after 120 days) 2-6 days
Gooneratne *et al.* 1994	Laboratory, warm	1080 in 1080-killed rabbit	1080 still present after 3 weeks
Wong *et al.* 1991	Laboratory, warm, moist	Loss of 1080 from baits - oat baits, 71% loss - meat baits, 14% loss	 4 weeks 4 weeks
Legal case* 1987	Field, winter	Sheep killed by baits	Still toxic at 6 weeks
Fleming and Parker 1991	Field, winter	Loss of 1080 from meat baits –75% –85%	 7 weeks 32 weeks
David and Gardiner 1966	Laboratory, warm, moist	Loss of toxicity to aphids feeding on plants in 1080-treated soil -at 10 ppm 1080 -at 50 pm 1080	 2 weeks 11 weeks

Modified from Office of the Parliamentary Commissioner for the Environment 1994.

* Gordon-Glassford v. Upper Clutha Pest Destruction Board, D.C. Alexandra, 20 March 1987, per Judge Aap Willy

2.1.1 Water

Compound 1080 is dissolved easily in water, so generally it is washed out of baits by rainfall. Once it is washed into the soil, common soil bacteria and fungi break it down (Walker and Bong 1981; Wong *et al.* 1991). Degradation of 1080 treated baits depends upon climatic conditions. Breakdown is most rapid at higher temperatures (Chenoweth 1949) and wet conditions and slower in cold and dry environments (Hamilton and Eason 1994; Batcheler 1978). To illustrate, on average the toxicity in carrot baits is reduced to about 10% or less of the original concentration when exposed to about 100 mm of rain (Livingstone and Nelson 1994). However, this study appears not to support the finding by Bowen *et al.* (1995) where it was reported that no decline in 1080 concentration after 200 mm was observed in carrot baits. Given the fact that the aerial application of 1080 is generally done during winter months, it is likely that 1080 could persist in cold water streams for some time because it might survive without breakdown long enough to be carried quite a considerable distance downstream.

Field water monitoring programmes for aerially sown 1080 baits undertaken between 1990 to 1997 demonstrated that generally, trace amounts of 1080 found close to the limit of detection (0.0003 mg L^{-1}) were in 5.8% of the 761 water samples tested (Eason 1997). Highest concentrations of 1080 found in some locations ranged between 0.2 µg L^{-1} to 3.5 µg L^{-1} One hundred tonnes of 0.08% 1080 cereal-based baits were aerially applied over 17 000 ha of forest in the Waipoua Forest Sanctuary and streams and rivers were monitored for 4 months. Similarly, Rangitoto Island was aerially sown with 20 tonnes of 0.08% 1080 cereal-based baits over 2 300 ha. There was no 1080 detected in any of the water samples tested (detection limit of 0.0003 mg L^{-1}) (Eason *et al.* 1992). Blackstone Hill was aerially treated with 0.023% 1080 carrot baits and streams and rivers were monitored for 4 weeks after the operation. Measurable amounts of 1080 occurred within 48 hours of the operation in two samples (0.0003 and 0.0006 mg L^{-1}) and no detectable levels of 1080 (detection limit of 0.0003 mg L^{-1}) was measured after the 48 hour period (Hamilton and Eason 1994).

In Taranaki, the possum control operation involved 11 000 ha of Egmont National Park, 1 900 of rateable bush and 4 090 ha of pastoral land. Variable traces of 1080 (<0.003 mg L^{-1}) were found in some samples (detection limit of 0.0003 mg L^{-1}) (Parfitt *et al.* 1994). Water analysis after major operations from 1990 to 2002 is shown in Appendix 1. In contrast, 1080 solutions prepared in distilled water and stored at room temperature for 10 years showed no significant breakdown. Additionally, 1080 in stagnant algal-laden water did not lose biocidal properties during 12 months (McIlroy 1981a). Eisler (1995) suggested that more research would be required to determine the persistence of 1080 in aquatic environments.

A recent study carried out by the National Institute of Water and Atmospheric (NIWA) Research Ltd. suggested that the water sampling programmes to date (see Appendix 1) showed a large number of "zero" detection levels of 1080 and its non-detection may reflect the absence of baits within streams (detection limits of 0.0003 mg L^{-1} and 0.0001 mg L^{-1}). Evidence to support this view is that both the Lewis Pass and Moana-Ruru streams 1080 drops had no baits in them (Suren and Lambert 2004). The fate of baits in moving water and the rate that 1080 leached from the baits were evaluated by laboratory experiments.

Suren and Lambert (2004) claimed that although the actual baits (Wanganui No.7) were expected to remain in a stream for up to 72 – 84 h before they disintegrated, examination of 1080 concentration in the baits showed that over 50% of this compound had leached from baits within the first 8 – 12 h after being submerged. By 24 h, the baits contained only 0.019% 1080, a loss of over 90% of the original 1080 in the baits (0.15%). Hence, the same authors concluded that water samples should be collected within 8-12 hours after 1080 operation but not after 24 hours to determine the presence of 1080. However, the 'over' 90% loss reported by Suren and Lambert was not factually correct as the loss only equated to 87% loss.

2.1.2 Soil

The fate of 1080 in soil has been studied extensively. It is water-soluble and residues from uneaten baits leach into the soil. Compound 1080 is degraded to non-toxic metabolites such as glycolate by soil microorganisms, usually through cleavage of the

C-F bond (Walker and Bong 1981; Wong *et al.* 1992b; Eason *et al.* 1993b). The soil microorganisms that can detoxify 1080 appear to be ubiquitous in the environment. In New Zealand soils, where the toxin does not occur naturally, several species of bacteria (*Pseudomonas* and *Nocardia*), fungi, and algae degraded fluoroacetate by defluorination (Kelly 1965; Batcheler 1978; Bong *et al.* 1979). Soil microorganisms capable of defluorinating 1080 include *Aspergillus fumigatus*, *Fusarium oxysporum*, at least 3 species of *Pseudomonas acidovorans*, *Pseudomonas fluorescens*, an unidentified *Pseudomonas* sp., *Nocardia* spp., *Penicillum purpurescens* and *Penicillum restrictum.* The most effective defluorinaters in solution and in soils were certain strains of *Pseudomonas*, *Fusarium*, and *Penicillium* (Wong *et al.* 1991, 1992a; Walker 1994) and in moist soils by the *Nocardia* groups (Batcheler 1978).

Compound 1080 was unlikely to be persistent in the environment for long periods of time. Biodegradation of 1080 depended on factors such as temperature, moisture, species of microorganisms present, availability of nutrients and the toxin to the microorganisms, and under some conditions may take several weeks or months. Parfitt *et al.* (1994) found that 1080 persists in bait, the soil, or in carcasses for several weeks or even months in cold or dry conditions.

Biodefluorination of 1080 by soil bacteria was maximal under conditions of neutral to alkaline pH and at soil moisture contents of 8-15% and temperatures ranging from 15-30°C. Biodefluorination of 1080 by soil fungi was maximal at pH 5 (Wong *et al.* 1992b). The defluorination of 1080 was low when 1080 was the sole carbon source. However, it was enhanced in the presence of an alternative source such as peptone-meat extract (Wong *et al.* 1991; Bong *et al.* 1979).

2.2 Exposure pathways

2.2.1 Secondary poisoning

Compound 1080 has posed a high degree of secondary hazard to humans and other susceptible species, both during and after the intended control operations. Secondary poisoning can occur when a predator or scavenger eats poisoned animal or poisoned baits (Calver and King 1986). Compound 1080 in carcasses can create a secondary

poisoning hazard to carnivorous predators (Bell 1972). Because of the vegetable origin of the baits, they may be eaten by other herbivores, such as sheep, cattle, or various species of native wildlife. This may then lead to both primary poisoning (i.e., the toxic bait was ingested directly) and secondary poisoning of non-target animals (McIlroy 1982). The potential risk of primary and secondary hazards from 1080 baiting depends upon many factors including the susceptibility of the target and non-target species, concentration in the bait, amount of bait applied, the number of consumed poisoned animals, the amounts of different consumed tissues or organs, and the time of year the bait is applied (McIlroy 1981a; Hegdal *et al.* 1986; McIlroy and Gifford 1992).

Although laboratory studies have suggested that theoretically 1080 poses hazards to non-target species through both primary and secondary poisoning, field data are available to assess the effects of 1080 on non-target populations, such as that of Powlesland *et al.* 2003, Powlesland *et al.* 2005. Secondary poisoning has been recorded in New Zealand for dogs, stoats, ferrets, cats, and harrier hawks (Batcheler 1978). Dogs are highly susceptible to 1080, and thus are at greater risk of toxicity (Rammel and Flemming 1978). Dogs generally die as a result of secondary poisoning after eating the carcasses of poisoned animals that have undigested 1080 baits in their stomachs (Livingstone 1994; DoC, AHB and MAF 1994; Meenken and Booth 1997), eating a single cereal pellet, or by licking some 1080 paste (Livingstone 1994; Livingstone and Nelson 1994).

Previous studies have shown that mink are among the more sensitive species to 1080 (Hornshaw *et al.* 1986) suggesting that mink might be a good model for studying secondary toxicity of 1080. However, when the gastrointestinal tract of the 1080 poisoned rabbit had been removed from the carcass, no mink died when fed with the poisoned rabbit, suggesting that secondary toxicity from 1080 may be primarily due to consumption of the unmetabolised compound from the gut of prey species and not from the muscle tissue (Aulerich *et al.* 1987).

A study by McIlroy and Gifford (1992) suggested that foxes, dingoes, dogs and cats appeared to be at greater risk of secondary poisoning than native birds and mammals, particularly from eating the muscle tissue from poisoned rabbits containing 1080

ranging from 0.01 to 4.88 mg of 1080 per rabbit. This is expected because muscles generally contained the highest amount of 1080 given their high proportion of total body weight. Secondary poisoning in man caused by eating venison, hearts or liver was regarded as unlikely, as is chronic poisoning from daily ingestion of tissues containing up to 9.2 ppm (Clarke *et al.* 1981). In New Zealand, the Maximum Residue Limits (MRL) for 1080 in food was specified as 0.001 mg kg^{-1} (default value) or at about the limits of detection. This value was estimated to be 9000 fold lower than 9.2 ppm mentioned by Clarke *et al.* (1981).

The concentration of 1080 used in baits and the amounts of bait eaten by different animals may also affect the risk that carrion-eaters face from secondary poisoning (McIlroy and Gifford 1992). Domestic cats may also be poisoned by eating rodents and birds killed by 1080-poisoned bait (Gosselin *et al.* 1984). Ground squirrel control with 1080 baits has caused secondary poisoning of dogs, cats, coyotes, bobcats, skunks, and kit foxes (Hegdal *et al.* 1986) and domestic ferrets that ate 1080-poisoned white-footed mice (*Peromyscus leucopus*) (Hudson *et al.* 1984). Similarly coyotes died after ingestion of 1080-poisoned ground squirrels (Casper *et al.* 1986; Marsh *et al.* 1987). However, there is no evidence of secondary poisoning seen in coyotes, domestic dogs, striped skunks (*Mephitis mephitis*), and black-billed magpies fed with dead coyotes poisoned by 1080 (Burns *et al.* 1986). Similarly, secondary poisoning in Virginia possums (*Didelphis virginiana*), and striped skunks was not observed after ingesting dead coyotes (Eastland and Beasom 1986; Burns *et al.* 1991). The risk of secondary poisoning to predators was minimal in the consumption of tissues of 1080-killed black-tailed prairie dogs (*Cynomys ludovicianus*) because of the very low level of 1080 in their tissues (Huggins *et al.* 1988).

Vomitus containing 1080 has been potentially hazardous to non-target animals that eat it (O'Brien *et al.* 1986). Because 1080 exerts an emetic action especially in coyotes and feral pigs, non-target animals were at risk of primary poisoning from eating the vomitus (Atzert 1971; McIlroy 1983; Rathore 1985; O'Brien *et al.* 1986, 1988). Pigs commonly vomit after ingesting 1080 (McIlroy 1983) and vomiting was an obvious and consistent early sign of 1080 intoxication in feral pigs, occurring as little as 10 minutes after ingestion. However, vomiting in no way assured survival. It has

occurred in all animals dying from 1080 intoxication and 94% of those that lived (O'Brien 1988). It has been suggested that this may enhance the survival of some pigs but increase the chance of killing other non-target species which eat the vomitus (O'Brien *at al.* 1986). Its main importance was its risk of secondary poisoning to non-target animals.

2.2.2 Human exposure

2.2.2.1 Drinking water

Under the Pesticides (Vertebrate Pest Control) Regulations 1983 (now repealed by the Hazardous Substances and New Organisms (HSNO) Act 1996), the Medical Officer of Health may grant a permit to apply 1080 in any water catchment area from which water was drawn for human consumption. The granting of a permit was mandatory provided the Health Act 1956 and the Pesticides (Vertebrate Pest Control) Regulations were not contravened. In granting permits, conditions may be imposed as the Medical Officer of Health has considered fit to meet local needs. Information provided by the local Public Health Units (PHUs) showed that all PHUs have granted permits to aerially apply 1080 on to drinking water catchments (see Chapter 7 and Appendix 7 relating to preliminary information collected by the author (NF) through the assistance of the PHUs). The HSNO Act also provides that designated authorities may grant permits to apply 1080 in a catchment area from which water is drawn for human consumption. Details of the current role of the Medical Officers of Health are provided in Chapter 7.

In a poisoning operation some of the 1080 may enter a water source and pollute a potable water supply. This could happen by rain that may leach the 1080 from bait lying on the ground; or the bait may be inadvertently dropped directly into the water supply; or a poisoned carcass may enter a water supply (Rammel and Flemming 1978). As 1080 is highly water-soluble and may be leached by rainfall from toxic baits into the environment, this source of contamination has generated major public concern, particularly after aerial application of 1080 baits (Thomas 1994).

The rapidity with which 1080 is leached out of baits by rainfall will depend on a number of factors including the amount of rainfall, what kind of bait it is, the exposed surface area of the bait in relation to its mass, and on the strength of the absorption sites within the bait. Therefore, thinner pieces of bait will leach 1080 faster than thicker pieces of bait (Rammel and Flemming 1978). Wheeler and Oliver (1978) suggested that following moderate rainfall nearly all of the 1080 is lost from the oats baits. As a general rule, 5 mm of rain will reduce the chemical toxicity by up to 20%, 10 mm by up to 70% and 20 mm of rain by up to 80% of toxicity (type of bait unspecified) (Taranaki Regional Council 1993). Thus, treated baits falling into a drinking water catchment could represent a significant source of contamination.

Compound 1080 is prone to dilution because it is water-soluble. Landcare Research Ltd (Wright 2007) has prepared a set of guidelines for water sample collection and handling to assist DoC and the regional councils in their 1080 operations activities. The analytical techniques for 1080-water residue analysis which can detect 1080 at extremely low concentrations in water were developed by Landcare Research based on the work of Ozawa and Tsukioka (1987). Testing is carried out using a gas chromatography method. The water sample is acidified with hydrochloric acid and 1080 is converted to the dichloroaniline derivative by using N,N'-dicyclohexyl carbodiimide and 2,4-dichloroaniline. The derivative is cleaned on a silica cartridge, eluted with toluene, and quantified by gas chromatography with electron-capture detection.

Ground and surface water after aerial-1080 operations in Waipoua, Rangitoto, Taranaki, Central Otago and Wairarapa were analysed for 1080 residues. The great majority of samples from poisoned catchments showed no traces of 1080 at the detection limit of 0.3 $\mu g\ L^{-1}$ (Eason *et al.* 1992). However, Taranaki and Central Otago samples showed trace levels (Meenken 1993). Single water samples were taken at different intervals, i.e., immediately after the application of the bait, after the first major rainfall, and during the first six weeks after the operation. According to several authors, such as that of Booth *et al.* 1997; Meenken and Eason 1995 and Parfitt *et al.* 1994 there was no evidence of significant or prolonged 1080 contamination in surface and ground water. In addition, no detectable levels of 1080 were present in reticulated water. It should be noted that the water analysis for detecting the presence of 1080 has

become three times more sensitive since this report was published and is now 0.1 μg L^{-1} (0.1 ppb) in a 50 ml water sample (Wright 2007).

Between 1990 and 2003, there were 1450 water samples tested (Fisher and Eason 2003). The water samples were collected following aerial application of 1080 baits in large-scale possum operations and one rabbit control operation. Approximately 5% of the water samples tested showed detectable levels of 1080 (Fisher and Eason 2003; Eason and Wright 2001)). Eason (2002a) concluded that significant contamination of waterways following aerial application of 1080 baits is unlikely. The highest concentrations of 1080 in areas where it was found to be present range from 0.2 to 9.0 μg L^{-1} (see Appendix 1). However, Eason (2002b) reported that the water sample with 9.0 μg L^{-1} was collected by a worker with 1080 dust on his overalls and hands.

2.2.2.2 Food

The general public is more likely to encounter 1080 exposure through ingestion of trace amounts in food such as meat or milk. There were incidents reported to the Ministry of Health relating to feral meat and milk 1080 contamination exceeding the maximum residue limit (MRL) in foods of 0.001 mg kg^{-1} (J. Sim pers. comm. 1998).
It was reported that 1080 had killed nine dairy cows after 1080 application in baits. The estimates showed that milk taken from surviving animals within the first 48 hours of the poisoning incident contained 1080 four times the allowable MRL in any food of 0.001 mg kg^{-1} even after the massive dilution within the silo milk. However, test results showed no detectable 1080 in the dry product or in the reconstituted milk (J. Sim pers. comm. 1998). The Ministry of Health issued a public statement that the dairy products were fit for human consumption. However, it would be of particular health concern if the milk taken directly from the cows was consumed by the public since it may contain unacceptable levels of 1080.

From July 2002, responsibility for all food safety and quality issues was transferred from the Ministry of Health to the New Zealand Food Safety Authority (NZFSA) (see section 7.2.4). NZFSA considers meat from wild animals containing toxic residues as unsafe. It does not guarantee the safety or fitness of wild animals' meat as fit for

human consumption because recreational catch meat has not been subjected to any hygiene or processing standards, control or inspections. Recreational hunting is not regulated and there is no established testing regime in place (NZFSA 2005b).

Rammell and Fleming (1978) estimated that a human would have to eat 750 g of meat from a deer killed by 1080 before any toxic effect would occur and 10 kg before death was likely. This estimate was based on seven deer (LD_{50} 0.5 $mgkg^{-1}$) that died from 1080 poisoning. This is a large amount and it is unlikely that an adult human would be able to consume this in one sitting. Temple and Edwards (1985) estimated that a 70 kg man would have to eat 25 kg of meat from ducks killed with 14 mg kg^{-1} doses of 1080 to receive a lethal dose. This calculation would equate to 5 mg kg^{-1} which is consistent with the conclusion made by Gosselin *et al.* (1984) that 5 mg kg^{-1} is probably the best single estimated lethal dose value for humans although the same authors estimated that the mean lethal dose in humans ranges from 2 to 10 mg kg^{-1}. Chenoweth (1949) reported a lower mean lethal dose (2 to 5 mg kg^{-1}). It would appear that the lower bound on the lethal dose is 2 mg kg^{-1}.

The risk to humans from eating meat of domestic animals accidentally poisoned with high sublethal concentrations appears to be minimal to low because 1080 is cleared rapidly from domestic animals, usually within a few days (Eason *et al.* 1994b). Using residue data from sheep, Eason (1993) and Rammell (1993) estimated that even in a worse case scenario, a 30 kg child would have to eat 500 g of meat from a sheep that had eaten one or two toxic baits within the previous 2-3 hours to receive a near-lethal dose of 1080. It is apparent that the older literature focussed on the lethal effect of 1080, as has been highlighted by the author (NF). 1080 decomposes at 200°C (Sunshine 1969). This temperature however is very high and would basically burn meat to a crisp.

In 1999, the Ministry of Health received a report that feral meat was contaminated with 1080. The highest concentration of 1080 found in meat was 0.028 mg kg^{-1} which well exceeded the MRL of 0.001 mg kg^{-1} (default value). This incident has highlighted some human health implications. The Ministry of Health estimated that the "safe" human exposure level for 1080 was 0.1 µg kg^{-1}bw day^{-1} (Durham 1998a). Estimation

of a "safe" human exposure level was calculated by using the NOAEL from the teratology study (Eason *et al.* 1998, 1999) of 0.1 mg kg^{-1} day^{-1} /1000.

Meat consumptions of 5 g, 150 g, and 624 g are shown below to demonstrate the likely exposure from eating contaminated meat. A 60 kg pregnant woman who had consumed 5 g of meat day^{-1} (consumption data from Food Standards Australia New Zealand then Australia New Zealand Food Authority), contaminated with 0.028 mg kg^{-1} (highest level found in meat) will receive a dose of 0.0023 µg kg^{-1} day^{-1} (5g * 0.028 mg kg^{-1}/60). This figure is 2.3% of the provisional "safe" human dose estimated at 0.1 µg kg^{-1} bw day^{-1} (with built in 1000 UF).

However, 5 g is a very tiny amount and 150 g of meat may be a more realistic figure. Therefore, a 60 kg pregnant woman who consumes 150 g of contaminated meat approaches a value of 0.07 µg kg^{-1} day^{-1} (150 g * 0.028 mg kg^{-1}/60 kg), which is still below an exposure of concern.

An estimate using an upper consumption limit of 624 g of beef (this value was used as a surrogate for deer consumption) demonstrated that a woman consuming this large quantity of contaminated meat will receive a dose of 0.29 µg kg^{-1} (624 g * 0.028 mg kg^{-1}/60 kg) (Durham 1998a) which is approximately 3 fold above the "safe" dose and should be further studied as it might be of particular health concern. These estimates were calculated prior to the 90-day subchronic study.

2.2.2.3 Air borne dust

Aerial 1080 poisoning operations are usually applied in areas away from home and dust from poisoned baits may travel in the atmosphere especially during windy days. The public have raised concerns that this could be a potential route of 1080 exposure.

An air-sampling programme was carried out during a 1080 aerial bait application (1080 bait concentration not specified) in the Tararua Ranges in the vicinity of Featherston, to ascertain whether 1080 dust was being carried in the atmosphere onto land bordering the drop zone. Bromley (1996) reported that three air samplers were

used for this purpose. Two samplers were placed at the edge of the drop zone and the third sampler was used to measure background levels. It was not reported whether dust formation is likely but the fibreglass filters were taken before, during and after 1080 aerial application and the presence of 1080 was measured. Bromley (1996) reported the levels of 1080 to be below the limit of detection of 0.01 μg on the filter.

The Ministry of Health concluded that airborne dust does not appear to represent a significant exposure (Durham 1998a).

2.2.2.4 Baits

The exposure to 1080 baits is to a limited degree either through accidental or intentional ingestion of 1080 (Pelfrene 1991). Bait exposures were excluded from the exposure assessment (see Chapter 6) because they were not relevant for the purposes of developing a TDI for 1080. Relevant exposure scenarios used in developing TDIs were drinking water, food, air, and soil intakes. Should there be any suspected exposure of the public to 1080 baits, the actual exposure (and risk) would be estimated separately as the need arises.

2.2.2.5 Exposure of children at home

Children form a unique subgroup within the population. They have higher exposures and some higher susceptibilities that are quite different from those of adults. As with adults, the potential for exposure to 1080 for infants and young children is through ingestion, inhalation, and percutaneous absorption. A detailed discussion of child exposure is provided in Chapter 5.

2.2.2.6 Others

Occupational exposure

Biological monitoring of occupationally exposed individuals was conducted in New Zealand, such as by O'Connor *et al.* (2000, 2001). Some urine results indicate an exposure higher than the Biological Exposure Index (BEI) set by the Department of

Labour (Workplace Services). It has been highlighted earlier that occupational exposures are outside the scope of this study and will not be discussed further. This information is mentioned here to illustrate that 1080 was detected while workers were engaged in 1080 related activities (see Appendix 8a carried out by this author (NF) with respect to 1080 worker's postal survey).

Chapter 3

Physical, Chemical, Toxicokinetics and Toxicodynamics

3.1 Identity, physical and chemical properties

Sodium monofluoroacetate is also known as Compound 1080 or ten eighty (1080). This name is derived from a laboratory testing number used for the chemical in early USA experiments. The empirical formula for sodium monofluoroacetate is $C_2H_3FNaO_2$ with CAS number 62-74-8. It is a colourless, odourless, tasteless, highly water soluble salt that decomposes at about 200°C (Pelfrene 1991) and should not be heated above 110°C (Egekeze and Oehme 1979).

It is hygroscopic when exposed to air, highly soluble in water, but relatively insoluble in organic solvents such as kerosene, alcohol or acetone or in animal and vegetable fats and oils. In general, 1080 is chemically stable due to the strength of the carbon-fluorine bond.

Its common name, Compound 1080 or 1080, will be used entirely throughout the text for simplicity.

3.2 Stability of C-F bond and carbon-fluorine compounds

The toxicity of 1080 depends on the stability of the C-F bond (Pelfrene 1991). Peters (1957) suggested that the C-F bond in fluoroacetic acid is very stable. The carbon-fluorine compounds are not toxic themselves but become toxic due to "lethal synthesis".

A defluorination system which cleaves the C-F bond of 1080 may serve as a protective mechanism in reducing the amount of fluoroacetate available for biotransformation to fluorocitrate (Kostyniak 1979). Kostyniak *et al.* (1978) have shown that defluorination *in vivo* may lead to a toxic response, but it is also possible that defluorination may

prevent the toxic effect and could minimise the production of fluorocitrate and the characteristic toxic response. The involvement of glutathione in the *in vivo* defluorination of 1080 in the rat liver has been verified by Kostyniak (1979) and the liver has been confirmed as the main site for defluorination of fluoroacetate (Twigg 1994). Twigg *et al.* (1986) and Twigg and King (1991) stated that once glutathione levels were low, fluoroacetate was no longer effectively detoxified and the inhibition of aconitate hydratase and/or citrate transport in mitochondria is increased. It was further stated that low levels of fluoroacetate remained present in the plasma of skinks under study, despite extensive defluorination, for at least 96 hours. The liver glutathione levels remained low for up to 14 days (Twigg 1986). It is likely, therefore, that individuals with low glutathione levels, or who are unable to rapidly restore diminished glutathione, may be more susceptible to the toxic effects of fluoroacetate as glutathione plays a major role in the detoxification process of the toxic metabolite. However, this has not been confirmed by the author (NF) and there do not appear to be any cases to support this.

The C-F bond was once assumed to be impregnable to biological attack. However, a number of reports offer evidence that the C-F bond may be relatively unstable (Gal *et al.* 1961) and the biological systems can defluorinate some of these compounds (Egekeze and Oehme 1979). For example, rats administered 5 ppm of 1080 in the drinking water for four months deposited as much fluoride in bone as did rats receiving 5 ppm of fluoride as sodium fluoride (Smith *et al.* 1977). This suggested an *in vivo* defluorination reaction of 1080 or one of its metabolites (Egekeze and Oehme 1979). However, the biochemical mechanism of the C-F bond break is unclear (Gal *et al.* 1961).

It is not well known what happens to degradation products of 1080, particularly fluorocitrate, which is the active toxic agent synthesised from 1080 by organisms and likely to be present in the bodies of animals poisoned by 1080. Various micro-organisms have the ability to catalyse the cleavage of the C-F bond of fluoroacetate, degrading fluoroacetate to glycolate and fluoride ions. This has been demonstrated by a number of researchers such as Goldman (1965), Goldman *et al.* (1968), Bong *et al.* (1979), and Wong *et al.* (1992a). Fluorocitrate is therefore assumed to be unstable in

the environment (Booth *et al.* 1999). Another study revealed a certain degree of instability of the C-F bond of the fluoroacetate administered to rats (Gal *et al.* 1961).

Carbon-fluorine compounds are potentially very toxic and toxicity must be clearly distinguished from fluorides. Poisoning with 1080 is totally different from that produced by fluoride ion. In fluoroacetate, the fluorine is tightly bound in a fluorine-carbon linkage, which can be split only by harsh treatment (Gajdusek and Luther 1950). This statement is inconsistent with the findings of Egekeze and Oehme (1979) because the *in vivo* enzymatic reactions which produced the free fluoride should not be considered as harsh treatment.

Fluorides are toxic when present in excessive amounts in soil and water. They can induce malformations of bone, fluorotic teeth in humans and other disorders in cattle. Skeletal fluorosis and an increased risk of bone fractures occurred at a total intake of 14 mg fluoride/day and an increased risk of bone effects at total intakes above about 6 mg fluoride/day. The lethal dose to the average adult has been estimated to be between 5 and 10g (32-64 mg fluoride per kilogram body weight) (IPCS 2002). Their action is different from that of the carbon-fluorine compounds such as 1080. The Drinking Water Standards New Zealand (2005) provides 1.5 mg/L Maximum Acceptable Value (MAV) for fluoride. For oral reasons, the Ministry of Health recommends that the fluoride content for drinking water be in the range of 0.7-1.0 mg/L (this is not a MAV).

3.3 Toxicokinetics and metabolism in laboratory animals

Compound 1080 is absorbed through the gastrointestinal tract, open wounds, mucous membranes, and the pulmonary epithelium. It is not readily absorbed through the intact skin (Atzert 1971). It is quickly distributed to tissues. Oral dosages were found to have similar toxicity to subcutaneous, intramuscular, intravenous, and intraperitoneal dosages (Gajdusek and Luther 1950; McIlroy 1981a, 1983).

The required time for elimination of 1080 from tissues varied among species. Dogs required 2-3 days, rats 36 hours, and sheep as long as 1 month (McIlroy 1981a). In another study (Eason and Gooneratne 1993b) rabbits, sheep, and goats were dosed

orally with 0.1 mg kg^{-1} 1080 (approximately one-quarter the LD_{50}). The plasma elimination half-life in rabbits, mice, goats and sheep was 1, 2, 5, and 11 hours, respectively, and tissue concentrations were consistently lower than plasma concentrations. This is consistent with the findings of Egekeze and Oehme (1979) Gal *et al.* (1961), Eason *et al.* (1993b) and Sykes *et al.* (1987) in that higher concentrations of 1080 were found in plasma than in major organs or tissues. Various species given 0.1 mg kg^{-1} of 1080 demonstrated rapid elimination from plasma (within 18 hours, 24 hours and 96 hours in goats, possums, and sheep respectively), and also from tissues (within 1-4 days in goats). Traces of 1080 detected amounted to less than 0.002 μg g^{-1} (Eason *et al.* 1994a). It would appear that elimination in small animals, such as rabbits and mice, is faster than in larger animals, such as sheep, goats, or possums (Eason *et al.* 1994a). It would, therefore, not unreasonable to think that the half-life would be even longer in humans.

Eason *et al.* (1994a) reported that the initial clearance of 1080 in urine in sheep dosed via a gastric cannula with an aqueous solution of 1080 at a dose of 0.1 mg kg^{-1} coincided with the decrease in 1080 plasma concentration during the first 48 hours. This suggests that approximately 70% of the dose is broken down in the gastrointestinal tract or metabolised *in vivo* (Eason *et al.* 1994b).

Rammell (1993) suggested that 1080 concentrations in the muscle from sheep dosed orally at 200 μg kg^{-1} reached a maximum of about 110 ppb in 4 hours and decayed exponentially thereafter, with an elimination half-life of about 12 hours. In the liver, the maximum concentration of about 40 ppb was found at 2 hours, with an exponential decay thereafter, and an elimination half-life of about 3 hours. Elimination half-life in the liver appears to be about four times faster than that in the muscle, presumably because it is metabolised there. For ease of comparison, the elimination half-lives of mammals are summarised in Table 2.

Table 2

Elimination half-life in plasma and muscle for sheep, goat, possum, rabbit, and mouse*

Species	Sample	Route of administration	Dose, mg kg^{-1}	Elimination half-life (hours)
Sheep	plasma	oral	0.1	11.0 [a]
	muscle	oral	0.2	12.0 [b]
Goat	plasma	oral	0.1	5.5 [a]
	muscle			n.d.
Possum	plasma	oral	0.1	9.0 [a]
	muscle			n.d.
Rabbit	plasma	oral	0.1	1.1 [c]
	muscle	oral	0.1	0.4 [c]
Mouse	plasma	iv injection	0.4	2.0 [d]
	muscle	iv injection	0.4	1.7 [d]

* Eason *et al.* 1994b

n.d. = not determined
[a] Eason *et al.* 1993b
[b] Rammel 1993
[c] Gooneratne *et al.* 1994
[d] Sykes *et al.* 1987

3.4 Toxicodynamics

Compound 1080 is a highly vertebrate toxic agent whose biochemical mode of action in vertebrates is known. The fluorine in 1080 is strongly bound to the ω- carbon atom in the substituted acetic acid (Figure 1, adopted from Rammel and Fleming 1978). The chemical similarity between acetate and fluoroacetate is the basis of 1080's toxicity.

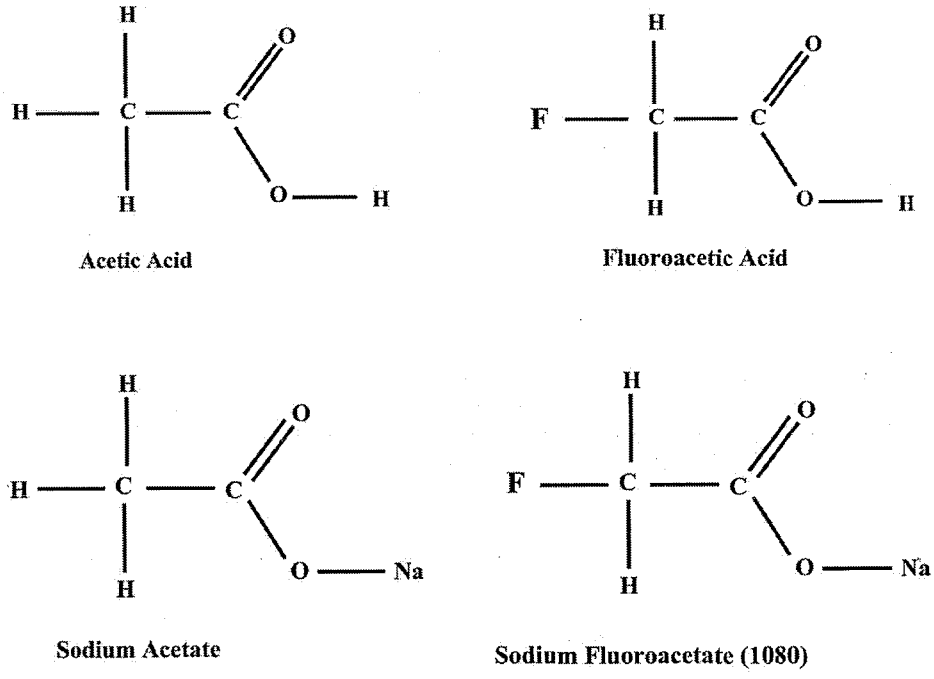

Figure 1

Relationship of 1080 and acetic acid

1080 disrupts the tricarboxylic acid (TCA) cycle (also known as the Krebs or the citric acid cycle), which is a complex metabolic pathway common to most organisms (Rammel and Fleming 1978; Peters and Wakelin 1953). The enzymes responsible for the reactions of the TCA cycle are all found in the mitochondrial fraction of the cell, mostly in the matrix, in proximity to the enzymes of the respiratory chain (Fruton 1972). 1080 reacts with coenzyme A (CoA) in the presence of adenosine-5'-triphosphate (ATP) to form fluoroacetyl CoA (Walker 1994). Fluoroacetyl CoA then combines with oxaloacetate to give fluorocitrate which in turn leads to aconitase inhibition which creates increased fluorocitrate and citrate. (In the normal TCA cycle, acetate condenses as acetyl-CoA with oxaloacetate to form citrate.). Figure 2 depicts the accepted view of biosynthesis of fluoroacetic acid to fluorocitrate (adopted from Egekeze and Oehme 1979).

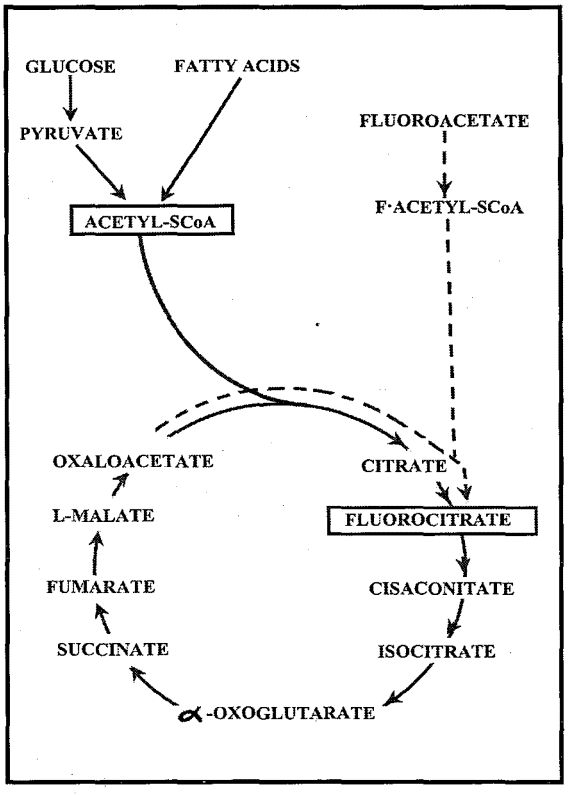

Figure 2

Accepted view of the biosynthesis of fluoroacetate to fluorocitrate in the animal cell and the block of the TCA cycle at the citric stage caused by fluorocitrate

Synthesis of fluorocitrate occurs in the mitochondria and the fluorocitrate formed inhibits mitochondrial aconitrate hydratase (aconitase) responsible for catalysing the conversion of citrate to isocitrate (Timbrell 2000) but does not appear to affect the cytoplasmic isozyme *in vivo* (Buffa *et al.* 1973). The inhibition arises from the fact that the aconitase is able to bind fluorocitrate but cannot carry out the dehydration to *cis*-aconitate as the carbon-fluorine bond is stronger than the carbon-hydrogen bond (Timbrell 2000). The aconitase inhibition leads to characteristic large citrate accumulation in certain tissues and is primarily responsible for the toxicity of 1080 (Peters 1952, 1957).

The accumulation of citric acid has been converted *in vivo* into fluorocitrate (Clarke *et al.* 1981; Fawaz and Fawaz 1953; Peters and Wakelin 1953). Fluorocitrate, a metabolite produced in 1080 synthesis, is believed to be the active toxicant and is specific in its blocking action on aconitase (Peters 1963). Peters (1952) coined the

term "lethal synthesis" to emphasise that the actual toxicant is fluorocitrate, a metabolite of 1080 (Figure 3).

Fluoroacetate

↓

Fluorocitric acid

↓

Inhibition of aconitase

↓

TCA cycle block

Figure 3

"Lethal synthesis"

Fluorocitrate competitively inhibits the TCA cycle enzyme, aconitrate hydratase (aconitase) (Carrell *et al.* 1970) and blocks the TCA cycle at the citrate stage (Morrison and Peters 1954). With disruption of the TCA cycle, energy production, in the form of adenosine triphosphate, falls. Citrate and other breakdown products of fats and carbohydrates accumulate and cell functions are severely impaired. Death may result from: (a) respiratory arrest following severe convulsions, (b) gradual cardiac failure or ventricular fibrillation; or (c) progressive depression of the central nervous system with either respiratory or cardiac failure as the terminal event (Peters 1957; Buffa *et al.* 1973; Twigg 1986; Chenoweth 1949).

Peters (1963) suggested that no mammalian enzyme has been found that was inhibited by fluoroacetate *in vitro*. However, *in vivo*, the ion undergoes synthesis to form fluorocitrate and this inhibits mitochondrial aconitase. Since the citrate synthetase continues to work, citrate accumulates in the tissues. The accumulation of citric acid is the best evidence available that the Krebs cycle functions while the animal is still alive (Buffa and Peters 1950).

Poisoning by fluoroacetate causes large increases in the citrate concentrations in mice and death occurs 24 hours after exposure to 1080 (Matsumura and O'Brien 1963).

Whereas Williamson *et al.* (1964) agreed that the initial effect of fluoroacetate is to produce fluorocitrate, they considered that the secondary inhibition of phosphofructokinase by the accumulated citrate was actually lethal because it deprived the cell of pyruvate, which would eventually overcome the inhibition of aconitase (Williamson *et al.* 1964). In addition, Buffa and Peters (1950) demonstrated that rats injected intraperitoneally with 5-10 mg kg^{-1} of 1080 produced large accumulations of citrate in most tissues within 1 h.

The actual mechanism by which 1080 causes the death of an animal is not fully understood despite the fact that considerable information is available into the biochemistry of 1080 intoxication (Buffa *et al.* 1973). A study conducted by Lauble *et al.* (1996) was unable to answer whether or not the inhibition of aconitase by 4-hydroxy-trans-aconitate (HTn) accounts for neurotoxic effects of fluoroacetate/fluorocitrate compounds despite the fact that HTn has been shown to be an extremely tight binding inhibitor of aconitase.

Fluorocitrate was found to be at least 100 times more toxic than fluoroacetate when injected directly into the brain under various experimental conditions. An intracerebral dose of 0.115 μg did not cause convulsions and failed to kill rats weighing about 250 g, while doses of 0.287 μg or greater caused convulsions and killed almost all the rats (Morselli *et al.* 1968). A dosage of 40-60 mg kg^{-1} is necessary to kill by the ip route, and an oral dosage of 40 mg constitutes an LD_{50}. The great difference was attributed to failure of fluorocitrate to reach aconitase within critical cells of the brain and the heart (Peters and Shorthouse 1971).

Research conducted by Gal *et al.* (1961) showed that rats metabolise 1080 to non-toxic metabolites and can excrete monofluoroacetate as well as its toxic metabolite, fluorocitrate, in the urine (Atzert 1971). Gal *et al.* (1961) demonstrated that during the four-day exposure period after ip administration of 1.77 mg kg^{-1} of radioactive 1080 into rats, 30-35% of a dose of 1080 administered to rats was excreted unchanged in the urine, and by the fifth day less than 0.2% was excreted. Furthermore, these authors concluded that there were unidentified metabolites present other than fluoroacetate and fluorocitrate. Urinary fluoroacetate sharply decreased after 48 hours while that of fluorocitrate reached maximum in 24 hours. The toxic metabolite fluorocitrate in the

urine represented only 3% of the total fluoroacetate-2-C^{14} administered. The same authors reported that the liver displayed no citrate accumulation, which may provide evidence that the conversion of fluoroacetate into fluorocitrate must be a minor pathway of fluoroacetate metabolism in the liver consistent with the findings of Buffa and Peters (1950).

Kostyniak (1979) stated that administration of 375 mg diethylmaleate enhanced the toxicity of fluoroacetate in rats injected intraperitoneally with 1, 1.5, 2.5, 3.5, 4, 4.5, or 5.5 mg kg^{-1} 1080 due to a decrease in activity of the liver glutathione-dependent defluorinating system. Twigg (1986) reported that 15% depletion of glutathione levels in the rat was associated with a significantly greater elevation of plasma citrate levels in animals dosed with 1.5 mg kg^{-1} of 1080. Reduced glutathione plays a significant role during fluoroacetate poisoning. Glutathione is involved in the defluorination mechanism and also partially protects aconitase from the harmful effects of fluorocitrate (Twigg 1986; Mead *et al.* 1979). Mead *et al.* (1985) reported that fluorocitrate exerts its toxic action by covalently binding two glutathione-dependent enzymes which are located in the inner membrane of mitochondria. These enzymes are responsible for transporting citrate into and out of this organelle.

The fluoroacetate defluorinating activity of several organs of the Swiss mouse was investigated by Soiefer and Kostyniak (1983). The liver contained the highest fluoroacetate defluorinating activity followed by kidney, lung, heart and testes with no activity detected in the brain. This result is consistent with the findings that the heart (Whittem and Murray 1963) and testes (Sullivan *et al.* 1979) are the critical organs to the toxic effects of 1080 demonstrating the least defuorination activity compared with other organs, such as the kidney and the liver. Fluoroacetate is metabolised in animals and undergoes defluorination by liver enzymes in the presence of glutathione.

It was also demonstrated that the tolerance of emu to the toxic effects of 1080 could be largely attributed to emu's considerable capacity to detoxify fluoroacetate by defluorination via an enzymatic glutathione-dependent mechanism or to low susceptibility of aconitate hydratase to the fluorocitrate produced (Twigg *et al.* 1988). The detoxification process resulted to low citrate accumulation in the plasma (Twigg 1986).

Adult rats administered with single doses of 1080 at 5.8, 3.3., and 1.8 mg kg^{-1} bw by stomach tube were sacrificed and the level of 1080 in their tissues analysed. Fasted rats given a total dose of 49.1 mg (equivalent to 5.8 mg kg^{-1} bw) and sacrificed at the end of five hours estimated 1.5 mg kg^{-1} 1080 in the liver and 6.4 mg/kg in the heart. In urine and faeces, 0.23 mg kg^{-1} and 0.30 mg/kg were recovered, respectively. Surviving animals dosed with a single oral dose of 3.3 mg kg^{-1} bw and sacrificed at the end of 24 hours showed levels of 1080 two-fold lower in sacrificed than dead animals which implied that animals continued to metabolise 1080 while still alive (Hagan *et al.* 1950). Hagan *et al.* (1950) also found that animals given a total dose of 1.4 mg 1080 and sacrificed at 48 h found 0.14 mg kg^{-1} in the entire animal (excluding skin) and 0.17 mg kg^{-1} was excreted in urine and faeces. This study suggested that among the target organs tested, the least amount of 1080 was always found in the liver consistent with previous studies presumably because of the role of the liver in detoxifying fluoroacetate.

Male albino rats and male albino mice were administered either ip or orally with fluoroacetate but only ip to mice. Tecle and Casida (1989) concluded in their study that the metabolic defluorination of fluoroacetate is attributable to both conjugation of fluoroacetate with glutathione and conversion to (-)-*erythro*-fluorocitrate, which is both an inhibitor of and a substrate for aconitase. The urine of rats and mice administered with fluoroacetate or (-)-*erythro*-fluorocitrate showed elevated levels of citrate and glucose and diminished urea consistent with disruption in the TCA cycle and ammonia metabolism.

The metabolism of fluoroacetate in the skink (*Tiliqua rugosa*) and the rat (*Rattus norvegicus*) was investigated by Twigg *et al.* (1986). Rats administered ip with 3 mg kg^{-1} bw in aqueous solution produced a five-fold increase in plasma citrate levels within 4 hours whereas skinks administered with 100 mg/kg bw showed a 3-4 fold increase in plasma citrate levels 48 hours after dosing.

3.4.1 Variation in susceptibility

The sensitivity and exposure of animals to 1080 has formed the basis for assessing the potential risk of non-target animals being killed by the poison during pest control programmes. In many cases, measurements of sensitivity can provide this function, indicating which species are particularly tolerant and likely to survive ingestion of poison baits or other poisoned animals.

Very young animals, such as the pouch young of marsupials, can be more sensitive to 1080 than other members of their population, either by eating baits directly or indirectly by ingesting 1080 in their mother's milk (McIlroy 1981b). The body weight is also important. Obviously the larger the body size of an animal is, the more 1080 it will have to ingest to receive a lethal dose (McIlroy 1982).

Compound 1080 exerts variable toxicity in different species. To illustrate, the LD_{50} varies from 0.06 mg kg^{-1} in the dog to over 500 mg kg^{-1} in the South African toad, *Xenopus laevis* (Chenoweth 1949). Amphibians and reptiles are more resistant to 1080 than mammals and birds because of their greater ability to detoxify fluoroacetate by defluorination, a reduced ability to convert fluoroacetate to fluorocitrate, and an aconitase hydratase enzyme that is comparatively insensitive to fluorocitrate inhibition. In reptiles, the LD_{50} value was greater than 54 mg kg^{-1} body weight (bw) while in amphibians the LD_{50} value was greater than 44 mg kg^{-1} bw (Eisler 1995).

Warm-blooded species varied considerably in their response to 1080. A study of species sensitivity showed that among the warm-blooded species, primates and all types of birds were generally the least susceptible to 1080 poisoning, whereas the carnivora and wild rodents appeared to be particularly sensitive (Chenoweth 1949). Among the 171 species of mammals for which there are data, variability was considerable in the time until signs of poisoning became apparent (0.1 hour to greater than 7 days), the time to death (0.1 hour to greater than 21 days), and the time until animals began to show signs of recovery (2 hours to 18 days) (McIlroy 1986).

Mammals with low metabolic rates such as marsupial carnivores seemed to be more tolerant than mammals with higher metabolism such as eutharian carnivores to a poison such as 1080 that interferes with metabolism (McIlroy 1981a, 1981b). Likewise, amphibians and reptiles, which have lower metabolic rates than birds and mammals, are less sensitive to 1080, while non-passerine birds, which mostly have lower metabolic rates than passerine birds, often seem to be more sensitive to 1080 (McIlroy 1984). The differences in sensitivity to 1080 appeared to be caused by species-specific metabolism, but it is not clear what exactly was involved (McIlroy 1984).

The toxic effects vary amongst different animals. In some, it affected the heart while it caused tonic convulsions in others (Peters 1963). Among herbivores, 1080-induced deaths were due primarily to cardiac disorders; among carnivores, deaths were from central nervous system (CNS) disorders; and among omnivores, deaths were from both cardiac and CNS disorders (Atzert 1971). Some mammals also displayed parasympathetic nervous system effects including increased salivation, urination, and defecation and eventual cardiac failure (Hudson *et al.* 1984). There remain unexplained species differences in fatal 1080 poisonings. Dogs died from convulsions or respiratory paralysis, but monkeys, horses, and rabbits died from ventricular fibrillation (Murphy 1986).

Compound 1080 acts mainly on the central nervous system and the heart. It seems that there are species in which fluoroacetate affected chiefly the heart, such as the rabbit, the goat, and the horse, and others in which only the central nervous system was affected, such as the dog, the guinea pig, and the frog. In the cat, the rhesus monkey, domestic pig, and birds, both systems are involved (Pelfrene 1991).

In rats treated with 3mg kg^{-1} of fluoroacetate, a five-fold elevation in serum citrate and 15-fold increase in heart citrate accumulation were observed. In contrast, citrate accumulation in dogs was less pronounced exhibiting a 2-3 fold increase in the heart and serum (Bosakoswki and Levin 1986). Correlations were demonstrated between serum citrate levels and various biochemical changes in rats and dogs intoxicated with fluoroacetate. For dogs, serum citrate correlated well with heart citrate accumulation, elevated serum glucose, and depressed serum total calcium. For rats, serum citrate was

well correlated with heart citrate accumulation, heart ATP depletion, and elevated serum glucose (Bosakoswki and Levin 1986). Heart ATP depletion in dogs was not significantly affected in contrast to rats. Death is believed to result from repeated and prolonged convulsions and respiratory arrest, and not from cardiac changes (Chenoweth 1949). Dogs showed a longer latent period than for rat, even though dogs displayed a higher susceptibility to fluoroacetate. Although species differences were noted, serious clinical signs and death were always associated with highly elevated serum citrate levels.

Signs of 1080 intoxication, such as nausea, vomiting, and heart or respiratory failure occurred in most species within 0.5 to 2 hours after ingestion (Eason *et al.* 1994b). Most of the deaths in mammals generally occurred between 8 and 48 hours after ingestion of a lethal dose (Eason *et al.* 1994b).

3.4.2 Latent period

A characteristic feature of fluoroacetate poisoning is the latent period, which usually ranges from 30 minutes to 2 hours before the onset of symptoms (Pattison and Peters 1959; Atzert 1971; Twigg 1994). The length of the delay or latent period until signs of 1080 poisoning appear has been accounted for by the time necessary for its metabolism and biochemical mode of action (Chenoweth 1949; Atzert 1971; McIlroy 1982; Pelfrene 1991). Fluoroacetate metabolism was generally rather slow in most animals (McIlroy 1981a). Hence, the latent period following the administration of 1080 and response via any route was unusually long and variable. This has been demonstrated in numerous studies (Chenoweth 1949; Atzert 1971; Hudson *et al.* 1984; McIlroy 1986; Batcheler 1978). Rabbits, mice, goats and sheep that received small sub-lethal doses of 1080 showed clinical signs, metabolised and excreted 1080 within 1-4 days, and then recovered (Eason *et al.* 1994b). In general, herbivores such as possums exhibited signs of cardiac failure after ingestion of a lethal dose. In contrast, carnivores experienced predominantly central nervous system disturbances and convulsions with death due to respiratory failure (Egekeze and Oehme 1979).

3.4.3 Tolerance to sub-lethal doses

Tolerance to 1080 is a time related phenomenon and exposure to repeated sub-lethal doses of 1080 has increased the tolerance of some species to the toxic effects of 1080 (Atzert 1971). Kalmbach (1945) noted that laboratory white rats appeared to have acquired tolerance to 1080 by the ingestion of sublethal doses for a period of 5-14 days. Cessation of dosing for 7 days caused a loss of tolerance. Miller and Phillips (1955) found that a dietary level of 20 mg kg^{-1} (20 ppm) in rats inhibited the growth rate sharply during the first week. Rats gained tolerance to 1080 for less than two weeks and their growth rate gradually became normal within 3 to 4 weeks. Rats that had adjusted to 1080 showed a second retardation of growth when returned to a dietary level of 20 ppm after two weeks on a normal diet. It was also noted that rats conditioned to a dietary level of 20 ppm were then able to adapt to a dietary level of 40 ppm. The amount of food given to test animals was not specified although the report mentioned that the dose was greater than the single LD_{50} dose per day.

Mink and ferrets may also acquire some tolerance for 1080 (Hornshaw *et al.* 1986). This was evident when animals were given lower concentrations of 1080 in their diets during the first two weeks of the test. The same animals were able to tolerate greater concentrations of 1080 during the third and fourth weeks of the exposure period.

Animals have developed tolerance to fluoroacetate in places, such as Australia and South Africa, where indigenous plants produce fluoroacetate. However, the biochemical mechanisms responsible for the tolerance remain poorly understood (Twigg 1994).

Chapter 4

Toxicological Hazards

4.1 Effects on Laboratory Animals and *in vitro* systems

Beasley (1996) highlighted that there have been many studies conducted on the acute toxicity of 1080, in particular studies characterising the lethal dose. Although acute toxicity is outside the scope of this project, an overview has been provided in this chapter, as it has contributed to the greater understanding of the toxicological hazards of 1080. Only studies containing information that may assist in the human health risk assessment have been reviewed in detail.

Studies on the possible toxic effects from repeated exposures are limited, and the few chronic studies available have employed relatively high doses, and/or unusual routes of administration, such as intraperitoneal injection. The results therefore may not be applicable to human exposures, since relevant exposures are by ingestion, inhalation or dermal absorption. However, Chenoweth (1949) suggested that it appeared that there was no striking difference between non-percutaneous routes of exposures on the resulting toxic effects of 1080, i.e., whether it is administered orally, subcutaneously, intramuscularly, intraperitoneally or intravenously. Chenoweth (1949) further said that this phenomenon was uncommon in the field of pharmacology. This could probably due to the long latent period before symptoms can be produced, which allows time for absorption. Hence, all studies which are relevant to human exposures mentioned earlier have been considered for health risk assessment purposes.

4.1.1 Acute toxicity

Acute toxicity for purposes of this discussion is expressed as the median lethal dose (LD_{50}), which is defined as the statistically derived single dose of a chemical that can be expected to cause death in 50% of a given population of organisms under a defined set of experimental conditions (IPCS 2000a) unless otherwise specified.

Acute oral toxicity

Compound 1080 lacks one of the properties desirable in an ideal vertebrate toxic agent. It is a potent poison for all mammals, including humans. Compound 1080 is highly toxic to a wide range of animals by all common routes of administration. Most unadapted mammals have been fatally poisoned by less than 2 mg kg^{-1} (Atzert 1971). Estimates of the mean lethal dose in humans range from 2 to 10 mg kg^{-1} (Gajdusek and Luther 1950; Harrison *et al.* 1952). A lethal dose of 1080 in humans caused either nervous system (e.g., convulsions) or cardiac effects after a latent period (Harrison *et al.* 1952). Symptoms of 1080 intoxication included laboured breathing, vomiting, lethargy, muscular incoordination, weakness, and tremors (Chenoweth 1949; Atzert 1971; Hudson *et al.* 1984; Murphy 1986; Eason and Frampton 1991).

Mammals were the least resistant tested group against 1080 but a wide difference in the LD_{50} between mammals was also noted. Individuals of sensitive species died after receiving a single dose of 0.05-0.2 mg kg^{-1} bw. The difference in sensitivity by a number of species including the route of administration is illustrated in Table 3.

Table 3

Acute toxicity after single administration of 1080*

Species	Route	LD_{50} (mg kg^{-1})
Rat	Oral	0.22
Rat	Oral	2.5
Rat	Oral	1-2
Rat	Intraperitoneal	3-5
Mouse	Subcutaneous	19.3
Mouse	Subcutaneous	17.0
Mouse	Intraperitoneal	10.0
Mouse	Intraperitoneal	16.5
Mouse	Intraperitoneal	14.7
Guinea pig	Oral	0.4
Guinea pig	Intraperitoneal	0.37
Rabbit	Subcutaneous	0.28
Dog	Oral	0.06
Cow	Oral	0.39
Calf	Oral	0.22
Possum	Oral	0.79
Mallard duck	Oral	4.8
South African clawed toad (*Xenopus laevis*)	Oral	500

* Source: Pelfrene 1991

Acute dermal toxicity

Four dose levels of 1080 paste (vehicle unspecified) were dermally applied to rabbits and the estimated LD_{50} was 324 mg kg^{-1} for females and 277 mg kg^{-1} for males. Based on these data, 1080 was classified as a dermal toxicant (Fagerstone *et al.* 1994). Atzert (1971) suggested that 1080 is poorly absorbed in intact skin. However, the results from this study demonstrate that the oral toxicity is 200 times more than the dermal toxicity and this implies that less than 1% absorption occurs.

a. Primary dermal irritation test

One percent 1080 (vehicle unspecified) was kept in contact with the skin of rabbits for 4 hours. The compound did not cause significant erythema and oedema and mild or slight dermal irritation was observed at 72 hours (Fagerstone *et al.* 1994).

b. Primary eye irritation test in rabbit

One percent 1080 solution (vehicle and volume not stated) was applied to the conjunctival sac of the eye, causing slight conjunctival irritation and no corneal opacity or iritis (Fagerstone *et al.* 1994).

4.1.2 Single/Repeated exposure

a. Reproductive toxicity

Effects on testes

Reduction in plasma testosterone concentrations and degeneration of seminiferous tubules were observed in lizards exposed to repeated sublethal doses equivalent to 100 and 200 mg kg^{-1} day^{-1} for 15 days (Twigg *et al.* 1988). Savarie (1984) also observed that 1080 exposures resulted in testicular damage and elevated concentrations of citrate after the 15-day exposure period (Twigg *et al.* 1986). Degeneration of seminiferous tubules was observed in testes from some of the lizards treated at a single dose of 100

or 250 mg kg^{-1}. Some lizards received multiple doses of 5 (5x), 20 (5x), or 50 mg kg^{-1} day^{-1} (5x) for 15 days. The lowest dose in the study was 5 mg kg^{-1} which was 20-fold higher than the highest dose used in the pivotal study exhibiting overt signs of testicular toxicity in rats. Sullivan *et al.* (1979) considered that the testis was the organ most vulnerable to 1080 poisoning. Overt signs of toxicity were observed in rats weighing 165-180 g after 7 days exposure to 1080 at concentrations of 6.6 ppm (ingested a daily average of 0.037 mg rat $^{-1}$ or 0.18 mg kg^{-1}) or 20 ppm (ingested a daily average of 0.14 mg rat $^{-1}$ or 0.71 mg kg^{-1}). Six rats per group were euthanised daily during the 7-day treatment and others at 3, 7, 14 and 21 days after the end of each treatment period. These effects included decreased testicular weight, morphological damage to the testes, degeneration of seminiferous tubules, and altered spermatogenesis. Regeneration started to occur on the 7th day of treatment and spermatogenesis was still abnormal by day 21 after treatment. Testicular changes in rats exposed to 2.2 ppm 1080 (ingested a daily average of 0.016 mg rat $^{-1}$ or 0.078 mg kg^{-1}) were not as widespread as those exposed at higher concentrations of 1080 and all testes were histologically normal 7 days after treatment. Because of the short exposure time, this study is not comparable to the 90-day study of Eason *et al.* (2001) and Eason and Turck (2002) where the rats under study did not recover during the 56-day recovery period.

Five Sprague-Dawley rats weighing 400-450 g were administered 20 ppm fluoroacetate in drinking water for 7 days. There were sharp decreases in sperm counts during treatment, but the sperm counts of all animals, after treatment, were practically zero in approximately 3 weeks. Sixty-five days after treatment, partial sperm count recovery was observed in two of these rats. The five treated rats all showed advanced patchy degeneration changes, primarily sloughing and aggregation of spermatozoa, which fused to form striking multinucleated forms. Several tubules also showed an intermediate coagulative necrosis. In all five rats, both epididymides contained luminal cellular necrosis (Al-Juburi *et al.* 1989). Al-Juburi *et al.* (1989) claimed that the rats were treated with doses of fluoroacetate similar to those used by Sullivan and co-workers (1979) and that the results were similar. However, direct comparison cannot be made because Al-Juburi *et al.* (1989) only provided the concentration of 1080 while the water intake was actually measured by Sullivan *et al.* (1979), which permitted estimates of fluoroacetate ingested by animals.

In another study, laboratory rats exposed for a period of approximately four months to 26 ppm of 1080 in drinking water (consumption volumes not specified) showed severe damage of the testes, characterised by massive disorganisation of the seminiferous tubules, nearly total loss of functional cells, absence of sperm, and damage to the Sertoli cells (Smith *et al.* 1977). Regressive modifications of the seminiferous tubules were observed by Mazzanti *et al.* (1965) in the testes of albino rats. No NOAEL[1] was established from this older study. The main objective was ascertaining the presence of fluoride in the skeletal system. This study was written in Italian and only a very short summary was provided in English, describing only the testicular effects of 1080.

Eisler (1995) noted that sublethal effects of 1080 included testicular damage in rats after exposure to 0.07-0.71 mg kg^{-1} drinking water for 7 days. This study demonstrated that testicular effects of 1080 were manifested after a relatively short period of time and consistently at high levels of exposures.

A dose-response relationship was observed in minks and ferrets after dietary exposure to 1080. Minks suffered severe impaired reproduction presumed to be due to oligo- or aspermia, or spermatopathy after dietary exposure to 0.80 ppm of 1080 for two months (Hornshaw *et al.* 1986). Animals were fed with diets containing 0.05, 0.20 or 0.80 ppm of 1080, resulting in estimated average dose of 0.01, 0.045, and 0.165 mg day^{-1}, respectively based on their daily food consumption. No NOEL/NOAEL was reported from this study. In the same study, young ferrets were exposed to 1.08, 1.94, and 3.50 ppm of 1080, resulting in an estimated average dose of 0.26, 0.40, and 0.60 mg day^{-1}, respectively based on their daily food consumption. Reduction in testes weights was observed at 1.94 and 3.50 ppm of 1080 (significantly different from control, $p \leq 0.05$). In comparison, adult ferrets were exposed to 4.76, 8.56, and 15.40 ppm of 1080, resulting in estimated average doses of 0.66, 0.84, and 0.80 mg day^{-1}, respectively, based on their daily food consumption. Testes weights, although reduced, were not significantly different from the control. This illustrates that young ferrets were more

[1] NOAEL is the highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects (IPCS 2000a)).

susceptible to the toxic effects of 1080 than adults with regard to testes weight because their food consumption is almost twice than the adults, i.e., cumulative food intake for 4 weeks is 6,937 g vs 3,528 g.

In another study (Shinoda *et al.* 2000), single oral doses of 1080, either 0.5 or 1.0 mg kg^{-1} was administered for a short period of time. Sprague-Dawley rats showed signs of testicular toxicity after a single oral dose of 1.0 mg kg^{-1} and were sacrificed 6 to 72 hours later. Necrosis in spermatids, probably resulting from rapid and severe adenosine triphosphate (ATP) depletion, and apoptosis in spermatogonia from gradual and partial ATP depletion, was observed. At a later stage, it was noted that 1080 inhibited spontaneous spermatogonial apoptosis.

In an investigation carried out by Wolfe (1988) to evaluate the subchronic toxicity of 1080, Sprague-Dawley rats were dosed by oral gavage with 0.05, 0.20, and 0.50 mg $kg^{-1}day^{-1}$ 1080 for a period of 13 weeks. Treatment-related findings included decreased testes/epididymides weights, testicular changes and immature/abnormal and reduced number of sperms in the epididymal ducts and epididymides. A NOEL of 0.05 mg $kg^{-1}day^{-1}$ was reported in this study. In another study (Eason *et al.* 2001; Eason and Turck 2002), Sprague-Dawley rats, about 6 weeks of age, were dosed with 1080-treated water at 0.025, 0.075, and 0.25 mg $kg^{-1}day^{-1}$ by oral gavage for 90 days. Findings at necroscopy (date of terminal sacrifice not specified) included severe hypospermia of the epididymis and severe degeneration of the seminiferous tubules of the testes in male rats dosed with 0.25 mg $kg^{-1}day^{-1}$. It was confirmed that recovery from testicular damage did not occur even after 56 days without treatment. The NOAEL for rats administered with 1080 via oral gavage for 90 days was 0.075 mg $kg^{-1}day^{-1}$. The spacing between doses in these two studies is relatively close with one another, therefore the LOAELS and NOAELS should not be considered significantly different.

b. Myocardial toxicity

Rammel (1993) and Eason *et al.* (1994b) claimed that cumulative damage to the heart or other organs from repeated exposure to large sublethal doses of 1080 can occur in sheep (*Ovis aries*). Smaller doses of 1080 given at regular intervals produced

cumulative effects (Annison *et al.* 1960) and resulted in myocardial damage in sheep, probably due to increased accumulation of citrate in the heart. The cumulative effect of 1080 has been noted in other species, such as the rat. This has been attributed largely to the slowness of the kidney in clearing fluoroacetate in the body (Chenoweth 1949). Sheep were affected differently from rats in that further doses following the initial administration of 1080 proved to be fatal. Rats were able to tolerate non-fatal dose of 1080 for the next 24 to 36 hours following further administration of 1080. This finding appeared to suggest that larger animals are affected differently than smaller animals. However, there has been little reliable information on 1080's action and toxicity in the larger domestic animals (Annison *et al.* 1960) and therefore the observed differences could not be directly compared. Whether or not elimination mechanisms in larger animals, such as sheep, are relevant to humans has remained unknown.

It has been suggested that 1080 was rapidly eliminated in all species tested, hence it is not cumulative (Rammell 1993), but repeated exposure to sublethal doses of 1080 can result in cumulative damage to the heart or other organs (Peters 1963; Annison *et al.* 1960). Inflammation of the heart occurred in rats exposed to 1080 at dosages of 0.05, 0.20, and 0.50 mg $kg^{-1}day^{-1}$ for 13 weeks by oral gavage (Wolfe 1988).

Merino sheep treated with a single high dose of 0.5-1.0 mg kg^{-1} bw 1080 dosed by stomach tube on Lucerne hay exhibited myocardial lesions which were sometimes inconspicuous. Multifocal areas of necrosis in various stages of development were observed in animals subacutely and chronically treated (over 167 days in one sheep) at a lower dose range of 0.05-0.1 mg $kg^{-1}day^{-1}$ (Schultz *et al.* 1982). This latter experiment was conducted at various duration of exposures, e.g., 41, 66, 33 days.

The citrate content of hearts of rats injected intraperitoneally with 20 mg kg^{-1} bw was examined, and citrate accumulation was observed in 1080-poisoned tissues (Williamson *et al.* 1964). The 1080 treatment was given 30 minutes before the hearts were removed. The results suggested that although the initial effect of fluoroacetate is to give rise to fluorocitrate and disrupt the TCA cycle, the secondary inhibition of phosphofructokinase by the accumulated citrate was lethal. This was due to the cell's

deprivation of pyruvate which would eventually overcome aconitase inhibition (Williamson *et al.* 1964).

Acute multifocal injury to the myocardium, after 1080 doses as low as 0.11 mg $kg^{-1}day^{-1}$ for 3-7 days, was observed in several research studies carried out in Australia (Eason *et al.* 1994b). Whittem and Murray (1963) demonstrated mild but characteristic cardiac histopathology in sheep dosed with 0.055 mg $kg^{-1}day^{-1}$ of fluoroacetate by stomach tube, and typical cardiac histopathology at 0.11 mg kg^{-1} day^{-1}. However, the duration of this study was not specified. The same authors compared the poisoning arising from the gidea plant (*Acacia georginae*) and potassium fluoroacetate poisoning in sheep. One group of sheep was fed with powdered gidea and another with purified potassium fluoroacetate at similar dose rates, i.e., 0.22 mg potassium fluoroacetate kg^{-1} day^{-1} equivalent to 7.3 g powdered gidea leaf kg^{-1} day^{-1}. This comparison was made based on the assumption that all organically bound fluorine in gidea was as toxic as potassium fluoroacetate, for an unspecified period of exposure. Because palatability became a problem, sheep were fed by stomach tube with either a watery suspension or various extracts of finely hammer-milled gidea leaves. Similar symptoms, such as sudden collapse, spasmodic breathing, and typical cardiac histopathology, such as acute myocardial damage were observed in animals fed gidea which suggested that fluoroacetate in gidea was as toxic as potassium fluoroacetate. In the same study, similar acute myocardial lesions were found in the hearts of sheep and guinea pigs treated with potassium fluoroacetate. Whittem and Murray (1963) suggested that the most susceptible target organ is the myocardium as revealed by the pathologic lesions.

Peters *et al.* (1972) and Savarie (1984) suggested that fluorocitrate was present in smaller amounts than fluoroacetate and it was not as toxic as fluoroacetate after oral ingestion or parenteral administration. These authors further concluded that the decreased fluorocitrate toxicity was apparently due to its larger molecular size, which would not be so readily absorbed through tissues. The toxic principle in gidea was identified as the fluoroacetate ion by conversion to the butyl ester and the use of gas chromatography. Infra-red absorption spectra confirmed the identification of fluoroacetate (Oelrichs and McEwan 1961).

Eason *et al.* (2001) and Eason and Turck (2002) noted increases in heart weight in both male and female Sprague-Dawley rats, about 6 weeks of age, when compared with controls. The test animals were treated with 1080 in drinking water at doses of 0.025, 0.075, and 0.25 mg $kg^{-1}day^{-1}$ by the oral route for a period of 90 days. No effects were noted in the lower dose groups. Cardiomyopathy was only seen in 50% (10/20) of males dosed with 1080 at 0.25 mg $kg^{-1}day^{-1}$ and 5% (1/20) female rat, suggesting a gender difference. The NOAEL for rats was reported to be 0.075 mg $kg^{-1}day^{-1}$ by the same authors.

c. Developmental toxicity (teratogenic effects))

Spielmann *et al.* (1973) found no macroscopically visible malformations in female rat embryos after exposure to single doses of 1 mg kg^{-1} 1080 on days 9, 10, or 11 of pregnancy and killed at day 20. No abnormalities were detected by examination of skeletons stained to detect abnormalities (stain not stated) and retardation of ossification. The authors concluded that 1080 was not teratogenic. However, this conclusion was in contrast to the findings of De Meyer and De Plaen (1964) who found that 1080 administered intraperitoneally on the 9th day of pregnancy in rats at a dose of 600 µg had caused eye anomalies, syndactylia and evisceration. The authors did not provide further details about the teratogenic study and the teratogenic effects reported were only mentioned in the introduction of their paper.

A more recent study by Eason *et al.* (1998, 1999) confirmed that 1080 caused developmental defects in rats when pregnant females were exposed to 0.10, 0.33 and 0.75 mg $kg^{-1}day^{-1}$ of 1080 diet by the oral route on a daily basis during the period of organogenesis (from days 6 through to 17 of gestation). The highest dose (0.75 mg $kg^{-1}day^{-1}$) showed irreversible limb abnormalities and the next highest dose (0.33 mg $kg^{-1}day^{-1}$) showed reversible rib defects. A NOAEL was reported at 0.10 mg kg^{-1} day^{-1}. Although Spielmann *et al.* (1973) used a higher dose than that used by Eason *et al.* (1998, 1999), the two studies cannot be directly compared since only a single dose was used by Spielmann *et al.* (1973) as opposed to the multiple doses used by Eason *et al.* (1998, 1999). De Meyer and De Plaen (1964) also confirmed positive teratogenic effects although no further information was provided, as mentioned earlier.

The Ministry of Health considered that this teratology study demonstrated that 1080 was a teratogen in the rat strain in that it caused irreversible abnormality in offspring at exposure levels (in the dams) which were below those that caused maternal toxicity (Durham 1998a).

d. Renal toxicity

An earlier study by Cater and Peters (1961) investigated acute 1080 poisoning in rats and reported swelling and blockage of the proximal convoluted tubules and distension of the Bowmans capsule. High doses of 1080 administered intraperitoneally were applied in this case, i.e., 60 or 80 mg kg^{-1} causing death in some animals within about 2 hours. Rats subjected to multiple doses of fluorocitrate totalling 150 mg kg^{-1} (15 mg kg^{-1} on day 0, 10 mg on day 1, 5 mg/day on day 2 and 3, 10 mg on day 4, 15 mg on day 7, 60 mg on day 9 and 30 mg on day 10) in 10 days, showed changes similar to those found in the kidneys of patients dying with lipid nephrosis, i.e., fatty degeneration in the walls of the arcuate, interlobular and glomerular arteries (Cater and Peters 1961). The exact period of exposure was not stated and the expression "in about" was used consistently in the report. As acknowledged by the authors, the single doses used were lethal and multiple doses were consistently very high. The doses applied were several fold higher than the maximum dose used by Eason *et al.* (2001) and Eason and Turck (2002) of 0.1 mg kg^{-1}.

Single intraperitoneal injection of large doses of 1080 (15 or 60 mg kg^{-1} bw) in rats resulted in swelling of the proximal convoluted tubules of the kidney at 15 mg kg^{-1}. This change persisted in the distal segments and involved widespread necrosis at 60 mg kg^{-1}. The extent of the damage was dose dependent and cellular damage was reversible at 15 mg kg^{-1} (McDowell 1972a). In another study, McDowell (1972b) demonstrated that administration of 1080 at 3.5, 20 and 60 mg kg^{-1} bw by intraperitoneal injection caused swelling of the proximal convoluted tubules of the kidney and the change was reversible at 3.5 mg kg^{-1}. Compound 1080 also damaged the proximal convoluted tubules of the rat kidney but the effect was not dose-dependent.

An investigation of the 1080 effects on the rat testis by Sullivan *et al.* (1979) included examining its effects on the kidney. Exposure concentrations used were 2.2 (0.016 mg rat^{-1} or 0.07 mg kg^{-1}), 6.6 (0.037 mg rat^{-1} or 0.18 mg kg^{-1}), and 20 ppm (0.14 mg rat^{-1} or 0.71 mg kg^{-1}) in drinking water for a period of 7 days. Results showed normal organ weights, ATP concentrations, and histological appearances. A significant accumulation of citrate was noted in kidneys of rats exposed to 20 ppm of 1080.

It is evident from studies that have been analysed that the kidney responded to the overt effects of 1080 only when rats were exposed to high doses. Later repeated-dose studies at lower doses, such as that of Eason *et al.* (2001) and Eason and Turck (2002), did not report the kidney as a target organ. No published article has claimed that the kidney was a critical organ to the adverse effects of 1080. Supporting this notion were observations made by Chenoweth (1949) and Chung (1984) that the kidney tissue was observed to be very sensitive *in vitro* but the renal dynamics did not seem to be affected to any significant extent *in vivo*. This may explain why the kidney appears not to be a critical organ for toxic effects of 1080.

4.1.3 Genotoxicity

Eason *et al.* (1999) showed that 1080 was not mutagenic using three complementary cell mutation and chromosomal aberration tests (Ames assay, mouse lymphoma assay and the micronucleus test). The results comprised negative results and hence there is good (but not conclusive) evidence that 1080 is not genotoxic. Genotoxicity testing only provides information about possible genotoxic potential, and substances with this potential are suspected of being carcinogenic. However, the final proof can only be determined from long term animal exposure (Kroes 1995).

4.2 Effects on humans

Human data

No epidemiological studies have been identified to date designed to ascertain the chronic effects of 1080 following long-term exposure in humans. However, there have been some reported cases on acute 1080 poisoning which may provide an understanding of the toxic effects of 1080 in humans. The symptoms observed were limited to cases of acute poisonings.

The main symptoms of acute poisoning in humans were vomiting, CNS disorders including convulsions, heart failure, and death. Typically, symptoms first appeared 1 to 2 hours after ingesting the 1080, although the onset of symptoms depended upon the dose received (Rammel and Flemming 1978). Both the heart and the CNS were affected, death usually resulting from respiratory failure during convulsions, and occasionally due to ventricular fibrillation (Trabes *et al.* 1983). The high levels of fluoroacetate in the urine indicated rapid urinary excretion. This was significant because in spite of gastric lavage, death usually ensued by about 17 hours after ingestion of the poison (Harrison *et al.* 1952). Of particular interest, however, is the case of a 17-year old boy who lived for five days after ingesting 1080 (Brockmann *et al.* 1955).

According to Reigart *et al.* (1975), the CNS effects were agitation, depressed consciousness, seizures, and eventually coma. The cardiovascular effects, which often resulted in death, may be ventricular tachycardia and fibrillation. Children appeared to be more prone to myocardial failure than to ventricular fibrillation. After successful resuscitation from cardiac arrest, a poisoned child was left with severe neurologic impairment (McTaggart 1970). The response in adults to 1080 may be identical to that of the rhesus monkey (Chenoweth 1949), with death usually due to ventricular fibrillation (Murphy 1986).

Based on fatal or near fatal cases of human poisonings, the dangerous dose for humans was estimated to be 0.5 - 2.0 mg kg^{-1} bw (Chenoweth 1949; Rammel and Flemming

1978). Human poisoning with 1080 further illustrates differences in the clinical picture observed among mammals. Cardiac and CNS effects were both important, the CNS effects predominating. The clinical picture was somewhat similar to that observed in the cat, pig and rhesus monkey, but most close to that of the cat (Gajdusek and Luther 1950).

There were two 1080 poisoning incidents related to occupational exposures. The first report of chronic poisoning by 1080 concerned a New Zealand rabitter (Parkin *et al.* 1977; Gosselin *et al.* 1984). However, the alleged chronic 1080 poisoning was disputed by Peters (1977), Rammel *et al.* (1977), and Ramsay (1977) as there was no evidence that 1080 was involved. These authors claimed that analysis of fluorine in urine was not a validated indicator of 1080 exposure. It was noteworthy that the autopsy revealed petechial haemorrhages and congestion of the organs that included diffuse tubular degeneration of the kidneys (Pelfrene 1991). In the second case, neurologic, liver, kidney, and thyroid dysfunction was observed in an exterminator who was repeatedly exposed to 1080 during a 10-year period (Parkin *et al.*1977).

In an unusual case of occupational exposure, a gust of wind blew 1080 powder into a worker's face, and some was inhaled. Symptoms observed were immediate tingling sensation around corners of the mouth and in nasal passages, salivation, loss of speech, numbness of the entire face, and blurred vision. Although paraesthesia spread to arms and legs and violent convulsions and coma followed, the worker recovered completely (Grant 1986).

From 1971 to 1981, the National Poisons Centre of Israel collected 111 cases of accidental or unintentional poisoning with 1080. These cases included three cases of death and one case of mass accidental poisoning affecting 30 children. A small number of wheat grain baits impregnated with 1080 were involved and those affected did not suffer from clinical symptoms of poisoning (Roy *et al.* 1982 [2], as cited by Pelfrene 1991). In addition, there were five cases of acute 1080 poisoning collected between 1975 and 1981 in Taiwan. Acute reversible renal failure or frank uraemia was

[2] The original is published in Hebrew.

observed in cases where large amounts of 1080 (close to the estimated human LD_{50} of 5 mg kg^{-1} bw) ingested (Chung 1984).

At least 16 fatalities have been reported from high acute exposure by Pattison and Peters (1959). One child following ingestion of wheat impregnated with 1080 was left with severe neurologic impairment after successful resuscitation from cardiac arrest (McTaggart 1970). There were also reported cases of visual impairment in patients, but the nature and basis of blurring of vision have not been established either clinically or experimentally (Grant 1986).

A boy aged 2 years was accidentally poisoned by licking the 1080 crystals from the screw top of a 1080 poison bottle. Six hours after exposure, the boy exhibited signs of poisoning that included both central nervous signs (tonic convulsions) and cardiac signs. The dose received was unknown (Gajdusek and Luther 1950). Another case report described CNS abnormalities in a 15-year-old female intentionally ingested 1080. Immediate clinical features of intoxication were tachycardia, grand mal seizures, psychomotor agitation, and deterioration of consciousness. Neurological examination established dysfunction and moderate diffuse brain atrophy (Trabes *et al.* 1983).

In New Zealand, the only documented human fatality from 1080 was an apparent suicide. Twelve non-fatal human poisonings from 1080 have also been reported. However, no additional information is available relating to these events, as the database is incomplete (PCE 1994). Human poisonings from indirect sources, such as contaminated water or dead animals, have not been documented in New Zealand or overseas (PCE 1994).

4.3 Human Health Effect Toxicity End Points

This thesis is focussed specifically on the health effect toxicity end points needed to complete the health risk assessment and health risk management processes in order to address the public health implications of 1080 in relation to its continued use. These were repeated dose toxicity, genetic toxicity, and reproductive and developmental toxicity. The description for repeated dose toxicity was taken from the Organisation

for Economic Co-operation and Development's (OECD) Manual for Investigation of High Production Volume Chemicals (2004). Other terms are defined as prescribed in the Harmonised Integrated Hazard Classification System for Human Health and Environmental Effects of Chemical Substances (1998). It is important that these terminologies be defined to avoid varying interpretations.

Acute toxicity provides information on adverse health effects likely to arise from short-term exposure to a relatively high dose of chemical. It can be expressed as: *Acute oral toxicity* when the adverse effects occur within a short time of oral administration of a single dose of a substance or multiple doses given within 24 hours; *Acute dermal toxicity* when the adverse effects occur within a short time of dermal application of a single dose of a test substance; and *Acute inhalation toxicity* when the total of adverse effects is caused by a substance following a single uninterrupted exposure by inhalation over a short period of time (24 hours or less) to a substance capable of being inhaled.

Repeated dose toxicity (or subchronic toxicity) includes the adverse health outcomes resulting from a repeated dose of a chemical with duration of administration generally lasting for 14, 28, or 90 days.

Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring.

Developmental toxicity includes any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, up to the time of sexual maturation. The major manifestations of developmental toxicity include death of the developing organism, structural abnormalities, altered growth and functional deficiencies. Developmental toxicity can be considered a component of reproductive toxicity, and often it is difficult to distinguish between effects mediated through the parents and direct interaction with developmental processes.

Genetic toxicity applies to processes which alter the structure, information content, or segregation of deoxyribonucleic acid (DNA), including those which cause DNA damage by interfering with normal replication processes, or which in a non-physiological manner (temporarily) alters its replication.

Chronic toxicity includes adverse effects resulting from exposure over the animal's lifetime, or a major fraction thereof. The duration of the chronic study has been under debate for many years and different requirements exist in different countries (from 6-24 months). It also varies with species and parameters being studied.

4.4 Criteria in reviewing adequacy of toxicological data

4.4.1 Repeated-dose toxicity

In the area of repeated-dose toxicity, it is important to distinguish the following:

Short-term repeated dose study is performed to obtain information on the toxicity of a chemical after repeated administration and as an aid to establish doses for subchronic studies. It is obviously of shorter duration than a subchronic toxicity study. The duration is generally 14 or 28 days with the compound administered daily. As in the subchronic study, a dose range and number of doses should be chosen to allow demonstration of a No-Observed-Adverse-Effect-Level (NOAEL) or Lowest-Observed-Adverse-Effect-Level (LOAEL)[3].

Subchronic repeated dose study can last for different periods of time, but 90 days is the most common test duration. The animals must be given sufficiently high doses to elicit relevant toxic effects, and examined or tested in such a way as to document the toxic effects.

Subchronic studies for pesticide registration are usually conducted in two species, one of which is a rodent, by the route of most likely exposure (usually oral). The test is not

[3] The LOAEL is the lowest concentration or amount of a substance, which causes an adverse alteration of morphology, functional capacity, growth, development or life span of the target organism distinguishable from normal (control) organisms of the same species and strain under the same defined conditions.

capable of determining those effects that have a long latency period for development because the study duration is not necessarily sufficiently long to reveal delayed or chronic effects.

4.4.2 Chronic study

Long-term or chronic exposure studies are performed similarly to subchronic studies except that the period of exposure is longer than three months. In rodents, chronic exposures are usually for six months to two years. Chronic studies in non-rodent species are usually for one year but may be longer.

4.4.3 Reproductive study

Reproductive toxicity includes adverse effects on fertility in males and females. It covers any effect interfering with normal development both before and after birth, from conception to sexual maturity. The oral route is preferred. The highest dose should produce toxicity but not mortality in parents, and the lowest dose should not produce toxicity. It should include a NOAEL or a LOAEL. Two generations of animals with one litter per generation are generally utilised as the minimum reproductive study.

4.4.4 Developmental study

Developmental studies are intended to detect the potential for substances to produce embryotoxicity and birth defects. A properly conducted teratogenicity study should provide a satisfactory estimation of a NOAEL or a LOAEL as well as an obvious effect level for maternal toxicity. Embryotoxicity or teratogenicity occurring only at maternally toxic dose levels have less relevance than similar effects produced by doses that have no adverse effects on the dams.

The selection of species is particularly important because there may be wide differences in sensitivity as evidenced by the lack of teratogenicity of thalidomide in rats. It is generally considered essential that a second non-rodent species be studied and the rabbit is the most commonly used second species.

Chapter 5

Health Risk Assessment

5.1 Health risk assessment

Risk is described as the likelihood that an adverse outcome will occur when a person or group is exposed to a particular concentration or dose of a substance for a specific period of time (Paustenbach 1989; IPCS 2000b). Risk therefore can be expressed as risk (R) equals toxicity (T) times exposure (E), or $R = T * E$.

Risk assessment puts the concepts of toxicity, hazard, and risk into a consistent framework (Yosie 1987). Risk is determined by the combined relationship between exposure and toxicity, specifically in determining whether adequate exposure benchmarks exist to compare with toxicologically acceptable levels or levels of concern, which needs urgent attention (Covello and Merkhofer 1993). The classic pesticide risk assessment paradigm is a four-step procedure consisting of hazard identification, dose response, exposure assessment, and risk characterisation (NRC 1983).

It is recognised that in the absence of risk assessment, policies and actions will generally be based on an approach that is likely to be less rigorous and more limited than risk assessment. Alternatively, a policy that is dictated purely by evidence alone, as in the case of traditional epidemiological approaches, may take decades to form.

Furthermore, risk assessment is used as a tool by decision makers to help in:

- identifying research needs and setting research priorities aimed at reducing important scientific uncertainties, and
- providing a framework for analysing the potential adverse consequences of alternative risk management policies or actions (Covello and Merkhofer 1993).

Purchase (1986, page 55) has characterised the importance of toxicological risk assessment by saying that:

"Toxicology is one of the few scientific disciplines that can have an immediate and enormous effect on public policy. It is difficult to think of any other scientific discipline that, from the simplest result, can create major policy impacts."

In the process of health risk assessment, toxicology data from animal studies and human epidemiology and clinical studies, if available, are evaluated. The dose response relationship at low doses is predicted using mathematical formulae. In addition, the information on the degree of exposure is used to predict quantitatively the likelihood that a particular adverse response will be seen in a specific human population (Paustenbach 1995). Risk assessment has received broad acceptance among regulatory agencies, in particular the United States (Paustenbach 1989), and among members of the public. Its use has been increasingly vital to providing information for developing environmental health policy and also assisting decision makers by providing estimates of the health effects associated with local environmental exposures and their potential distribution in the population (Privalova *et al.* 2001).

Silbergeld (1993) stated that the usefulness and effectiveness of risk assessment have been debated because data and scientific understanding were often insufficient. It could also be considered as an admission that a certain amount of risk is acceptable. However, it should be remembered that health risk assessment is not an exact science. For many aspects of risk assessment, reliable information may or may not be available and scientific uncertainty is a fact of life. Therefore, it is important to understand the strengths and limitations of each assessment and to communicate this information to those involved and the public (Ohanian 2000). Because of the many uncertainties about exposure and effects, risk assessment is as much a policy-driven as a science-based process (NRC 1994). In this sense, science informs, but policy decides (NRC 1994).

A basic premise of risk assessment is that chemicals that can cause a specific toxic effect in animals can cause similar effects in humans (Eaton and Klaassen 2001). To put this statement into perspective, the International Agency for Research on Cancer (IARC) stated that all human carcinogens that have been adequately tested in animals produce positive results in at least one animal model (IARC 1994, 2000). This association cannot establish that all agents and mixtures that cause cancer in experimental animals also cause cancer in humans. Nevertheless, in the absence of adequate data on humans, it is biologically plausible and prudent to regard agents and mixtures for which there is sufficient evidence of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans (IARC 1994).

Rats have been predominantly employed in predictive toxicological evaluation because they are relatively cheap, available in large numbers, and no other animal model, in a general sense, uniformly simulates the responses of humans to foreign substances (Calabrese 1991). On the other hand, there is no absolute certainty that a substance that has not been found to produce any adverse effects in animal models, i.e., rodents or primates will also be safe for humans.

In this context, the assessment of human health hazards associated with 1080 exposures presents interesting challenges. While animal experiments at relatively high doses have been carried out, the public health impacts of long term, low dose 1080 exposures are still unknown and health risk assessment should be treated with caution. The primary aim of this health risk assessment is assessing the relevance to humans of the possible risk associated with a particular level of 1080 exposure.

5.1.1 Process

The *first step* is to identify the possible hazards that may be presented by the chemical. Hazard is an intrinsic property of the chemical. The dose response relationship helps to describe the hazardous properties of the chemical under different exposure conditions. In order to assess hazard, animal studies are conducted with different exposure levels, or doses, as well as varying durations of exposure.

In the case of compound 1080, possible hazards are assessed by determining whether 1080 produces adverse effects, and identifying the nature of those effects. Any adverse effects are identified through a thorough review of toxicological literature (Paustenbach 1995). This is crucial to answering the question of whether exposure to 1080 could (at any dose) cause an increase in the incidence of adverse health effects (e.g., birth defect, etc.) in humans. One of the primary objectives of hazard identification is the choice of the most appropriate end point/s for further dose-response assessment.

Determining the dose-response relationship of the substance is the *second step*. Dose-response evaluations define the relationship between the experimental dose of 1080 and the probability of a specific adverse effect in laboratory animals. In this context, the specific adverse effect at the lowest dose is referred to as the critical effect, and its highest concentration or dose that will not cause an effect is the NOAEL (Haber *et al.* 2001; Paustenbach 1995).

The *third step* is to determine the exposure by quantifying the available dose of the chemical received by humans by the oral, inhalation, and dermal routes of exposure (or a combination of such exposures). The concentration of the chemical that humans are likely to be exposed to is estimated (Paustenbach 1995), for instance during the period of pregnancy or over a lifetime.

Characterising the risk constitutes the *final step* of the process. In risk characterisation, the important risk conclusions and related uncertainties are identified and highlighted. Apparent thresholds are discussed, and potencies are described. A discussion of uncertainty includes comment on issues such as the quality and quantity of available data, use of default assumptions, incomplete understanding of the general biologic phenomena, and scientific judgements or science policy positions that were employed to bridge information gaps. In many cases, this is achieved by providing estimates of the type and magnitude of health effects associated with environmental exposures and their potential distribution in the population (Privalova *et al.* 2001).

Risk characterisation is the starting point for risk management considerations and the formulation of regulatory decision-making (Paustenbach 1995). It is described as a

bridge between science and policy (Hertz-Picciotto 1995). Furthermore, it is considered an essential tool in helping decision makers to develop policies and actions to inform decisions about the extent to which a potential risk needs to be managed or regulated (Covello and Merkhofer 1993; Silbergeld 1987, 1993). Characterisation of risk is consistently the weakest component of a risk assessment as numerous aspects of science and regulatory policy appropriately describing whether a significant human health hazard exists in a specific setting are illustrated (Paustenbach 1989).

5.1.1.1 Health hazard identification

A major component of the hazard identification process is the use of animal bioassay data. Animal models have been used to predict the responses of humans to chemical and physical agents for hundreds of years (Calabrese 1991). The purpose of hazard identification is to evaluate the weight of evidence for adverse effects in humans based on assessment of all available data on toxicity and mode of action. It is intended in this thesis to address (a) whether 1080 may pose a health hazard to humans, and (b) under what circumstances an identified hazard may be expressed. The result is a scientific judgement as to whether 1080 can cause an adverse effect in humans. As noted by Kimmel (1990), determining a hazard is often dependent on whether or not a dose-response relationship is present.

There is convincing evidence that the toxicity of 1080 is mediated principally through its metabolite, fluorocitrate as described by Peters (1963). However, it is thought that 1080 toxicity is not due primarily to the accumulation of citrate per se but to the blockage of energy metabolism (Pelfrene 1991). Although some aspects of 1080 metabolism such as the conversion to fluorocitrate are clear, the overall fate of 1080 in animals is unknown (Rammel and Fleming 1978). Uncertainties exist regarding whether or not the likely pathways involved in the metabolism of 1080 in animals are qualitatively and quantitatively similar in humans.

Selection and adequacy of pivotal study

In general, human exposure data for prediction of human response to 1080 are quite limited. Hence, animal bioassay data have served as the primary basis for most

quantitative risk assessments. Traditionally, threshold approaches have been applied to the assessment of noncancer endpoints (Ecobichon 2001).

The toxicity and adverse health effects of 1080 have been analysed in Chapter 4. In principle, human data are preferred for risk assessment, although some authors disagree with this statement. The use of acceptable human studies avoids the problems of interspecies extrapolation and, therefore, confidence in the estimate is often greater (Paustenbach 1995). However, there are no known human studies available to date to evaluate the potential public health implications of 1080. Therefore, data from well-conducted animal studies have had to be used. Animal test results often represent the only means by which toxicity in humans can be effectively predicted. In some cases, it may not be possible to use the most desirable animal for testing because of animal welfare or cost considerations (Calabrese 1991). For example, use of monkeys is restricted to special cases, even though they represent the species that may react in a manner most closely to humans. Hence, in the absence of data from a more relevant species, data from the most sensitive animal species tested, are generally used. In addition, the route of administration must be considered when choosing the critical study from among quality toxicity tests. In general, the preferred exposure route is that which is considered most relevant to environmental exposure.

For risk assessment, the most sensitive endpoint from the most appropriate or sensitive species forms the basis for selecting the pivotal study. For 1080, the most sensitive endpoints of toxicity in animals identified were testicular and myocardial toxicity, and teratogenicity. These, then, are the critical effects of 1080.

A review of the relevant animal data revealed that the studies of Eason *et al.* (1998, 1999, 2001) and Eason and Turck (2002) provide the most appropriate studies for health risk assessment as they are more recent, of good scientific quality, followed standard guidelines, used recognised Good Laboratory Practice (GLP) and were able to establish NOAELs for critical effects in sensitive target organs. Therefore these studies were chosen as the pivotal studies. The pivotal study is the study from which the NOAEL was derived. The importance of using GLP was that this ensured that the study report/s accurately stated what was done and what the results were (Lu 1996).

GLP was also applied to all studies conducted to satisfy guideline requirements for product registration with the US EPA (1979) and OECD (1989).

There were no available chronic exposure studies by any route of exposure. Therefore potential tolerable concentrations for exposures were calculated using the subchronic studies with application of appropriate uncertainty factors.

Critical endpoint/s and critical effects

The critical end point used in dose response assessment is the effect occurring at the lowest exposure dose (Barnes and Dourson 1988). Available data suggested that the studies reported by Eason *et al.* (2001) and Eason and Turck (2002) could be considered for health risk assessment, as they were most recent and complied with the GLP procedures. The toxicological end points for which the dose response relationship was best characterised were the developmental (Eason *et al.* 1998, 1999) reproductive and myocardial toxicities observed in the subchronic study in rats by Eason *et al.* (2001) and Eason and Turck (2002). Whittem and Murray (1963) drew a similar conclusion that the heart was the most susceptible organ to pathologic lesions, while Sullivan *et al.* (1979) considered the testis as the organ most vulnerable to the toxic effects of 1080.

Table 4 shows the critical effects, the NOAELs, and experimental doses of 1080 in animals tested for the critical toxicity end points. This author (NF) considers the critical effects to be "adverse", hence the use of the term NOAEL rather than NOEL used by Eason and Turck (2002) and Eason *et al.* (2001).

Table 4

Summary of critical toxicity end points and effects arising from 1080 exposure in rats

Critical Endpoint	Parameter	Experimental dose	Critical Effect
Teratogenicity [1]	NOAEL	0.10 mg/kg bw/day	Malformations, – irreversible alterations of skeletal development
	LOAEL	0.33 mg/kg bw/day	
Testicular toxicity [2]	NOAEL	0.075 mg/kg bw/day	Severe hypospermia in epididymis, severe degeneration of seminiferous tubules of the testes
	LOAEL	0.25 mg/kg bw/day	
Myocardial toxicity [2]	NOAEL	0.075 mg/kg bw/day	Cardiomyopathy
	LOAEL	0.25 mg/kg bw/day	

[1] Eason *et al.* (1998, 1999)
[2] Eason *et al.* (2001); Eason and Turck (2002)

5.1.1.2 Dose-response assessment

The dose-response relationship is a fundamental and essential concept in the practice of toxicology (Barnes and Dourson 1988). The response to toxic effects generally increases as the dosage of the toxicant is increased. In considering toxic effects at various dose levels, the dose range of interest is generally the low-dose. For health risk assessments, dose response relationships are frequently based on animal studies. Doses are usually presented per unit body-weight (e.g., mg kg^{-1} day^{-1}) (IPCS 1999).

Previous sections of this thesis have focussed on the characterisation of hazards to 1080 (Chapter 4) and potential sources of human exposures to 1080 (section 2.2.2). In order to bring these issues together and provide an adequate characterisation of risk, the relationships of exposure to dose and ultimately, to response are evaluated. The dose-response relationship provides a basis to infer a point of departure for extrapolation for noncancer risks. Similarly, these relationships provide insight into the shape of the dose-response below the point of departure, which can help inform choices for extrapolation models (IPCS 1999).

Suitable data that describe a dose response relationship for 1080 in animals are quite limited. Available studies included acute and subchronic exposures in animals and some information on acute poisonings in humans.

Characterisation of threshold

Systemic (non-cancer) toxicity is usually assumed to have thresholds below which no effects occur (IPCS 2000a). For these toxicities, safety assessments are carried out with establishment of TDIs, which are seen as doses below these thresholds. The threshold concept led to the logical conclusion that exposure to substances at doses below the threshold was safe and therefore acceptable. From this concept, guidelines were derived and standards designed to protect public health.

The derived TDI usually includes an uncertainty factor (UF). The derived UF is generally based on the adequacy of the pivotal study, an assumed degree of inter-and

intraspecies variation, the adequacy of the overall database, and the nature (severity) of toxicity (Gephart *et al.* 2001).

For toxic effects, other than heritable mutations and genotoxic carcinogenicity, considered to have a threshold, a number of different estimates may be used as an approximation of the threshold (NRC 1983). The non-cancer endpoints are distinguished from carcinogenic and mutagenic endpoints, which are often treated as non-threshold processes.

The threshold concept is considered important in the regulatory context. The individual threshold hypothesis states that a range of exposures from zero to some finite value could be tolerated by the organism with essentially no chance of expression of the toxic effect (NRC 1983). Further, it is often prudent to focus on the most sensitive members of the population. Therefore, regulatory efforts are generally made to keep exposures below the population threshold, which was defined as the lowest thresholds of the individuals within a population.

Quantitative response analysis included determining a NOEL/NOAEL and/or LOEL/LOAEL for each toxicity end point under study (Hayes 2001).

No-observed-adverse-effect-level (NOAEL) vs No-observed- effect-level (NOEL)

The regulatory focus for the NOAEL is normally on the highest dosage which causes no effects. The NOAEL for the critical toxic effect was sometimes referred to simply as the NOEL, i.e., the term NOEL has been used to mean the equivalent of a NOAEL. However, the use of NOEL is ambiguous in that there may be observable effects that are not of toxicological significance, i.e., they were not "adverse". Scientists within the US EPA's Office of Pesticide Programs (OPP) traditionally defined NOEL as the dose that did not cause an adverse effect and there was no distinction made between NOEL and NOAEL (M. Dourson pers. comm. 2005). In 1980, other U.S. EPA scientists introduced the term NOAEL to distinguish it from NOEL. The distinction between the two terms only relates to the term "adverse". It is also considered important to determine whether adverse effects are seen for chemicals with RfDs based

on NOELs, rather than NOAELs, if NOELs are to be used to developing RfDs (M. Dourson pers. comm. 2005).

Although a NOAEL is an experiment's subthreshold (whereas the LOAEL is the experiment's threshold dose) the NOAEL is sometimes incorrectly viewed as a level that is always without adverse effects (Gaylor 1992). However, the true risk of exposure at the NOAEL can vary from zero to >20%, depending on the background of variability of end points, spacing of doses, and numbers of animals used, or alternatively it could be many-fold lower than a true population threshold (Leisenring and Ryan 1992; Gaylor 1992; Renwick and Walker 1993). This could particularly be the case if the effect modelled was an adaptive change and not necessarily adverse. Therefore, the NOAEL is not the same as the biological threshold and may underestimate or overestimate the true no-effect level (Renwick and Walker 1993).

The dose-response data are used to identify either an NOAEL or LOAEL for the critical effect. Approaches for characterising threshold dose-response relationships include the identification of NOAELs or LOAELs. Traditionally, the use of the NOAEL from the pivotal study is the primary basis for the scientific evaluation of the risk posed to humans from systemic toxicity (Barnes and Dourson 1988). The NOAEL approach identifies the greatest experimental dose not associated with a statistically significant increase above background in the most sensitive adverse effects, and then UFs and modifying factors are applied to derive the TDI (Allen *et al.* 1996).

Dose-response modelling

Benchmark Dose (BMD) methodology

It has been suggested by Crump (1984) that dose-response modelling, i.e., the benchmark dose (BMD) methodology, rather than the traditional NOAEL approach, should be generally applied to systemic toxicity. Dose-response modelling is a commonly accepted method of estimating the response associated with a given exposure. Dose-response models are expressed as functions of dose possibly

covariates and set of constants (parameters) that govern the details of the shape of the resulting curve (details are presented in the following sections).

A variety of dose-response models are available for calculating a benchmark dose. However, not all human observations (if available) or animal experiments are amenable to dose-response modelling (Crump 1995): for instance, if there is a biologically significant increase in a rare malformation where it was found to be not statistically significant.

The US EPA BMDS 1.3 software (US EPA 2001) was developed as a tool to facilitate the application of BMD methods. It was employed in the dose-response modelling for the purposes of this study. The minimum data set for calculating a BMD should at least show a significant dose-related trend in the selected critical end point/s. It is preferable to have a study or studies with one or more doses near the level of Benchmark Response (BMR) to give a better estimate of the BMD, and thus, a shorter confidence interval. The BMR is a response level, generally expressed as in excess of a background used to define a BMD. A study or studies in which all the dose levels show changes compared with the control values (i.e., when there is no NOAEL) can be utilised in BMD analyses, unless the lowest response level was much higher than the BMR.

The BMDS software does not analyse statistical power (J. Zhao pers. comm. 2006). In the benchmark analysis, smaller studies tend to result in smaller BMDLs, whereas the opposite is true for NOAELs. The NOAEL has an undesirable property in that the fewer animals used, the lower the statistical power to detect effects, therefore resulting in higher NOAEL values all other factors being equal (Gaylor 1996). The BMD method resolves the less statistical power issue by providing a lower BMDL (R. Howd pers. comm. 2006).

In the BMD methodology, the selection of a BMR can also be based on the statistical power provided by the data. For example, Gaylor and Aylward (2004) concluded that with a sample size of five animals per group the NOAEL would be at the risk-based BMD_{10} while the NOAEL would be near the risk-based BMD_{05} with a sample size of ten animals per group. The BMD method is not specifically designed for conducting

meta-analyses and it does not allow the data to be stratified in the data modelling in order to distinguish the difference between studies (J. Zhao pers. comm. 2006).

Benchmark Dose

The BMD is the dose (Barnes *et al.* 1995) calculated to be associated with an increase in the response (called the Benchmark Response, BMR) (Gaylor 1992) for a given incidence (e.g., 5 or 10% incidence) of effect estimated from all toxicity data on that effect within the study (Crump 1984, 1995). The use of the BMDL has encouraged better experiments to be conducted to obtain tighter confidence limits, resulting in higher TDI values (Gaylor 1996) and is therefore more accurate which makes subsequent health risk management decisions better.

Benchmark dose (BMD) vs No-observed-adverse-effect level (NOAEL)

The BMD approach is considered to be an alternative method of providing a more quantitative dose-response evaluation (Hayes 2001). The NOAEL approach has been criticised in several ways, as it does not consider all of the dose-response data, is highly dependent on the number of animals used, and it may be inconsistent from study to study because a NOAEL is constrained to one of the experimental doses (Allen *et al.* 1996; Gaylor 1996; Castorina and Woodruff 2003). Similarly, studies which have utilised more reliable exposure measures or more sensitive end points, are likely to achieve a lower NOAEL (Jacobson *et al.* 2002), thus potentially discouraging well-designed studies. An example of a more reliable exposure measure is measuring the amount of feed consumed rather than assuming that everything has been ingested, especially when the chemical in feed causes a taste aversion in the dose groups versus just measuring the animal body weight.

It is well known that the NOAEL does not necessarily show that there is a zero risk below a threshold dose. Gaylor (1992) showed, for example, in a review of developmental toxicity studies, that the estimated risk of stillborn or resorbed or malformed fetuses ranged from 0 to 4.5% at the NOAEL.

The BMD approach has been used in recent years as an alternative approach for calculating TDIs to avoid the shortcomings associated with the NOAEL (Crump 1984). It has gained wide acceptance in carrying out health risk assessment and has been frequently used by various regulatory agencies, such as the US EPA and the WHO (Fowles *et al.* 1999).

The BMD approach uses all of the experimental data to fit one or more dose-response curves. These curves are used in turn to estimate a BMD corresponding to a specified level of risk. The selected level of risk is typically set at the lower end of the range of responses that can be detected experimentally (e.g., the 1, 5, or 10% risk level for quantal responses). In using the NOAEL approach to calculate a TDI, the only data point used is the NOAEL (Gaylor *et al.* 1998). The BMD approach is not restricted to experimental NOAELs/LOAELs but also makes use of dose response data and sample size.

Two types of quantitative toxicological data

The quantitative toxicological data used in this study were basically of two types: quantal and continuous. Quantal data consist of "yes-no" information specifying whether or not a subject had an abnormal response (Crump 1995). It also specifies the number of animals affected, but does not give a measure of the magnitude of the effect (Gephart *et al.* 2001). It provides the simplest case for estimating BMDs (Gaylor *et al.* 1998). On the other hand, with continuous data, the effects are measured on a continuum (Crump 1984), such as sperm count and body weight. Modelling for continuous data has been recognised to be complicated (Barnes *et al.* 1995). One difficulty identified is differentiating between normal variation and an adverse effect, and another is modelling the change in the mean versus proportion of individuals outside the normal range. Tables 5 and 6 summarise the data used for the quantal and continuous models, including the species, route of exposure, dose levels, and the effects at each dose.

Table 5

Toxicological studies and quantal critical end points

Doses, mg/kg/bw	Study	Sample size	Number affected	Critical end points, dictating NOAEL	Species and sex	Route of exposure
0.0	Short term [1]	26	0	Malformations – irreversible forelimb malformations	Female rats	Diet
0.10		26	0			
0.33		26	1			
0.75		26	11			
0.0	Subchronic [2]	20	0 (T); 1 (E)	Severe hypospermia in epididymis, severe degeneration of the seminiferous tubules of the testes	Male rats	Drinking water
0.025		10	0 (T); 0 (E)			
0.075		10	0 (T); 2 (E)			
0.25		20	10 (T); 10 (E)			
0.0	Subchronic [2]	20	0 (M); 1 (F)	Cardiomyopathy	Male and female rats	Drinking water
0.025		10	0 (M); 0 (F)			
0.075		10	0 (M); 0 (F)			
0.25		20	10 (M); 1 (F)			

[1] Eason *et al.* (1998, 1999)
[2] Eason *et al.* (2001) Eason and Turck (2002)
M = male; F = female; T = testicular; E = epididymis

Table 6

Toxicological studies and continuous critical end points

Doses, mg/kg/bw	Study	Sample size	Critical end points	Mean values	Species and sex	Route of exposure
0.0	Short term [1]	25 (M); 25 (F)	Fetal weight	4.1 (M); 3.9 (F)	Male and female rats	Diet
0.10		26 (M); 26 (F)		4.0 (M); 3.9 (F)		
0.33		25 (M); 25 (F)		3.9 (M); 3.8 (F)		
0.75		25 (M); 25 (F)		3.5 (M); 3.3 (F)		
0.0	Subchronic [2]	20	Sperm count (no. x 10^8/g)	8.76	Male rats	Drinking water
0.025		10		8.66		
0.075		10		7.89		
0.25		20		2.22		
0.0	Subchronic [2]	10	Sperm count post 56-day recovery	8.76	Male rats	Drinking water
0.025		-		-		
0.075		-		-		
0.25		10		1.57		

[1] Eason *et al.* (1998, 1999)
[2] Eason *et al.* (2001); Eason and Turck (2002)
M = male; F = female

Benchmark dose models

For the data investigated in this study, three models for each of the quantal and continuous data sets were investigated to determine which of the three models best fit the data. The models were used to calculate the BMDLs for the quantal and continuous response variables at the 95% lower confidence limit and 10% level of extra risk. These models are summarised with their respective mathematical equation below as adopted from the US EPA (1995).

(a) Quantal data BMD models:

Quantal Linear $P(d) = c + (1-c)*\{1-exp[-q1*d]\}$

Weibull $P(d) = c + (1-c)*\{1-exp[-q1*d^k]\}$

Log-Probit $P(d) = c + (1-c)*F(a + b*ln(d))$,

where $F(x)$ is the cumulative normal density function,

$$F(x) = \frac{1}{2}[1+erf(x/sqrt(2))]$$

(b) Continuous data BMD models

Power $m(d)= c+q_1(d-d_o)^k$

Polynomial $m(d)= c+q_1(d-d_0)+...+q_k(d-d_o)^k$

Linear $m(d)= c+q_1(d-d_o)$

where $P(d)$ is the probability response at the dose d; c is background at zero dose, $m(d)$ is the mean response at the dose d, c and $q1$, …, qk are parameters estimated from the data, do is the threshold dose, $erf(.)$ is the error function.

Measurement variables

a. Quantal variables

Data on quantal variables are commonly presented as a fraction or percent of individuals that exhibited the given condition at a given dose or exposure level. For such data, probability density models such as probit, Weibull, logistic, quantal linear, etc., are selected. These models give predictions that lie between zero and one for any possible dose, including zero. For the purposes of this study, Weibull, probit and quantal linear models were used to calculate the BMD for the quantal response variables based on their model performances.

b. Continuous variables

Data for continuous variables are often presented as means and standard deviations or standard errors, but may also be presented as a percent of control or some other standard. Continuous models, namely power, polynomial and linear, were used in this study in calculating the BMDs for the continuous response variables at a 10% effect level.

Test of goodness-of-fit

Goodness-of-fit tests evaluate the hypothesis that a particular model fits the data effectively (Golden 2000). The Pearson χ^2 test (US EPA 1995) is used to assess the fit of the models to the observed dose-response data. It statistically measures the dispersion of data about a dose-response curve in order to provide a test for rejection of a model due to lack of an adequate fit, e.g., a *P*-value of 0.1 (US EPA 2001). Observed and expected numbers of affected test animals were determined in each dose group and the observed and expected number of affected animals would be relatively close if a model fits well. The Chi-square residuals for each dose group were also specified.

The purpose of using a goodness-of-fit value from the BMD calculation was different from that of the *p*-value routinely used in statistical analysis. In conventional statistical analysis, a null hypothesis of no difference between the treated group and the control is tested by determining the probability of getting the results that one did if indeed there was truly no difference in the population whence samples came. In this case, the objective is to make a "yes" and "no" decision about the result with a stringent criterion, which is usually 0.05 or 0.01 for model acceptance.

In BMD modelling the null hypothesis is that the data are adequately represented by the BMD model chosen. In this case, the US EPA (2003) recommends a minimum goodness of fit p value of p=0.1 be used instead of the conventional values of 0.05 or 0.01 for model acceptance since it would be particularly important that the value be adequately modelled for BMD calculation. Therefore the higher the *p*-value, the better the model is deemed to fits the data.

P-values only identify those models that are consistent with the experimental results. For the assessment of fit, degrees of freedom for the test statistics were determined as *n-p*, where *n* is the number of dose groups while *p* is the number of model parameters estimated from the data. BMDs do not assign degrees of freedom to parameters related to a constraint, so that a model usually has only 2 degrees of freedom, while the models with unconstrained parameters have 3 (US EPA 2000).

For the purposes of this study, a *p*-value from the chi squared test of < 0.1 was set as the rejection level to test the hypothesis of adequate modelling. *P*-values from the chi-squared test for each model (Table 7) were obtained using the US EPA BMDS 1.3 software (USEPA 2001). Models that met the default statistical criteria for adequacy and visually fit the data were retained in determining the BMDLs.

All models met the χ^2 test criterion except for the Weibull model for the cardiomyopathy in female rats (unable to run the data which suggested that this model does not fit the data) (Table 7), power and linear models for the sperm count post 56-day recovery period and the linear model for the female fetal weight. A *p*-value of 1 was obtained for the polynomial model while a *p*-value <0.0001 for the power and linear models for the sperm count post 56-day recovery period was obtained (Table 7).

It should be noted that there were only two data points for this end point, i.e., the control group and the top dose level. The two mid ranges were not examined as there were only 20 rats allocated to recovery groups, 10 to the control group and 10 to the top dose group. Gaylor (1992) cautioned that data should contain two nonzero response levels; if not, nearly any curve can be drawn through a single effect point and a control value. In this regard, the BMD modelling required at least two treated dose groups in addition to a control group for the minimum model (E. Hack pers. comm. 2004). Hence, the sperm count after the 56-day recovery period was not included in this analysis as the data were not appropriate for BMD modelling. The linear model for the female fetal weight was rejected for not meeting the statistical criterion, $p \geq 0.1$.

Table 7

Goodness-of–fit tests for quantal and continuous models for various toxicity end points at 95% confidence limit with BMR of 10%

Quantal models ***P*-value [a]**

Toxicity end point	Probit	Quantal linear	Weibull
Epididymis [2]	0.5211	0.5495	0.3213
Testicular [2]	1.0	0.4105	1.0
Cardiomyopathy [2]			
Male	1.0	0.4105	1.0
Female	0.5929	0.5971	§
Teratogenic effects [1]	0.9337	0.1297	0.9892

§ eliminated due to calculation failure

Continuous models ***P*-value [a]**

Toxicity end point	Polynomial	Power	Linear
Sperm count [2]	0.896	0.957	0.235
Sperm count post 56 days [2]	1.0	<.00001♦	<.0001♦
Fetal weight, [1]			
Male	0.526	0.212	0.614
Female	0.967	0.315	0.08♦

[a] P-value from chi-squared test at <0.1 is the rejection level
♦ rejected model
[1] Eason *et al.* (1998, 1999)
[2] Eason *et al.* (2001); Eason and Turck (2002)

Benchmark response rate (BMR)

The BMR is a response level used to define a BMD, the lower limit of which is used as the point of departure (BMDL). For compounds with BMD values based on quantal data, the BMR is expressed in terms of a percent increase in risk of adverse outcome compared with background. The upper confidence limit (UCL) of this BMR can be used to determine the lower limit of the BMD, which is used as the point of departure and is referred to as the BMDL (Crump 1995). The UCL refers to the upper limit of the slope of the dose response curve at the BMR. Thus, if the BMR is 10%, then the UCL refers to the upper limit of the slope at 10%. This upper limit will be above the 10%, of course, but when extrapolated downward in dose, will eventually cross the 10% response line. The dose where this crossing occurs is the BMDL.

A TDI is most often developed from the BMDL. The BMR is typically set at the lower end of the range of responses (e.g., 10% or 5% change) that can be detected experimentally. Use of this approach can help avoid uncertainties associated with low-dose extrapolation using models that result in widely different values that may not reflect biologic realities (Crump 1995).

Since the BMDs at the 1% risk level are often not precisely estimated, Auton (1994) suggested using a BMD corresponding to a 5% risk for teratology data, showing that the BMDL will be comparable to the NOAEL for most datasets. Similarly, Gaylor (1992) concluded that the BMD at the 5% effect level was similar to the NOAEL determined by statistical tests of trend. Currently, there is no scientific rationale for preferring a 5% or 10% effect level, and it appears that selection of one over the other would have minimal effect on the derived TDI in most cases (Barnes *et al.* 1995). For the purposes of this study, a BMR of 10% was used in calculating the BMD. This 10% value is consistent with the 10% BMR recommended by the U.S. EPA (2003). In most cancer and some non-cancer bioassays, the 10% response is at or near the limit of sensitivity (US EPA 2003).

For compounds with BMD based on continuous data, the BMR may be expressed as a percent change in mean response compared with control or in terms of standard

deviations from the control mean response (US EPA 2003). For continuous end points, a BMR of 10% increase in risk was used for the purposes of this study as recommended by the US EPA.

Model Performance

The goodness of fit of the model to the data is a statistical procedure that provides a measure of the goodness of fit of a dose response model to a set of data (US EPA 2001). The degree of fit is an indication of how well the model reflects the data. Akaike's information criterion (AIC) is used for comparison between models and selection of the model for BMDL calculations. The AIC values were obtained using the US EPA BMDS software (US EPA 2001).

AIC can be calculated using the equation

$$AIC = -2 \log L + 2p,$$

where L is the value of the likelihood function at the maximum likelihood estimates (MLE) for the parameters, and p is the number of parameters estimated in the model (Sand *et al.* 2002). Although the AIC does not reach a conclusion about "statistical significance" and does not "reject" any model, it determines how well the data support each model. Lower AIC values were preferred according to this procedure for estimating the BMD and the BMDL (Sand *et al.* 2002). The model with the smallest AIC was selected among all plausible models and this criterion was used for final model selection.

The AIC values for the dose-response models used in the study are listed in Table 8. Analysing the overall model performance of various models, the model with the lowest AIC was chosen to estimate the BMD. If the BMDL estimates were within a factor of 3, they were considered indistinguishable, and the model with the lowest AIC was selected to provide the BMDL (US EPA 2003). Since the BMD was chosen within or near the experimental dose range, it was relatively insensitive to the choice of the dose-response model. In addition, an adequate fit to most of the experimental data was achieved with all the models (Gaylor *et al.* 1998).

The three quantal models gave comparable AIC values. However, the probit model was used in deriving the BMDs for all the quantal end points except for the teratogenic effects, where the Weibull model was chosen using the AIC criterion. For both models, the power and background parameters were estimated by the maximum likelihood estimates. For the continuous end points, the linear model gave the lowest AIC for sperm count and the power model had the lowest AIC for male and female fetal weights. The power, background, and intercept parameters and slope, background, and power parameters were used for the power and polynomial models, respectively. Details of the AICs are shown in Table 8.

Table 8

Model performance for quantal and continuous models for various toxicity end points

Quantal models

	Akaike's Information Criterion (AIC) [1]		
Toxicity end point	**Probit**	**Quantal linear**	**Weibull**
Epididymis [3]	51.5434	51.773	53.2315
Testicular [3]	31.7259	34.6013	31.7259
Cardiomyopathy [3]			
Male	31.7259	34.6013	31.7259
Female	21.4352	21.4528	♦
Teratogenic effects [2]	48.125	53.3508	47.9442

Continuous models

	Akaike's Information Criterion (AIC) [1]		
Toxicity end point	**Polynomial**	**Power**	**Linear**
Sperm count [3]	118.47	120.59	116.59
Fetal weight, [2]			
Male	-124.96	-122.80	-126.38
Female	-138.11	-136.10	♦

♦ rejected model
[1] AIC is the statistical measure of how well the model fit the data
[2] Eason *et al.* (1998, 1999)
[3] Eason *et al.* (2001); Eason and Turck (2002)

Calculation of BMDs and BMDLs

As starting points for estimating safe exposure levels, there has been a recent movement to use BMDs instead of NOAELs and LOAELs (Bailer *et al.* 1999). One of the suggested advantages of the BMD method is that it could be applicable in situations when NOAELs do not exist (Sand *et al.* 2002). Like the NOAEL and LOAEL, BMD values can be interpreted to correspond to negligible or very low risk levels, rather than to precise numerical values. A BMDL has been proposed as a replacement for the NOAEL in setting acceptable human exposure levels (Crump 1995). The exposure levels that result from reducing NOAELs and LOAELs (or BMDs) by uncertainty factors may simply be expected to provide adequate safety and no specific risk connotations are necessarily attached to them (Bailer *et al.* 1999).

The dose associated with the BMR is determined using the dose-response curve. The dose corresponding to a given BMR is considered the BMD. The BMD or BMDL is then used in place of a NOAEL to derive the TDI.

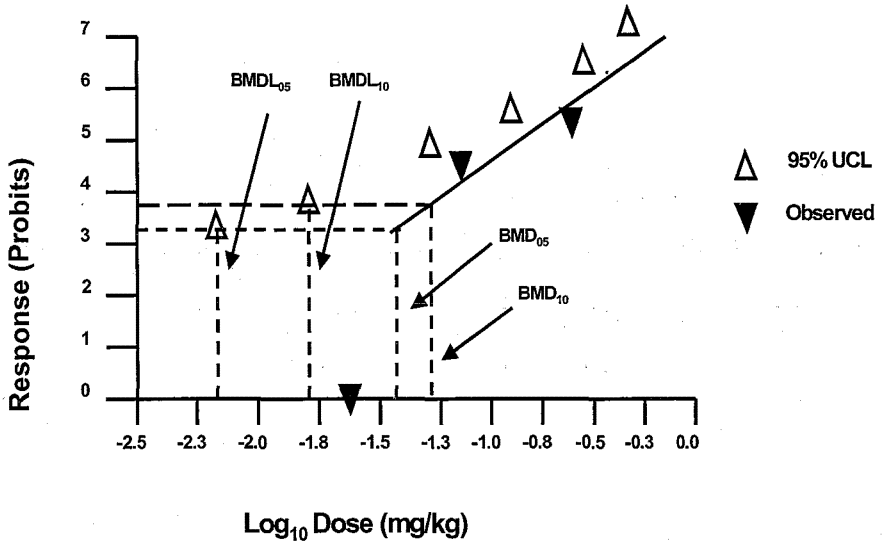

Figure 4

Illustration of a benchmark dose (BMD) approach

Figure 4 shows a BMD calculated using a 5 or 10 percent BMR (the horizontal dashed lines) and a 95% lower confidence bound on dose. The probits are the proportions of abnormal responses. The $BMDL_{10}$ (corresponding to a lower confidence limit on the dose resulting in the BMR of 10% increase in risk) is used as an alternative to the NOAEL value for TDI calculations and used for the purposes of this study. In benchmark analysis the BMDL, defined as the lower bound of the 95% confidence interval for the BMD, is used as the principal criterion for regulatory purposes. The BMDL was used instead of the BMD to provide a margin of safety and at least to ensure that the most sensitive individuals in the population are protected (Jacobson *et al.* 2002). This statement is correct when the standard BMR of 10% is chosen as the basis of the extrapolation. The use of a BMDL in experimental animals does not impact the choice of uncertainty factor for within human variability. Note also that the use of a BMDL from a human study, similarly does not impact the choice of an uncertainty factor for within human variability. However, if a BMR of something less

than 10% is used, an argument could be made that a different choice of an uncertainty factor for within human variability needs to be made. Analyses have been made with BMDs, BMDLs, NOAELs and LOAELs. A 5 or 10% choice represents either a NOAEL or perhaps LOAEL (M Dourson pers. comm. 2007), and thus is consistent with the standard NOAEL/100 approach.

a. Quantal end points

Calculation of the BMDs followed the framework given by Crump (1995). A brief outline is presented here.

Quantal data are modelled using a mathematical expression for the probability $P(d)$ that an individual subjected to a dose d has an abnormal response (Crump 1995). The BMD can be defined as the dose that results in a prescribed additional or extra risk which are the two common ways of expressing risk (Gaylor and Slikker 1990). If the proportions responding in the control and treated groups are $P(0)$ and $P(d)$, the additional risk is:

Additional risk (AR) is defined as:

$$AR(d) = P(d) - P(0)$$

The extra risk (ER) may be interpreted as the probability of a response at dose (d) conditional on the fact that no response would have resulted from dose zero. In the absence of background risk $(P(0)=0$, additional and extra risk are identical (Crump and Howe 1985). Therefore, the extra risk is defined as:

$$ER(d) = [P(d) - P(0)]/[1 - P(0)]$$

where $P(d)$ is the probability of response at dose (d), and $P(0)$ is the probability of response in the absence of exposure or the background exposure ($d = 0$).

Extra risk was used in estimating the BMD for the purposes of this study.

The BMDs and the BMDLs were estimated using the US EPA BMDS version 1.3 software (US EPA 2001) for the corresponding models chosen according to the criteria adopted for the purposes of this study. BMDLs were calculated using the maximum likelihood method. As can be seen, the BMDs were typically only slightly higher than the BMDLs (Table 9). For the purposes of this study, the point of departure for BMD modelling for quantal end points is the BMDL associated with 10% BMR. Figures 5 to 8 demonstrate the dose-response curves for 1080 and the models chosen to fit the data on various quantal end points. The error bars indicate 95% confidence intervals for the fraction affected. The fraction of animals affected in each dose group is indicated by circles. The BMR was an extra risk of 10%. The dose labelled BMDL corresponds to the lower end of a one-sided 95% confidence interval for the BMD. The short dashed curve indicates the BMDL for a range of BMRs.

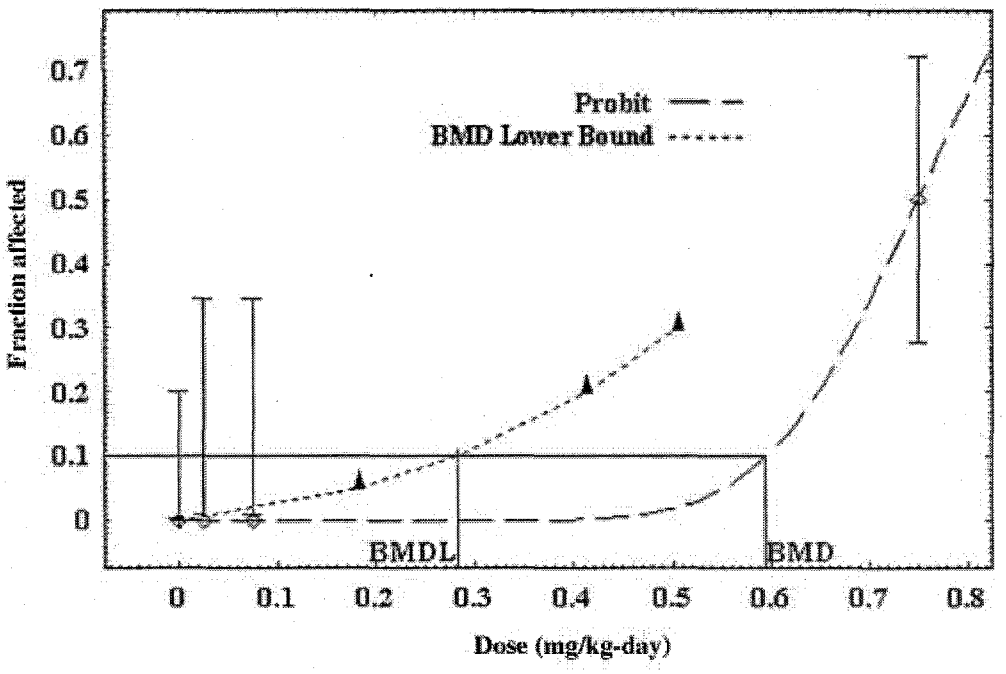

Figure 5

Testicular and male cardiomyopathy (Probit model)

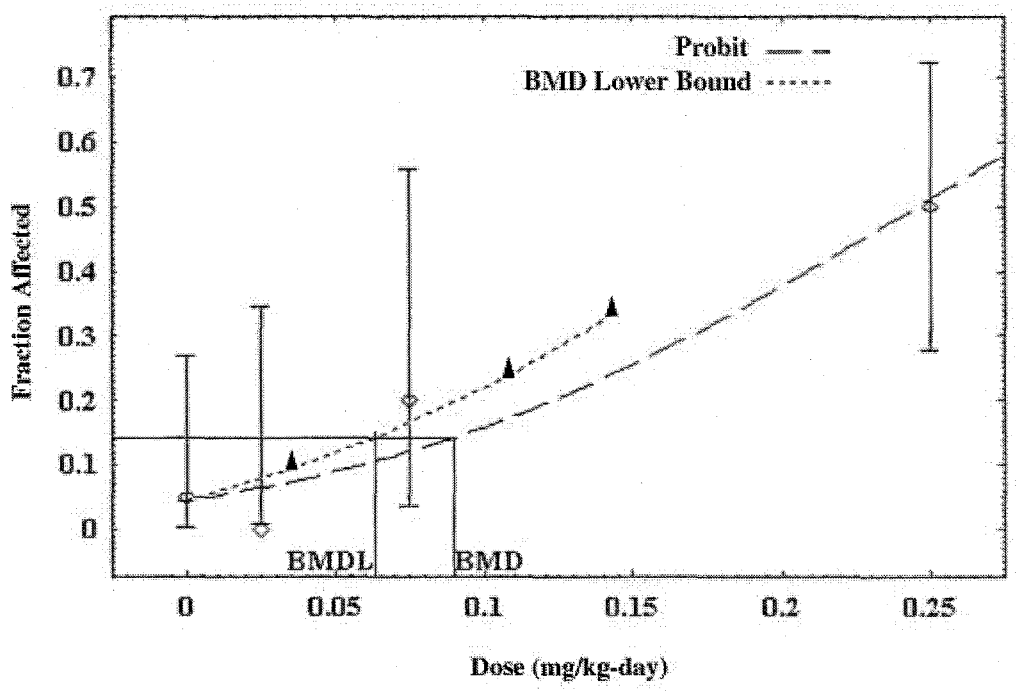

Figure 6

Epididymal effects (Probit model)

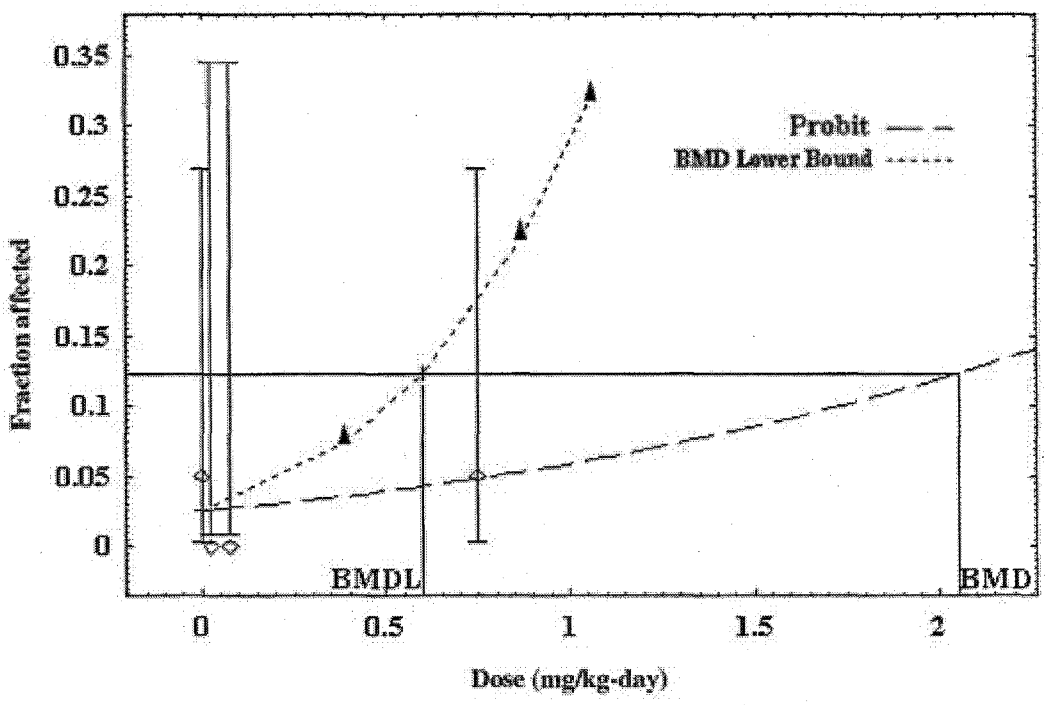

Figure 7

Female cardiomyopathy (Probit model)

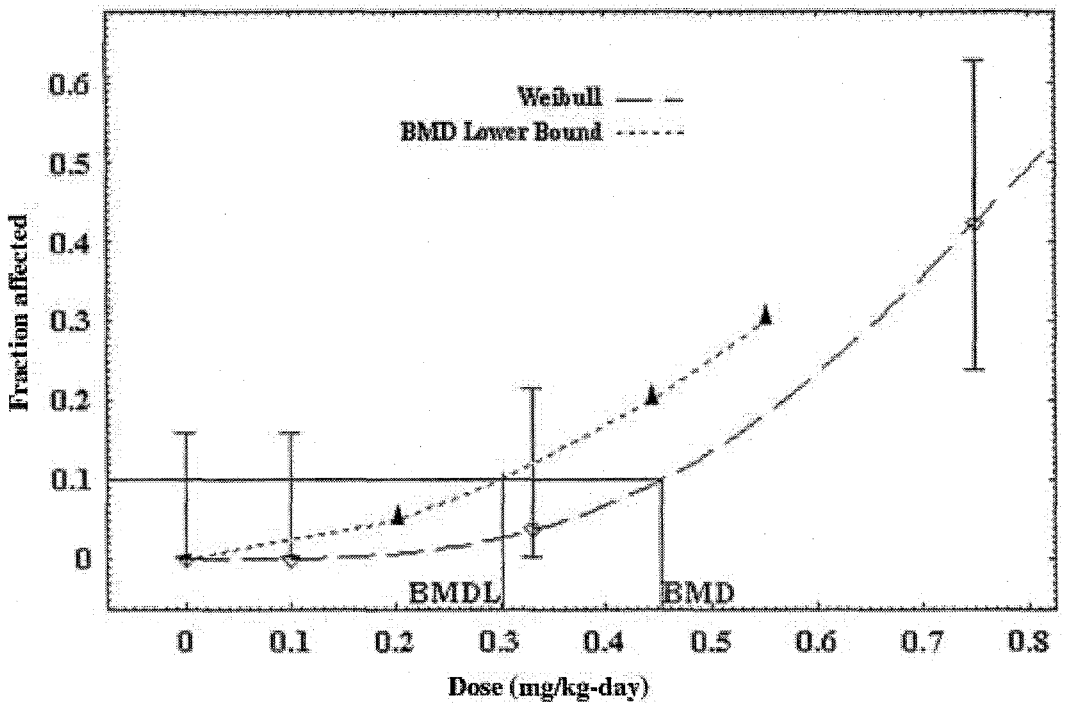

Figure 8

Teratogenic effects (Weibull model)

Table 9

Modelling results with quantal endpoints at a 10% response rate (BMD) and its lower 95% confidence limit (BMDL)

Critical end point	BMD mg/kg			BMDL mg/kg		
	Weibull	Quantal Linear	Probit	Weibull	Quantal Linear	Probit
Forelimb malformations [1]	0.45	0.23	0.48	0.30	0.15	0.36
Testicular effects [2]	0.22	0.05	0.21	0.07	0.03	0.11
Epididymis [2]	0.07	0.04	0.09	0.03	0.03	0.06
Cardiomyopathy [2]						
Male	0.22	0.05	0.21	0.07	0.03	0.10
Female	♦	1.83	0.89	♦	0.20	0.21

♦ rejected model
[1] Eason *et al.* (1998, 1999)
[2] Eason *et al.* (2001); Eason and Turck (2002)

The BMD approach generates a slope term, which is a new parameter not available in the NOAEL approach. The BMD and the BMDL are derived from the slope of the dose-response curve at the BMD (Gaylor 1992). It has been recognised that the slope could provide significant information to the assessor. Most likely the threshold is more quickly approached with steep dose response curves than shallow slopes, all other items being equal.

For the purposes of this study, the slope was taken to be the slope term q1, where the x-axis is the dose and the y-axis corresponds to the number of animals responding adversely. A dose-response curve is fitted to the experimental data and the lower confidence limit on the dose corresponding to the BMR is obtained. This dose represents the estimate of the dose that produces a 10% increase in risk in the context of this paper. Thus, the $BMDL_{10}$ is the lower confidence limit of the dose that gives a 10% excess in abnormal responses above the spontaneous background level.

The NOAELs and LOAELs, and BMDs and BMDLs slopes for various critical quantal end points are shown in Table 10. The probit model was used in deriving the BMDs and the BMDLs for testicular, epididymis, male and female cardiomyopathy and the Weibull model for teratogenicity based on AIC criteria.

Table 10

NOAEL and LOAEL values and dose-response slopes with corresponding BMD and BMDL values from various quantal end points

Toxicity end point	NOAEL mg kg^{-1}	LOAEL mg kg^{-1}	q1 Slope term	BMD mg/kg/	BMDL mg kg^{-1}	BMD Model (best fit)
Epididymis [2]	0.075	0.25	6.83	0.09	0.06	Probit
Testicular [2]	0.075	0.25	31.73	0.21	0.11	Probit
Cardiomyopathy, male [2]	0.075	0.25	31.73	0.21	0.10	Probit
Cardiomyopathy, female [2]	0.075	0.25	0.88	0.89	0.21	Probit
Teratogenicity [1]	0.10	0.33	1.42	0.45	0.30	Weibull

[1] Eason *et al.* (1998, 1999)
[2] Eason *et al.* (2001); Eason and Turck (2002)

The BMDs and BMDLs calculated for each model were compared to one another and to the NOAELs (Table 10). The BMDLs for all quantal end points, using the best fit models, were about three times higher than the NOAELs for teratogenicity and female cardiomyopathy; and almost the same for the other end points (Foronda *et al.* 2007a, see published article in Appendix 2). Given that the BMDL estimates from the three models were within a factor of 3, except for the epididymis which had the lowest BMDL, they were considered to show no appreciable model dependence and were considered to be indistinguishable in the context of the precision of the methods. The results were consistent with that of Gaylor *et al.* (1998).

The probit model demonstrated steeper slopes for testicular and male cardiomyopathy while a shallower slope was observed for female cardiomyopathy and epididymal

pathology. Shallower slopes were observed for teratogenicity using the Weibull model.

b. Continuous end points

The general method for determining continuous end points, the framework given by Crump (1995), was followed in calculating the BMDs. A brief outline of this framework is summarised as follows:

For a given dose d, there is a resulting continuous response X governed by a distribution function F. One of the parameters of F, $\Theta(d)$, depends upon d, and the remaining parameters, represented by α (slope), do not. Given the distribution function F and the background response value po, a cut off response x_0 can be calculated with responses more extreme than x_0 considered abnormal. Using the above notation when larger responses are more adverse, the probability of having an abnormal response given a subject's dose d is given by

$$P(d) = 1 - F[x_0; \Theta(d), \alpha,],$$

If BMD corresponds to an extra risk of 0.10 (BMR), then, $p(BMD)$ is the proportion of affected animals at the BMD, and $p(0)$ is the proportion in the control group, BMR is defined to be:

$$BMR = [p(BMD) - p(0)]/[1-p(0)]$$

This equation can be rearranged to yield

$$p(BMD) = p(0) + [1-p(0)]BMR)$$

While the primary focus on BMD methodology in the literature has been on quantal end points, a few investigators have explored applications to continuous variables (Kavlock *et al.* 1995). The application of the BMD approach to continuous data is more complex as some judgement is required about the magnitude of an effect that one would consider to be "abnormal" or "adverse" (Barnes *et al.* 1995).

Generally, with continuous data there is not a clear demarcation between normal and adverse measurements (Gaylor *et al.* 1998). Continuous data can be quantised but Gaylor *et al.* (1998) recommend analysing the continuous data instead of converting them to quantal data. Gaylor's recommendation was adopted for the purposes of this study.

There were two continuous end points investigated in this study. These were the fetal weights for male and female rats under study and the sperm count for male rats. A summary of the modelling results using power, polynomial and linear models is presented in Table 11. The BMD values were higher than the BMDLs, the difference ranging from 1.1 to 2-fold higher. The dose response curves for the sperm count and male and female cardiomyopathy are presented in Figures 9 to 11.

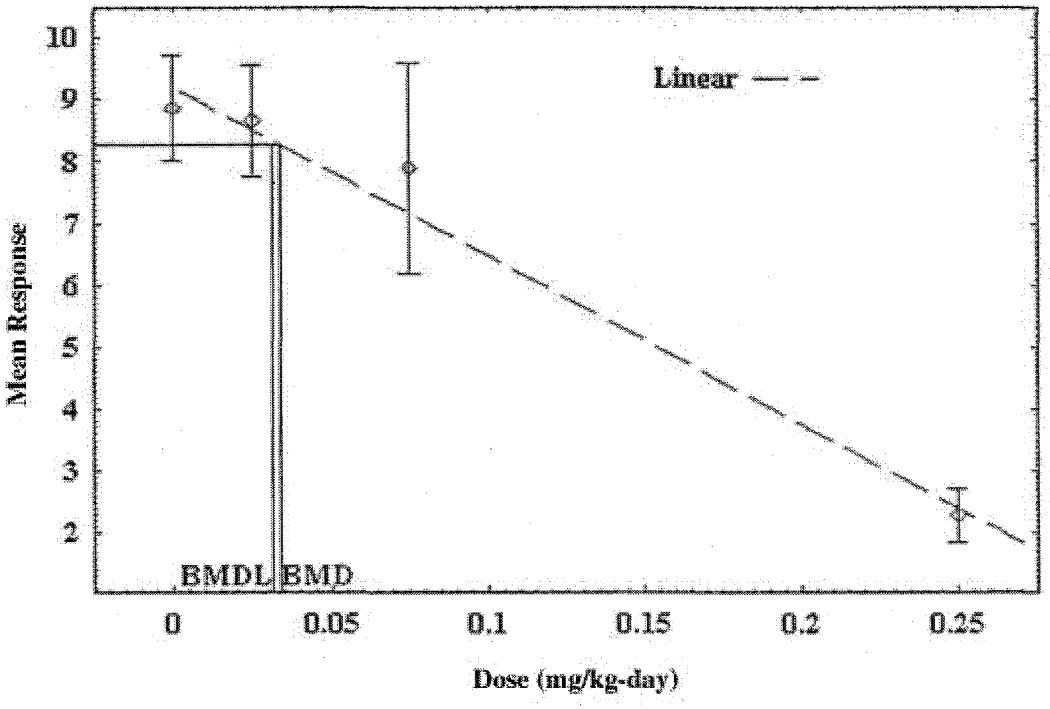

Figure 9

Sperm count (Linear model)

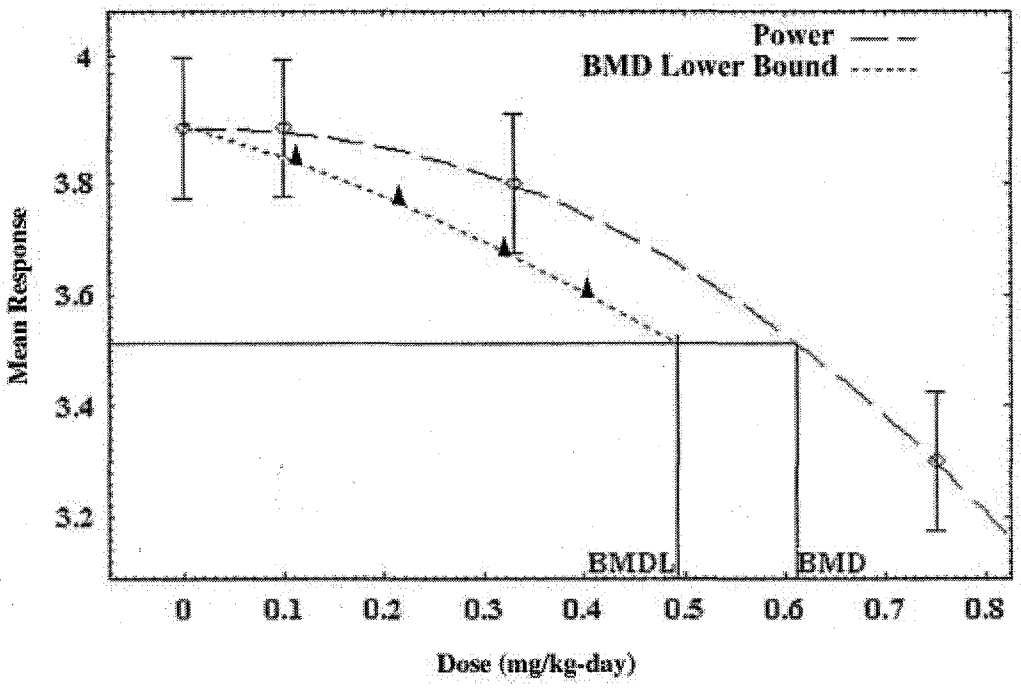

Figure 10

B. Female fetal weight (Power model)

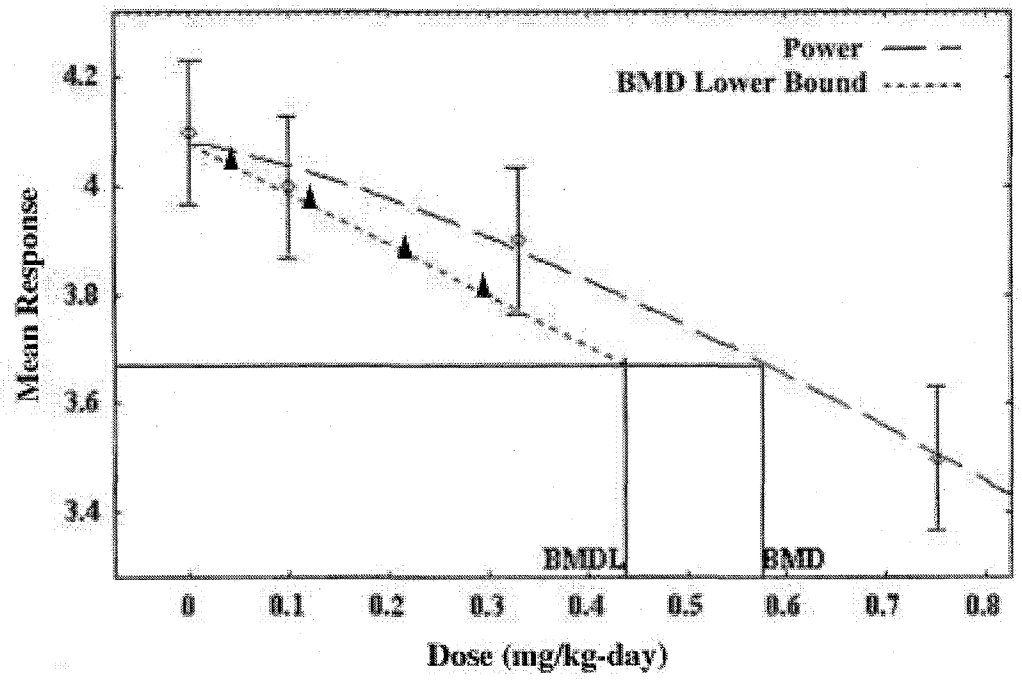

Figure 11

Male fetal weight (Power model)

Table 11

Modelling results with continuous endpoints at the lower 95% confidence limit and 10% reduction in sperm count and fetal weights

Critical end point	BMD mg kg^{-1}			BMDL mg kg^{-1}		
	Power	Polynomial	Linear	Power	Polynomial	Linear
Sperm count [2]	0.10	0.08	0.10	0.09	0.04	0.09
Fetal weight, [1] male	0.58	0.58	0.52	0.44	0.41	0.43
Fetal weight, [1] female	0.61	0.61	♦	0.49	0.50	♦

[1] Eason *et al.* (1998, 1999)
[2] Eason *et al.* (2001); Eason and Turck (2002)
♦ rejected model

The BMDs calculated for the chosen model were compared to the defined NOAELs (Table 12). The BMDLs were similar to the NOAELs for all the end points.

The continuous linear model gave a steeper slope for sperm count while shallower slopes were observed using the power models for the fetal weights (Table 12). The same slopes were noted for both the female and male fetal weights but a slight difference is present in the BMDs and BMDLs. This could be due to a difference in background and power parameters.

Table 12

NOAEL and LOAEL values and dose-response slopes with corresponding BMD and BMDL values from various continuous end points

Toxicity end point	NOAEL mg kg^{-1}	LOAEL mg kg^{-1}	q1 Slope term	BMD mg kg^{-1}	BMDL mg kg^{-1}	BMD Model (best fit)
Sperm count [2]	0.075	0.25	-8.70	0.10	0.09	Linear
Fetal weight, [1] male	0.33	0.75	-0.57	0.58	0.44	Power
Fetal weight, [1] female	0.33	0.75	-0.57	0.61	0.49	Power

[1] Eason *et al.* (1998, 1999)
[2] Eason *et al.* (2001); Eason and Turck (2002b)

The use of uncertainty factors

Uncertainty in health risk assessment results from the lack of certainty with respect to exposure dose, dose-response relationship, and individual susceptibility for a substance. In most cases, the data are inadequate to draw precise conclusions with respect to the range of variability in human responses. Because of this uncertainty and the desire to provide protection to the high-risk segments of the population, the concept of an uncertainty factor (UF) has evolved (Clarke *et al.*1981).

An UF is a mathematical expression of uncertainty that is used to protect populations from hazards which cannot be assessed with high precision (IPCS 1992). Dourson *et al.* (1996) argued that the use of the UF approach in risk assessment was justified on the rationale that low dose risks remain largely unknown for both carcinogens and non-carcinogens. The application of the UFs is also seen as a combination of scientific judgments about low-dose exposures and risks.

Applying UFs to the NOAEL is the primary approach used in threshold-based risk assessments. It is used in the extrapolation of results of standard toxicity tests to the human situation. The choice for these UFs is based on limited toxicological data. Typically, UFs range in value from 1 to 10 (IPCS 2000b). Implicit in the use of UFs is the assumption that true conversion factors for the various types of extrapolation are random independent variables. Furthermore, it is assumed explicitly that the value of each individual factor used (e.g., 10) is large enough to capture a high percentage of the range over which that factor varies (Kodell and Gaylor 1999).

The uncertainties inherent in health risk assessment are especially evident in the assessment of chronic health effects due to low level of exposures to toxic chemicals. In health risk assessment, selection of assumptions is taken into policy considerations because of these uncertainties (Covello 1989). When uncertainty is great, health risk assessment can produce a false sense of accuracy. However, when uncertainties are fully documented, they can be extremely large, which may lead to a conclusion that the health risk assessment results are so imprecise as to be nearly useless (Covello and Merkhofer 1993).

a. Inter- and intraspecies extrapolation

Traditionally, toxicological data from high-dose animal experiments have been extrapolated to low-dose human exposure using UFs. The application of a 100-fold UF to NOAEL results from long-term animal studies is a long-standing practice. It has been interpreted as resulting from the product of two 10-fold safety factors: one factor to account for animal-to-human differences, and another factor of 10 to extrapolate from average humans to potentially sensitive human subpopulations (Dourson and Stara 1983; Lehman and Fitzhugh 1954; Klaassen and Doull 1980; Weil 1972). It was founded on a public health based rationale that assumes that an average group of humans may be as much as 10-fold more susceptible than the average group of animals under study (Calabrese *et al.* 1992). The value of 10 is considered a health-protective value and is generally used as the UF for standard setting by the US EPA and the California Office of Environmental Health Hazard Assessment (Alexeeff *et al.* 2002).

Although humans are qualitatively similar to other animals with respect to many health outcomes following chemical exposures, an UF of 10 has been used to compensate for the uncertainties surrounding interspecies differences (Pohl and Abadin 1995). Dourson and Stara (1983) supported the use of this UF based on empirical evidence in the literature suggesting that a 10-fold reduction in animal dose is sufficient to extrapolate to a practical human threshold dose (e.g., a NOAEL). Calabrese (1985) concluded that the commonly used UF of 10 seemed to provide protection for 80 to 95% of the human population. On the other hand, some investigators considered that although humans are frequently more sensitive than animals in terms of milligrams per kilogram of body weight (Dourson and Stara 1983; Lu 1983), this is not always the case. Digression from the default UF of 10 may be warranted in some cases (Pohl and Abadin 1995).

A study conducted by Dourson *et al.* (2001) found that where there was a 10-fold UF for experimental animal to human extrapolation. Although the number of comparisons was only 22, 5 (23%) of RfDs or RfCs calculated from experimental animal data were higher than the US EPA's human based values. Based from this observation it would be reasonable to argue that the 10-fold UF was sufficient to protect human health for those RfDs and RfCs derived only from experimental animal data. However, exceptions often occur and thus results from experimental animals should always been reviewed against human information when available.

Variability between the genetically similar animals is small compared to the variability within the heterogenetic human population (Barnes *et al.* 1995). This rationale justified retaining the default UF of 10 for intraspecies differences between estimating a TDI on a BMD from animal data. In addition, the Barnes *et al.* (1995) report supported the view that UFs used to compensate for the use of subchronic studies rather than chronic studies, the lack of database completeness, for example should be retained when estimating a TDI based on a BMD.

Kalberlah and Schneider (1998) suggested that a factor of 10 might not be sufficient to cover sensitive subpopulations under all circumstances as the conventional default factor of 10 is not based on a large set of valid data for human variability. Main contributors to inter-individual susceptibility differences to chemicals include age,

illness, pregnancy, sex, and genetic predisposition. Human studies showed that further analysis is necessary to gauge the extent to which the variability of responses are representative for the general population and potentially vulnerable subgroups (Hattis *et al.* 1999a, b; 2001). Uncertainties associated with intraspecies extrapolation factors result from limited knowledge of the variability among humans for toxicokinetics and toxicodynamics, insufficient data on the susceptibility of special subpopulations and the mutual dependencies of these factors.

b. Duration of exposure

An up to 10-fold UF is generally used to extrapolate from a subchronic exposure to a chronic exposure. This factor is used for studies that involve less than lifetime exposure and is based on the assumption that if the chemical were given over lifetime of the animal rather than over a fraction of the lifetime, a smaller amount of chemical would result in the same effect. Based on this rationale, Dourson and Stara (1983) concluded that it seems reasonable to employ a 10-fold UF to account for differences between subchronic and chronic effect levels. Beck *et al.* (2001) concurred that extrapolation of subchronic to chronic exposures is generally accompanied by an UF of 10 for non-cancer effects with the assumption that an effect observed with a subchronic exposure is not likely to occur at less than one-tenth of that dose for a chronic exposure. The Food and Drug Administration (FDA) recommends an additional 10-fold factor where subchronic animal NOELs or NOAELs were available in two species due to the added uncertainty when estimating an ADI from adequate shorter-term toxicity data (Kokoski 1976 as cited by Dourson and Stara 1983.)

However, Shibko[4] (1981, as cited by Dourson and Stara 1983) has a slightly more conservative view as it was recommended that if subchronic data were available for only one species, an extra 2-fold UF is to be used as it seemed likely that the extra margin of uncertainty would probably include the range of sensitivity of two species which is normally required for toxicological evaluation. The logic for a 2-fold extra factor, i.e., a combined UF of 2000 instead of 1000, is for the database UF as discussed in subclause (c) on page 96 (M. Dourson pers. comm. 2005).

[4] Memorandum to Dr M. Dourson.

The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) proposed a value of 2-3 as default for extrapolation from subchronic to chronic exposure while other organisations favour a value of 10, such as the US EPA, the Agency for Toxic Substances and Disease Registry (ATSDR), and the German European Aerosol Federation (EAF) (Kalberlah *et al.* 2003). It was explained that the differences are due to differences in protection levels, where ECETOC aims at central estimates, while the US EPA or the German EAF tend to include higher percentiles of cases or substances in their extrapolations.

c. Completeness of overall database

An extra factor of 10 would be appropriate where major deficiencies in the data exist with respect to quality, quantity or omission, such as a lack of chronic toxicity studies (Dourson *et al.* 1992; IPCS 1994). In one review, more than a third of the substances (38 and 37%) had no appropriate chronic study to validate the RfD/TAD (Kalberlah *et al.* 2003).

Beck *et al.* (2001) suggested that when the database is limited, there is uncertainty as to whether the identified NOAEL might be significantly lower if other studies were performed, or whether a different NOAEL might have been identified if additional health endpoints had been evaluated. Beck *et al.* (2001) defines a complete database as having:

- two systemic toxicity mammalian studies in different species;
- one mammalian multigeneration reproductive study; and
- two mammalian developmental toxicity studies in different species.

d. Protection of children

The US Food Quality and Protection Act 1996 (FQPA) provides a new extra 10-fold safety factor to be added after the determination of the TDI to ensure that infants and children are protected (US EPA 1996). The additional safety factor under the FQPA is largely policy-based and not driven by scientific findings (Scheuplein *et al.* 2002). It has been recognised by both the US EPA and others (US EPA 2002; Fenner-Crisp

2001; Dourson *et al.* 2002), that the toxicity component of this safety factor overlaps with the database uncertainty factor discussed earlier, and that when the database factor is employed properly, no need exists for the toxicity component of the FQPA factor. Based on this rationale, no additional safety factor is proposed to be incorporated for children's increased susceptibility beyond that already incorporated to account for human variability.

e. Justification of UFs applied in estimating the tolerable daily intakes.

Uncertainty factors

- A default factor of 10 (U_A) is used to take into account the interspecies variation. For example, the toxicokinetics and toxicodynamics differences between humans and rats (the test species used in the pivotal study) are not known as no relevant data exist for 1080 in humans, although based on lethal effects, rodents might be as sensitive, or perhaps more sensitive, than other mammals such as humans.

- An uncertainty factor of 10 (U_H) is used to account for intraspecies differences (i.e., human variability) in response to toxic chemicals. This UF was introduced to protect sensitive individuals within a population. Age, sex, genetic composition, nutritional status, and pre-existing diseases may all alter susceptibility to toxic chemicals. To be assigned a factor of less than 10, a chemical must have more than just an adequate, peer reviewed human database (Abernathy *et al.* 2003). Information on toxicokinetics and toxicodynamics variability in humans would also be useful for considering an uncertainty factor other than the default value of 10.

- An UF of 10 (U_S) was used to account for the use of data from a subchronic study as a surrogate for results from a chronic study. This UF appears to be warranted based, for instance on the evidence that prolonged exposure (21 to 126 days) to 1080 in the drinking water of laboratory rats caused depletion of spermatids, formation of spermatid and spermatocyte giant cells, and seminiferous tubule atrophy (Smith *et al.* 1977). Exposure to 1080 for two

months severely impaired the reproduction of mink, which was presumed to be due to oligo- or aspermia (Hornshaw *et al.* 1986).

In addition, subchronic 90-day tests still have their limitations with regard to human health hazard assessment since exposure takes place only for a certain period (approximately 10% of the lifetime (Kroes 1997)). The length of this period may not necessarily be sufficiently long enough to reveal chronic effects, since the substance may produce different toxic responses when administered repeatedly over a long period of time, and the ageing process may alter tissue sensitivity, metabolism or physiological capability. Moreover, spontaneously occurring diseases may also influence the degree and nature of the effect of the substance.

Database uncertainty factor (U_D)

- In relation to completeness of the overall database, the Beck *et al.* (2001) definition of a "complete database" was applied. If these five studies are available, and if clear thresholds can be identified from them, then there is a high degree of confidence that one has approximated an appropriate point of departure. Unfortunately, there is no mammalian multigeneration reproductive toxicity study to date on 1080. There is only one species tested (rats), with regard to teratogenicity, whereas two species are normally required for toxicological evaluation. In case of this factor, professional judgment is required to determine the appropriate value, taking into account the scientific uncertainties of the studies and the overall database.

A U_D of 3 is proposed, considering the definition for a "complete database". A U_D of 3 is judged to be reasonable based on the availability of part of, but not the "complete database". The use of a 3-fold factor here, instead of a default value of 10 is also consistent with current practice (Dourson 1994) in that the use of more than 3 areas of uncertainty with default values of 10 leads to overly conservative estimates of TDI (or RfDs). The common practice is to use only a 3-fold factor for the 4^{th} area of uncertainty and an additional 3-fold factor for a 5^{th} area of uncertainty. Alternatively, the uncertainty factors other than for interspecies and intraspecies variability can be

viewed as all related to general database deficiencies and the overall factor for this area is between 1 and 100-fold (IPCS 1994).

Combined, the overall UFs and U_D that are proposed to be used in deriving the TDI for 1080 is 3000 (i.e., 10*10*10*3). The US EPA is currently using a cumulative maximum of 3000 UF in its risk assessments (Kodell and Gaylor 1999; US EPA 2002).

The IPCS (1994) has recognised the imprecision of the cumulative default factors and in order to maintain credibility of the risk assessment process, IPCS has suggested that the total default UF should not exceed 10 000. If the risk assessment leads to a higher factor, then the resulting TDI would be so imprecise as to lack meaning.

f. Use of statistically derived UF

Kodell and Gaylor (1999) have proposed using an estimate of the upper percentile, such as for instance 95th or 99th of the distribution of the product, $U_H * U_A * U_S * U_D$, of UFs as a statistically valid way of combining UFs, that will be sufficiently protective of the general population but not overly conservative. It has been demonstrated that several of these UFs behave as random variables and that their probability distributions may be approximately by the log-normal distribution (Dourson *et al.* 1996; Hattis 1998).

The upper percentiles of the distribution of the product as a combined UF were derived from the estimates of means and standard deviations of the approximately log-normal distributions of individual UFs. These values are used to replace the conventional product of default factors (Kodell and Gaylor 1999). In obtaining the representative mean (median) estimates, the expression $m_{\ln (U1)} = \ln (U_{1, 0.5})$ is applied ($U_{1, 0.5}$ = observed median of the distribution of uncertainty factor U_1 *(1 = L, S, A, or H)*). Estimates for representative standard deviations are solved for $s_{\ln (U1)}$ in the following expression

$$m_{\ln (U1} + Z_{\alpha} S_{\ln (U1)} = \ln (U_{1, 1-\alpha}),$$

where Z_α is the $100(1 - \alpha)^{th}$ percentile of the standard normal distribution and $U_{1, 1-\alpha}$ is the observed $100(1 - \alpha)^{th}$ percentile of the distribution of uncertainty factor U_1.

Kodell and Gaylor (1999) has used the data of Swartout (1996) in reaching to their conclusion that the estimated mean (median) of $\ln_{(US)}$ is $m_{\ln(US)} = \ln(2) = 0.69$, while the estimated standard deviation, $s_{\ln(US)}$, is found to be 1.30 by using the following formula

$$0.69 + z_{0.05}s_{\ln(US)} = \ln(17),$$

where 17 was the observed 95th percentile of the distribution of subchronic to chronic dose ratios. For both $\ln(U_A)$ and $\ln(U_H)$, the estimated mean (median) is $\ln(1) = 0$. The data of Dourson and Stara (1983) showed that 92% of 490 chemicals evaluated in acute lethality studies had interspecies adjustment factor values of at most 10. An estimated value of 1.64 was obtained for $s_{\ln(UH)}$ from the expression:

$$0 + z_{0.08}s_{\ln(UH)} = \ln(10).$$

The expression

$$U(95) = \exp\{m_{\ln(U)} + z_{0.05}s_{\ln(u)}\}$$

can be used to standardise the various factors in estimating the upper 95th percentiles, U(95).

Table 13 presents the point estimates for the 95th and the 99th percentiles for each individual UF, and the combination of three and four factors compiled from information in Kodell and Gaylor (1999) with some unknown and/or unspecified rationale for the distribution function. A point estimate for the upper percentile, e.g., 95th percentile of the combined range of uncertainty can be obtained from

$$U_{HASL}(95) = \exp\{ m_{\ln(UH)} + m_{\ln(UA)} + m_{\ln(US)} + m_{\ln(UL)} + 1.645 [S^2_{\ln(UH)} + S^2_{\ln(UA)} + S^2_{\ln(US)} + S^2_{\ln(UL)}] ½\}.$$

Table 13

Estimated upper percentiles of distributions of uncertainty factors

Uncertainty Factor	95th Percentile Point Estimate	99th Percentile Point Estimate	Product of Default Factors
U_S	17	41	10
U_A	15	48	10
U_H	15	45	10
U_{HA}	46	228	100[b]
U_{HAS}	161	998[a]	1 000[c]
U_{HASL}		4067	
			1000 x 3 = 3000[d] 998 x 3 = 2994[e]

[a] Maximum value for three uncertainty factors [with some unknown and/or unspecified rationale for the distribution function.] Kodell and Gaylor 1999
[b] Maximum conventional value for two uncertainty factors
[c] Maximum conventional value for three uncertainty factors
[d] Maximum conventional value for four uncertainty factors as suggested by the US EPA
[e] UF derived in section 6.1.1.2 based on Kodell and Gaylor 1999

The formula for U_{HAS} gives a combined UF that is less conservative (but almost similar) than the conventional NOAEL approach of simply multiplying together a set of UFs. Kodell and Gaylor (1999) stated that it is appropriate to use a larger percentile than the 95th percentile, but to still use a point estimate. Due to the limited information available, in particular the relevance of severe toxic end-points to humans, a more conservative approach appears to be warranted. Hence, the 99th percentile is proposed for the purposes of this study.

As can be seen in Table 13, the default maximum factor of 3000 recommended by the US EPA for four factors approaches the estimated 99th percentile. There were three UFs (U_{HAS} = 998) in this study plus an extra factor of 3 to take into account the incompleteness of the database. Since Kodell and Gaylor (1999) did not include database uncertainty factors in their analysis, U_{HAS} will simply be multiplied by the U_D of 3, bringing the total UF to 2994.

g. Use of human data

The presence of human data obviates extrapolating from animals to humans. Therefore, human studies, when available, are given first priority, with animal toxicity studies serving to complement them (Barnes and Dourson 1988). However, using human data in this context requires that the human study should be at least of comparable quality to an animal study that might be used to determine a risk value. Human data that are not directly useful as the basis of the NOAEL value may be compared with animal data to determine the most appropriate interspecies uncertainty factor, rather than a default factor of 10 (Dourson *et al.* 1996).

The principal strength of epidemiological studies is that they yield data for humans. They provide the strongest possible direct scientific evidence of risk to humans. Epidemiological studies also eliminate many of the problems encountered in conducting animal studies, especially those arising from the need to extrapolate from one species to another. However, it is known that well documented human toxicological data occur rarely. Kalberlah *et al.* (2003) have summarised that in two separate studies 92% and 83% of the substances have to use animal data to derive an oral RfD or tolerable absorbed dose (TAD). Even in cases where suitable human data could be found for RfD/TAD derivation, intraspecies extrapolation had to be performed (100 and 96%, respectively) as no data on sensitive subpopulations existed.

An important limitation of epidemiological studies is the difficulty in detecting adverse health effects at low exposure levels. Furthermore, if such studies are available, they often lack quantitative information on the concentrations to which the people have been exposed or to what else the populations have been simultaneously exposed (Ministry of Health 1995a). As in laboratory animal studies, observed associations are usually less pronounced at low levels of exposure, which make the data difficult to assess due to chance, errors, biases, or confounding factors. As suggested by Covello and Merkhoffer (1993), epidemiological studies are not controlled laboratory experiments. The epidemiologist does not control exposure to the risk agent and generally the study is limited to exposures and diseases that occur naturally or

accidentally. Also, one needs to consider the ethical, practical, and legal restrictions associated with experiments involving humans.

Rall (1979) was strongly of the view to place primary reliance on laboratory test results, as human epidemiological studies cannot be used to predict or assure safety for several reasons. Epidemiology cannot demonstrate what effects a substance will have until after humans have been exposed to it and perhaps become ill. Also, it may be impossible to assess the effects of a substance, if exposure has been ubiquitous, because there is no unexposed control group. Furthermore, it is usually difficult to determine doses in human exposures and to identify small changes in common effects, which can be important if the population is large.

As both animal and human data have advantages and disadvantages, both types of data should be analysed when conducting health risk assessments to minimise the uncertainties.

Tolerable Daily Intake (TDI)

A TDI is defined as an estimate of the intake of a substance over a lifetime considered to be without appreciable health risk. Toxicological risk assessments for non-carcinogenic health effects usually result in point estimates for human limit values, such as "Acceptable Daily Intake", "Tolerable Intake" or Tolerable Daily Intake. These terminologies were developed by the World Health Organization (WHO) while "Reference Dose" (RfD) or "Reference Concentration" (RfC) are used by the US EPA (Kalberlah *et al.* 2003). The International Programme on Chemical Safety (IPCS) stated that the TDI is similar in definition and intent to terms such as the RfD and RfC and acceptable daily intake (IPCS 1994). An RfD or RfC is intended to be a level of exposure for the human population that is likely to be without appreciable risk of causing adverse effects for a lifetime (IPCS 1994).

Barnes and Dourson (1988) pointed out that the concept of the "acceptable daily intake" has been used in the field of regulatory toxicology for many years. However, the health significance of exposures to non-carcinogenic substances has received considerable scrutiny, resulting in the introduction of the concept of the term

"reference dose" in order to avoid the use of judgmental terms such as "safety" and "acceptable".

Although the scope of this study is in connection with potential long term exposures to 1080, a "tolerable intake" based on short-term exposure was estimated (see page 127). It needs to be borne in mind, however, that TDIs are based on assumption of lifetime daily exposure, which is the standard method of estimating standard limits, such as the ADIs or RfDs, and therefore is conservative when exposure is only for a short period of time.

For the purpose of this study, the TDI for 1080 was estimated to be 0.03 $\mu g\ kg^{-1}$ bw day^{-1}. (see section 5.1.1.5). The estimated TDI is compared with the estimated exposure. If the calculated TDI is greater than the estimated exposure, the likelihood of an adverse effect occurring in an exposed population is very small.

The term tolerable daily intake (TDI) is used throughout the text except when citing research studies, where the original terminology was retained, e.g., RfD.

5.1.1.3 Exposure Assessment

Exposure assessment determines the degree of contact a person has with a chemical and estimates the magnitude of the absorbed dose (CAAHEAP 1991). Several factors need to be considered when estimating the absorbed dose, including factors such as exposure duration and exposure route. By definition, "duration" is the "period of time over which the person is exposed" (CAAHEAP 1991).

For many health risk assessments, exposure assessment is the most difficult task as it often depends on factors that are hard to estimate and for which there are few data (Covello and Merkhoffer 1993). Critical information on the conditions of exposure is often lacking. This statement is particularly relevant in the case of 1080, as data on conditions of exposure are scant, which makes health risk assessment difficult to quantify. Default assumptions were generally used as the basis for the purposes of this study. It is also known that exposures to the general population are less well documented than occupational exposures (Covello and Merkhoffer 1993). This may

be due to greater uncertainty associated with the activities of the general population. It is known that occupational activity is easier to characterise. As noted by the National Research Council (1994), despite the presence of uncertainty, decision makers may be forced to face the reality that exposures have been either overestimated or underestimated for every member of the exposed population.

When risk is a function of time of exposure, exposure or dose profiles can be very useful. In these profiles, the exposure concentration or dose is plotted as a function of time (Aylward *et al.* 1996). Such profiles are important for use in health risk assessment where the severity of the effect depends on the pattern by which exposure occurs, rather than on the total exposure. For example, 1080, a developmental toxicant, may only produce effects if exposure occurs during a particular stage of development, i.e., the period of organogenesis. During the period of organogenesis, the embryo is most susceptible to the effects of teratogens, such as 1080. This period generally ends some time from the 10^{th} to the 14^{th} day in rodents and in the 14^{th} week of the gestation period in humans. For example, Lu (1996) pointed out that a brief exposure of a rodent to a teratogen on the 10^{th} day of gestation is expected to induce a variety of malformations. Similarly, a single acute exposure to a very high dose may induce adverse effects, even if the average dose is much lower than apparent no-effect levels (Paustenbach 2000).

It is important to identify and evaluate those populations, subpopulations and individuals that are potentially at greater risk of exposure and susceptibility, so that if warranted appropriate mitigation can be implemented. Individuals and groups are deemed to be at potentially higher risk if they are likely to be exposed to high concentrations of 1080, such as drinking water that has been highly contaminated with 1080. Inherent genetic variability, age, gender, pre-existing disease, environmental or lifestyle factors may, among other things, have enhanced the susceptibility (IPCS 2000a) to the toxic effects of 1080. Some subgroups may be especially susceptible to adverse health effects, such as pregnant women, the very young, the elderly, and persons with impaired health (Covello and Merkhoffer 1993).

Since children form a unique subgroup within the population, a separate risk analysis was carried out as a component of this study. Children have vulnerabilities to

chemicals that are quite distinct from those of adults (Morford *et al.* 2004). Children eat three to four times more food per kg of body weight than adults. The air intake of a resting infant is twice that of an adult on a body weight basis. Because of these interactions with their environment, children are easily exposed to more pollutants per kg of body weight than are adults (Fabian 1998; Wigle 2003). Children have immature metabolic pathways compared with those of adults. Therefore, the ability of the child to detoxify or activate and excrete certain toxins would be different from that of adults because of this biochemical immaturity. In addition, children's delicate developmental processes are easily disrupted as they undergo rapid growth and development (Bailer *et al.* 1999; IPCS 1986). Organs such as the kidneys and liver are not functionally developed enough to properly metabolise and excrete toxic chemicals which may lead to additional damage. Furthermore, some systems (e.g., immunological and neurological) are not fully developed and are easy targets for chemical injury (Pohl and Abadin 1995). As with adults, the potential for exposure to 1080 for infants and young children is through ingestion, inhalation, and percutaneous absorption.

The special vulnerability of the young becomes evident when the young and the adult experience the same dose. For example, many substances that can be used with relative safety by the pregnant mother can be quite harmful to her developing child, such as alcohol and tobacco (Kopecky and Koren 1998). The developing fetus may encounter 1080 *in utero* by the placental route – this has been demonstrated in animal studies, where it showed that 1080 was capable of causing malformations in rats (Eason *et al.* 1999). However, whether this occurs in humans is unknown.

Young children may be at risk if milk contaminated with 1080 is a major component of their diet. Cow's milk and those other domestic animals, for example, may also be contaminated with 1080. Although this rarely happens, the accidental contamination of milk has occurred in the past in New Zealand (J. Sim pers. comm. 1998).

The US National Research Council (NRC 1993) report "Pesticides in the Diets of Infants and Children" raised concerns that at least in some cases, children may not be protected adequately by then-current US regulatory policies. However, the relevant question is not whether children are inherently more sensitive than adults but whether

they are at greater risk (Scheuplein *et al.* 2002). If the exposure is greater in a child, then the risk should be greater, whether or not it is judged to be above the toxic effect threshold. Zero risk and absolute safety can hardly be achieved or proven but exposure to very low levels provides negligible or tolerable risk.

Very limited information is available on children's exposure to environmental toxicants. The primary routes of exposure to chemicals in the environment are ingestion of contaminated drinking water, food, inhalation of dusts, and dermal contact (Paustenbach 1995). These exposure pathways may also be relevant to 1080. Children's exposure to lead is an example where a number of studies have been documented. For example, children's exposure to lead is primarily through ingestion. Towards the end of the first year of life, oral exploration is common and it could be accompanied by ingestion of substances not normally regarded as food, a condition called *pica* (Murgueytion *et al.* 1996). Exposure from hand-to-mouth activity (e.g., surface dust and soil) is well documented in several studies such as WHO (1995) and Ruppel (1995). Atmospheric entry of soil into houses and soil brought indoors by animals or human beings (on bodies, clothes, shoes) are also possible sources of exposure. Calabrese and Stanek (1992) determined that approximately 30 percent of household dust was derived from outdoor soil and that the remaining 70 percent came from other household sources such as deteriorating lead paint.

Hand-to-mouth behaviour, such as putting toys and other objects in their mouths and eating food which has been on the floor are relevant, especially in children aged six to 72 months. Mouthing and *pica* are recognised to diminish with continuing development after the first year of life, however hand to mouth activity persists (Barltrop 1966). These factors result in eating less foreign matter by the age of four (WHO 1995). Accidental ingestion may also occur in early childhood as a consequence of increasing mobility and diminishing supervision.

5.1.1.3.1 Quantification of exposure levels

There are no adequate data to accurately quantify the various exposure scenarios for 1080. Estimating the magnitude of the potential dose of 1080 from drinking water requires knowledge of the amount of water ingested, the 1080 concentrations in the

water, and the body weight of the individual concerned. The amount of water ingested per day may vary with each person. When little is known about the specifics of exposure, a value of 2 litres per day for adults, 1 litre per day for children and 0.75 litres per day for infants are used as the default values (Beck *et al.* 2001; U.S. EPA 1992). The DWS NZ also employs 2 litres per day for adults as the default value.

It is important to note that intake is not equivalent to the absorbed dose (IPCS 2000b). Bioavailability data are important in the process of exposure risk assessment. Owen (1990) suggested that organisations such as the US Department of Health and Human Services assume 100% absorption if there is no valid evidence to the contrary. For the purposes of this study, 100% absorption was used as the default value unless appropriate data were available to the contrary. Notwithstanding the high water solubility of 1080 and its metabolite, it is probable that 100% is an overestimate.

*Adult exposure based on **actual concentrations** of 1080 in various media*

Humans can be exposed to 1080 through various routes of exposure. Exposure scenarios considered relevant for the purposes of this study are drinking water, food intake, and inhalation of dust from 1080 baits during aerial spraying programme. The values used in the exposure estimate are the highest concentrations of 1080 found in various media (excluding milk, tea, air and soil) (Table 14). A separate estimate is presented in Table 15 using the maximal allowable concentrations of 1080 in food and drinking water except for dermal and inhalation intakes where no standards are available. Hence, actual 1080 concentrations in air and soil were used.

The following exposure estimates are calculated as:

a. Intake from food

The methodology for estimating uptake via ingestion must account for the quantity of food ingested each day, the concentration of contaminant in the ingested material, and the body weight (kg) of the individual. In this instance, the most likely relevant sources would be contaminated meat (e.g., contaminated feral meat) and contaminated milk. The recommended intake from the Healthy Eating for Adult New Zealanders

(Ministry of Health 2000) of about 200 g day^{-1} meat (surrogate value used for contaminated feral meat) and 500 ml day^{-1} of milk were used for the purposes of this study. The highest 1080 concentration found in contaminated meat was 0.028 mg kg^{-1}, resulting to a likely intake of 5.6 µg 1080 day^{-1}. In milk, the reported value was 0.004 mg kg^{-1} giving an estimated intake of 2 µg 1080 day^{-1} (Table 14). Based on a 70 kg body weight, which is the representative body weight for adult New Zealander equates to 0.08 µg kg^{-1} bw
day^{-1} for meat and 0.028 µg kg^{-1} bw day^{-1} for milk.

It has been shown that 1080 is naturally present in tea. Twigg *et al.* (1996) have shown that a normal cup of tea contains about 0.001 nanograms ml^{-1} (0.001 µg/L) of 1080. An adult may consume an estimate of 450 ml of tea per day; this calculates to 0.00045 µg from tea (Table 14) or 0.0000006 µg/kg bw/day, based on a 70 kg adult. This estimate would be below the TDI.

b. Intake from drinking water

The responsibility for ensuring that drinking water used for human consumption conforms to the DWS NZ is within the purview of the Ministry of Health. The highest concentration of 1080 found in drinking water catchments was 4.0 ppb (this excludes the 9 ppb found in water samples apparently due to contamination by a worker with 1080 dust on his overalls and hands). It should be noted that 4 ppb is only slightly higher than the current PMAV of 3.5 ppb. The rationale in using 4 ppb is discussed in detail in section 7.11.2. Based on a 70 kg body weight (Ministry of Health 2005), the estimated intake from drinking water is 2 * 4 = 8.0 µg $day^{-1}adult^{-1}$ or 0.11 µg kg^{-1} bw day^{-1} (Table 14).

b(i) Water supply contamination

Assumptions:

Treated 1080 baits are spread at the rate of 3 kg of 0.15 % per ha. This is equivalent to 4.5 g of 1080. This amount is used in all three exposure scenarios to demonstrate the amount of contaminated drinking water needed to be consumed to reach the TDI of

0.03 μg kg^{-1} bw day^{-1}. The exposure scenarios set out on page 110 are illustrative and intended as examples only. It should be borne in mind that contamination may vary from one locality to another depending on the hydrology in the area and parameters used in various 1080 applications.

1) *Scenario a*

A house roof water supply is contained in a tank 0.75 m in radius (r), 3kg of bait is accidentally dropped onto the roof. Rain fell overnight, and all of the 1080 (4.5g) is leached out and drains into the tank. The depth of water in the tank is 0.8 m (*d*). The volume of water in the tank is:

$\pi r^2 d$
$= 3.14 \times (0.75 \times 0.75) \times 0.8\ m^3$
$= 1.41\ m^3$ or 1400 litres.

Therefore: The concentration of 1080 in the tank water is 4500 mg 1080/1400 L = 3.21 mg/L or 3214 μg/L.

A 70 kg adult with a dose rate of 0.03 μg kg^{-1} bw day^{-1} would be exposed to 2.1 μg 1080 day^{-1}. An adult weighing 70 kg would need to consume only 0.00065 L (0.65 ml) of the tank water in order to reach the TDI of 0.03 μg kg^{-1} bw day^{-1}.

2) *Scenario b*

The application rate described above was sown to one hectare of water catchment and the entire toxic load was leached from the baits directly into a stream by 25 mm rainfall. The volume of water is 250 m^3 or 250,000 litres.

Therefore: The concentration of 1080 in the water entering the stream is 4 500 mg 1080/250, 000 L = 0.018 mg/L or 18 μg/L.

A 70 kg with a dose rate of 0.03 μg kg^{-1} bw day^{-1} would be exposed to 2.1 μg 1080

day^{-1}. An adult weighing 70 kg would need to consume 0.12 L (120 ml) of this water to reach the TDI of 0.03 µg kg^{-1} bw day^{-1}.

3) *Scenario c*

Similar parameters were used as in "scenario b" but a 100 mm rainfall was used instead of 25 mm. The volume of water is 1000 m^3 or 1,000,000 litres.

Therefore: 4 500 mg 1080/1, 000, 000 L = 0.0045 mg/L or 4.5 µg/L.

A 70 kg with a dose rate of 0.03 µg kg^{-1} bw day^{-1} would be exposed to 2.1 µg 1080 day^{-1}. An adult weighing 70 kg would need to consume 0.46 L (466 ml) to reach the TDI of 0.03 µg kg^{-1} bw day^{-1}.

After the rain runoff enters the stream, the concentration of 1080 will be further diluted depending on the size and flow rate of the stream.

c. Intake from air

The Wellington City Council (WCC) carried out a study (Bromley 1996) to determine the level of 1080 in air addressing the concerns raised by members of the public that aerial application was causing significant 1080 dust in to the atmosphere. The Ministry of Health estimated, based from the WCC study, that airborne dust from 1080 was in the level of 0.0008 µg/m^3 (Durham 1998b). The US EPA (2002) has reported that an adult's intake of air is 20 m^{3}day^{-1}. Therefore, the estimated intake for an adult would equate to 0.0008 * 20 = 0.016 µg day^{-1}adult^{-1} or 0.0002 µg kg^{-1} bw day^{-1}.

d. Dermal intake

The parameters used in estimating the soil dermal absorption were taken from the Ministry for the Environment (MfE) and Ministry of Health (MoH) (MfE and MoH 1997) guidelines. The estimated intake arising from soil that has been contaminated with 1080 was calculated to be 4700 (skin contact area) * 0.5 (soil adherence) * 0.009 (1080 soil content) * 0.10 (dermal absorption) = 0.002 µg. Soil samples were tested

after three aerial applications using 0.15% 1080 cereal (pellet type unspecified) bait. Mean 1080 residues of 1080 in soil was estimated to be 0.009 ppm (Wright *et al.* 2002). The 10% dermal absorption was based on animal data that exists showing lower dermal toxicity.

Table 14 presents the potential 1080 exposure in food, water, air and soil.

Table 14

Summary of highest recorded estimates arising from 1080 exposure in adult**

1080 intake	Parameters used	Estimated daily intake
Intake from meat	Meat intake, 200 g/day [a] 1080 content, 0.028 mg/kg [b]	200 g * 0.028mg/kg = 5.6 µg
Intake from milk	Milk intake, 500 ml [a] 1080 content, 0.004 mg/kg [b]	500 ml * 0.004 mg/kg = 2.0 µg
Intake from tea	Tea intake, 450ml 1080 content, 0.001 µg/L [d]	450ml * 0.001 µg/L = 0.00045 µg
Intake from drinking water	Water intake, 2 L/day; [c] 1080 content, 4.0 µg/L/day [e]	2 * 4.0 µg/L = 8.0 µg
Intake from air	1080 in air, 0.0008 µg/m^3 [f] Air intake, 20 m^3/day [g]	0.0008 * 20 m^3 = 0.016 µg
Dermal absorption	Skin contact area, 4700 cm^2 [h] Soil adherence, 0.5 mg/cm^2 [i] 1080 content, 0.009 mg/kg [j] Bioavailability, 10%	4700 * 0.5 * 0.009 * 10% = 0.002 µg
Total daily 1080 intake = 5.6 + 2.0 + 0.00045 + 8.0 + 0.016 + 0.002 = 15.62 µg 70 kg adult^{-1} or 0.22 µg kg^{-1} bw/day^{-1}		

** excluding milk, tea, air, soil
[a] – Ministry of Health (2000)
[b] – J. Sims pers. comm. (1998)
[c] – Ministry of Health (2005)
[d] – Twigg *et al.* 1996
[e] – Eason (2002)
[f] – Durham (1998b)
[g] - US EPA (2002)
[h] - MfE and MoH (1997)
[i] – US EPA (1989)
j - Wright *et al.* (2002)

*Adult exposure based on **maximum allowable** 1080 in various media*

a. Intake from food

Using the default 0.001 mg kg^{-1} maximum residue limit specified in the New Zealand (Maximum Residue Limits of Agricultural Compounds) Food Standards 2004, the maximum likely intake was estimated to be 0.2 µg 1080 day^{-1} from meat (200g * 0.001) and 0.45 µg 1080 day^{-1} from milk (450 ml * 0.001) (Table 15). Using a 70 kg body weight gives an estimated intake of 0.003 µg kg^{-1} bw day^{-1} for meat and 0.006 µg kg^{-1} bw day^{-1} for milk. The same parameters were used for tea (450 ml * 0.001 = 0.45 µg or 0.006 µg kg^{-1} bw day^{-1} based on a 70 kg adult).

b. Intake from drinking water

It has been assumed by DoC, AHB and RCs that the Ministry of Health has reduced the Provisional Maximum Acceptable Value (PMAV) for 1080 in drinking water supplies as a response to the research findings by Eason *et al.* (1998, 1999, 2001) and Eason and Turck (2002). This is not the case. The PMAV in the DWS NZ (Ministry of Health 2005) has remained unchanged at 3.5 µg L^{-1}. The DWS NZ requires that where the concentration of a Priority 2 determinand[5] such as 1080 exceeds 50% of the maximum acceptable value (MAV) of 3.5 µg L^{-1}, then it should be continuously monitored until such time that the concentration falls to 2 µg L^{-1}. The MAV is defined in the DWS NZ as the concentration of a determinand below which the presence of the determinand does not result in any significant risk to a consumer over a lifetime of consumption.

The Ministry of Health developed a policy in 1998, as an interim measure, that only drinking water containing 2 µg L^{-1} 1080 or less would be acceptable for human consumption (Durham 1998b). The 2 µg L^{-1} was taken as an approximation to 50 percent of the PMAV in the DWS NZ (Ministry of Health 2005). Based on a 70 kg

[5] Priority 2 determinand is a constituent of the water that is present in a specific supply or distribution zone, usually a concentration that exceed 50% of the MAV (MoH 1995).

body weight, the maximum intake from drinking water was estimated to be 2 * 2= 4 $\mu g\ day^{-1}$ adult or 0.057 $\mu g\ kg^{-1}$ bw day^{-1} based on a 70 kg adult (Table 15).

c. Intake from air

The same parameters were used as in Table 14 because there is no standard for 1080 in air. The estimated intake for an adult equates to 0.0008 * 20 = 0.016 $\mu g\ day^{-1} adult^{-1}$ or 0.0002 $\mu g\ kg^{-1}$ bw day^{-1}.

d. Dermal intake

Similarly, the parameters used in Table 14 were adapted. The estimated intake arising from soil that has been contaminated with 1080 was calculated to be 4700 (skin contact area) * 0.5 (soil adherence) * 0.009 (1080 soil content) * 0.10 (dermal absorption) = 0.002 μg.

Table 15 presents the maximal acceptable potential 1080 exposure in food, water, air and soil.

Table 15

Summary of maximal possible exposures, under current acceptable limits, arising from 1080 exposure in adult

1080 intake	Parameters used	Estimated daily intake
Intake from meat	Meat intake, 200 g/day [a] 1080 content, 0.001 mg/kg [b]	200 g * 0.001mg/kg = 0.2 µg
Intake from milk	Milk intake, 500 ml [a] 1080 content, 0.001 mg/kg [b]	500 ml * 0.001 mg/kg = 0.50 µg
Intake from tea	Tea intake, 450ml[a] 1080 content, 0.001 mg/kg [b]	450ml * 0.001 mg/kg = 0.45 µg
Intake from drinking water	Water intake, 2 L/day; [c] 1080 content, 2.0 µg/L/day [d]	2 * 2.0 µg/L = 4.0 µg
Intake from air [j]	1080 in air, 0.0008 µg/m^3 [f] Air intake, 20 m^3/day [f]	0.0008 * 20 m^3 = 0.016 µg
Dermal absorption [j]	Skin contact area, 4700 cm^2 [g] Soil adherence, 0.5 mg/cm^2 [h] 1080 content, 0.009 mg/kg [i] Bioavailability, 10%	4700 * 0.5 * 0.009 * 10% = 0.002 µg
Total daily 1080 intake = 0.2 + 0.50 + 0.45 + 4.0 + 0.016 + 0.002 = 5.17 µg 70 kg adult^{-1} or 0.07 µg kg^{-1} bw/day^{-1}		

[a] – Ministry of Health (2000)
[b] – New Zealand (Maximum Residue Limits of Agricultural Compounds) Food Standards 2004
[c] – Ministry of Health (2005)
[d] – Durham (1998b)
[e] – Durham (1998b)
[f] - US EPA (2002)
[g] - MfE and MoH (1997)
[h] – US EPA (1989)
i - Wright *et al.* (2002)
[j] actual concentrations of 1080; no standards set in air and soil

Child exposure

Infants and children, particularly the former, are groups whose risks may differ qualitatively and quantitatively from those of adults. Infants and children differ from adults in their exposure both qualitatively and quantitatively, in part because they consume more food, drink more water and breathe more air per unit of body weight than adults do (IPCS 2000a). Traditional health risk assessments are carried out using adult data and have not examined the special vulnerabilities of infants and children. Adding an appropriate U_H, e.g., 10 is being used in lieu of such an examination. A default value of 10 is incorporated in most risk assessments.

Standards do not usually contain separate information for children. In this particular situation, there were no data for children, as values derived were all intended for adults. Young children aged 3 to 5 years old have a high food intake relative to their body weight and their mouthing behaviour makes them the highest exposed subgroups of the child population (Bailer *et al.* 1999). For the purposes of this study, exposure estimates target this particular age group.

*Child exposure based on **actual concentrations** of 1080 in various media*

The values used in the exposure estimate are the highest concentrations of 1080 found in various media (excluding milk, air and soil) (Table 16). Table 17 presents the exposure estimates using the maximal allowable concentrations of 1080 in food and drinking water except for dermal and inhalation intakes where no standards are available. Hence, actual 1080 concentrations in air and soil were used.

The following exposure estimates are made based on the following factors:

a. Intake from food

Ingestion of contaminated food is a potential pathway of exposure to 1080 among children. Contaminated meat and milk were the exposure pathways used in this

exposure estimate. It is known that children's exposure from food ingestion may differ from that of adults because of differences in the type and amounts of food eaten.

The same 1080 concentrations used in estimating adult exposures of 0.028 mg kg^{-1}, and the recommended intake from the Ministry of Health's Eating for Healthy Children Aged 2 to 12 (Ministry of Health 2002) of about 100 g was consumed = 2.8 µg of 1080. In case of recommended intake of milk of 500 ml, it would equate to 2 µg of 1080 (500 ml * 0.004 mg kg^{-1}). Tea has been excluded because it is not a beverage that children would normally consume.

b. Intake from drinking water

Water intake in a child aged 3-5 years has been estimated to be 0.87 L day^{-1} (US EPA 1997). Using the same parameters, the maximum intake from drinking water was estimated to be 0.87 * 4 = 3.48 µg $day^{-1}child^{-1}$ or 0.20 µg kg^{-1} bw day^{-1} for a 15 kg child.

c. Intake from air

Children are generally vulnerable to outdoor pollution because they often engage in physical activities or play outdoors. Also, they have relatively high air intake compared to adults (Wigle 2003). Based from the WCC study discussed earlier (Bromley 1996), the Ministry of Health estimated in 1998 that the 1080 airborne dust was around 0.0008 µg m^{3-1} (Durham 1998b). The US EPA (2002) has reported that a child's (3-5 years) intake of air was 8.7 m^3day^{-1}. Therefore, the child's intake of 1080 from air would equate to 0.0008 * 8.7 = 0.007 µg day^{-1} $child^{-1}$ or 0.0005 µg kg^{-1} bw day^{-1}.

d. Intake from soil

The ingestion of soil is particularly relevant for young children because of their mouthing behaviour. The mean soil ingestion rate for children recommended by the

EPA for risk assessment is 100 mg day^{-1} or 200 mg day^{-1} as conservative estimates (US EPA 1997).

A study by Wright *et al.* (2002) showed that the average 1080 residues from soil samples after bait application was 0.009 μg g^{-1}. Using a soil intake of 100 mg day^{-1} soil this would yield a value 0.0009 μg day^{-1}, assuming 100% bioavailability.

e. Dermal intake

Children may be more highly exposed to 1080 through dermal routes than adults as they often play and crawl on contaminated surfaces and are more likely to wear less clothing than do adults. In addition, children have a higher body surface area relative to body weight.

The parameters used in estimating the soil dermal absorption were taken from the MfE and MoH (1997) report. The maximum dermal intake arising from soil that has been contaminated with 1080 was estimated to be 2625 (skin contact area) * 0.5 (soil adherence) * 0.009 (1080 in soil) * 0.10 (dermal absorption) = 0.0012 μg.

Table 16

Summary of highest recorded estimates arising from 1080 exposures in children (3-5 years)**

1080 intake	Parameters used	Estimated daily intake
Intake from meat	Meat intake, 100 g/day [a] 1080 content, 0.028 mg/kg [b]	100 g * 0.028mg/kg = 2.8 µg
Intake from milk	Milk intake, 500 ml [a] 1080 content, 0.004 mg/kg [b]	500ml * 0.004 mg/kg = 2 µg
Intake from drinking water	Water intake, 0.87L/day; [d] 1080 content, 4.0 µg/L/day [e]	0.87 * 4.0 µg/L = 3.5 µg
Intake from air	1080 in air, 0.0008 µg/m^3 [f] Air intake, 8.73 m^3/day [g]	0.0008 * 8.73 = 0.007 µg
Intake from soil	Soil intake, 100 mg/d [d] 1080 in soil, 0.009 µg/g soil [3] [h] Assuming 100% bioavailability	0.009 * 100 * 100% = 0.0009 µg
Dermal absorption	Skin contact area, 2625 cm^2 [1] [i] Soil adherence, 0.5 mg/cm^2 [j] 1080 in soil, 0.009 µg/g soil [3] [h] Bioavailability, 10%	2625 * 0.5 * 0.009 * 10% = 0.0012µg
Total 1080 intake = 2.8 µg + 2 µg + 3.48 +0.007 µg + 0.0009 µg + 0.0012 µg = 8.3 µg 1080 15 kg child^{-1} or 0.55 µg kg^{-1} bw day^{-1} 15 kg child^{-1}		

** excluding milk, air, soil
[a] –Ministry of Health 2002
[b] – J. Sims pers. comm. (1998)
[d] – US EPA 1997
[e] – Eason 2002
[f] – Durham 1998b
[g] - US EPA 2002
[h] - Wright *et al.* 2002
[i] - MfE and MoH 1997
[j] – US EPA 1989

*Child exposure based on **maximum allowable** 1080 in various media*

The following exposure estimates are made based on the following factors:

a. Intake from food

Meat and milk complying with the New Zealand (Maximum Residue Limits of Agricultural Compounds) Food Standards 2004 will have a maximum residues limit of 0.001 mg kg^{-1}. Assuming the recommended intake from the Ministry of Health's Eating for Healthy Children Aged 2 to 12 years (Ministry of Health 2002) of about 100 g was consumed, this would equate to 0.1 µg of 1080. In the case of the recommended intake of milk of 500 ml, it would equate to 0.5 µg of 1080 (500 ml * 0.001 mg kg^{-1}). Tea has been excluded because it is not a beverage that children would normally consume.

b. Intake from drinking water

Water intake in a child aged 3-5 years has been estimated to be 0.87 L d^{-1} (US EPA 1997). Using the same parameters, the maximum intake from drinking water was estimated to be 0.87 * 2 = 1.74 µg $day^{-1}child^{-1}$ or 0.116 µg kg^{-1} bw day^{-1} for a 15 kg child.

c. Intake from air

Using the same parameters as in Table 16, the child's intake of 1080 from air would equate to 0.0008 * 8.7 = 0.007 µg day^{-1} $child^{-1}$ or 0.0005 µg kg^{-1} bw day^{-1}.

d. Intake from soil

Similarly, using a soil intake of 100 mg day^{-1} soil and 0.009 µg g^{-1} 1080 concentration in soil would yield a value 0.0009 µg day^{-1}, assuming 100% bioavailability.

e. Dermal intake

The parameters used in estimating the soil dermal absorption were taken from the MfE and MoH (1997) report. The maximum dermal intake arising from soil that has been contaminated with 1080 was estimated to be 2625 (skin contact area) * 0.5 (soil adherence) * 0.0009 (1080 in soil) * 0.10 (dermal absorption) = 0.0012 μg.

The maximum acceptable potential 1080 exposure in food, water, air and soil is presented in Table 17.

Table 17

Summary of maximal possible exposures, under current acceptable limits, arising from 1080 exposures in children (3-5 years)

1080 intake	Parameters used	Estimated daily intake
Intake from meat	Meat intake, 100 g/day [a] 1080 content, 0.001 mg/kg [b]	100 g * 0.001mg/kg = 0.1 µg
Intake from milk	Milk intake, 500 ml [a] 1080 content, 0.001 mg/kg [b]	500ml * 0.001 mg/kg = 0.5 µg
Intake from drinking water	Water intake, 0.87L/day; [d] 1080 content, 2.0 µg/L/day [e]	0.87 *2.0 µg/L =1.74 µg
Intake from air	1080 in air, 0.0008 µg/m^3 [f] Air intake, 8.73 m^3/day [g]	0.0008 * 8.73 = 0.007 µg
Intake from soil	Soil intake, 100 mg/d [d] 1080 in soil, 0.009 µg/g soil [3] [h] Assuming 100% bioavailability	0.009 * 100 * 100% = 0.0009 µg
Dermal absorption	Skin contact area, 2625 cm^2 [1] [i] Soil adherence, 0.5 mg/cm^2 [j] 1080 in soil, 0.009 µg/g soil [3] [h] Bioavailability, 10%	2625 * 0.5 * 0.009 * 10% = 0.0012µg
Total 1080 intake = 0.1 µg + 0.5 µg + 1.74 µg + 0.007 µg + 0.0009 µg + 0.0012 µg = 2.35 µg 1080 15 kg child^{-1} or 0.16µg kg^{-1} bw day^{-1} 15 kg child^{-1}		

[a] – Ministry of Health 2002
[b] – New Zealand (Maximum Residue Limits of Agricultural Compounds) Food Standards 2004
[d] – US EPA 1997
[e] – Durham 1998b
[f] – Durham 1998b
g - US EPA 2002
[h] - Wright *et al.* 2002
[i] - MfE and MoH 1997
[j] – US EPA 1989
* actual concentration of 1080; no standards set in air and soil

5.1.1.4 Derivation of Tolerable Daily Intakes (TDIs)

In general, TDIs are used to provide information on potential long-term toxic effects of the substance in question (Bender 2002). Toxicity risk assessment currently relies on the estimation of TDIs based on the use of the NOAELs or BMDLs divided by the UFs (Allen *et al.* 1994). However, the TDI value does not guarantee an absolute certainty as there is a low probability that adverse effects might occur and the absence of all risk to all people cannot be assured at this level (Barnes and Dourson 1988). The existence of different TDIs need not imply that any one of them is more "wrong" or "right" than the rest. It is more a reflection of the difference in scientific judgement of risk assessors (Barnes and Dourson 1988).

The TDI can be derived using either the NOAEL or the BMDL divided by UFs, for instance, by Dourson and Stara (1983) and Dourson and DeRosa (1991). The calculation of a TDI by applying a UF to a NOAEL will be referred to as a 'NOAEL approach' since the point of departure was the NOAEL for the critical adverse effects. The estimation of TDIs based on the use of the BMDL based on these same effects and divided by UFs will be called the 'BMD approach'.

For the purposes of this study, the assessments and calculations of TDI were undertaken according to the WHO recommendations as described in the International Programme on Chemical Safety's "Environmental Health Criteria 104, Principles for the Toxicological Assessment of Pesticide Residues in Food" (IPCS 1990).

It should not be categorically concluded that all doses below the TDIs are "acceptable" (or will be risk free) and that all doses in excess of the TDIs are "unacceptable" or will result in adverse effect (Barnes and Dourson 1988). It is important to note that TDIs resulting from the use of large uncertainty factors are quite imprecise, at least 3 fold or down. Any value within this approximately 10-fold range is the same number (M Dourson pers comm. 2007).

To derive the TDI, this can be represented mathematically using the following formula (UFs are used multiplicatively):

Tolerable Daily Intake (TDI) = NOAEL or BMDL/ (U_A*U_H*U_S * U_D* U_L)

where:

NOAEL = no-observed-adverse-effect level (mg/kg/day)
BMDL = benchmark dose's lower bound confidence limit (mg/kg/day)
U_A = interspecies extrapolation
U_H = intraspecies extrapolation
U_S = using subchronic data
U_D = using incomplete database
U_L = extrapolation from LOAEL to NOAEL (if needed), not used with BMDL

The following information shows the steps in deriving the TDI.

Step 1. Identify the pivotal study from the toxicity studies conducted for 1080. There are two pivotal studies chosen: (1) subacute teratology study in rat with a NOAEL of 0.10 mg kg^{-1} bw day^{-1} and (2) the 90-day study in rat with a NOAEL of 0.075 mg kg^{-1} bw day^{-1}. For the purposes of this study, the NOAEL for testicular and myocardial effects from the subchronic study (Eason *et al.* 2001; Eason and Turck 2002) was used in calculating the TDI, i.e., 0.075 mg kg^{-1} bw day^{-1}.

Step 2. Determine the appropriate UFs.

Step 3: Calculate the TDIs for 1080 by dividing the NOAEL or BMDL by the appropriate UFs.

The calculated TDIs from an aggregate exposure to 1080 from all possible combined sources are shown in Tables 16. The aggregate TDIs include combined exposure from food (i.e., meat and milk), drinking water, dermal contact and inhalation exposures. In

the case of children, non-dietary (residential/public) exposure may be more of relevance.

TDI calculations for various scenarios.

(1) Derive the TDI based on NOAEL of 0.075 mg kg^{-1} bw day^{-1}.

Uncertainty factors (UF)

10	U_A
10	U_H
10	U_S
3	U_D

Total = 3000

Therefore: TDI = 0.025 µg/kg bw/day

EPA recommends an UF of 3000 should be the maximum used for risk assessment to be meaningful (Kodell and Gaylor 1999).

Therefore: TDI = 0.025 µg kg^{-1} bw day^{-1} according to US EPA methods.

For the purposes of this study, the statistically derived 99^{th} percentile point estimate of 2994 (see Table 13) was chosen as the UF in estimating the TDI to protect the general population. Rounding off to 3000, the TDI derived gave the same value as the TDI applying the US EPA 3000 UF which equates to 0.025 µg kg^{-1} bw day^{-1}.

TDI values

Comparative TDIs from the NOAEL and BMDL values are shown in Table 18.

Table 18

Comparative TDIs from NOAEL and BMDL values using various UFs

Quantal Toxicity endpoint	NOAEL TDI, µg/kg bw/day		BMDL TDI, µg/kg bw/day	
UF	3000 [a]	2994 [b]	3000 [a]	2994 [b]
Epididymis	0.025	0.025	0.010	0.010
Testicular	0.025	0.025	0.037	0.037
Cardiomyopathy, Male	0.025	0.025	0.033	0.033
Cardiomyopathy, Female	0.025	0.025	0.070	0.070
Teratogenic	0.033	0.033	0.10	0.10

Continuous Toxicity endpoint	NOAEL TDI, µg/kg bw/day		BMDL TDI, µg/kg bw/day	
UF	3000 [a]	2994 [b]	3000 [a]	2994 [b]
Sperm count	0.025	0.025	0.03	0.03
Fetal weight, Male	0.11	0.11	0.15	0.15
Fetal weight, Female	0.11	0.11	0.16	0.16

[a] Maximum conventional value for four uncertainty factors as suggested by the USEPA
[b] Maximum value for four uncertainty factors as derived in section 5.1.1.2

Thus, comparing the NOAEL and the BMDL TDI derived values using the two UFs (Table 18), demonstrated that the TDIs for both approaches gave consistently similar values, with the TDIs derived from the BMDLs resulting in slightly higher values for all aspects except for the epididymal effects. Rounding off, the TDIs were the same or very similar using the 3000 UF and the 2294 UF.

Several BMDLs could be used to establish the TDI. The BMDL computed for male cardiomyopathy (0.10 mg kg^{-1} bw day^{-1}) and for testicular effects (0.11 mg kg^{-1} bw day^{-1}) were chosen as these effects were considered to be the most sensitive end points (Foronda *et al.* 2007a, see published article in Appendix 2) as discussed in earlier sections of this thesis, for instance by Sullivan *et al* (1979), Eason *et al* (2001), Eason and Turck (2002), Whittem and Murray (1963), and Wolfe (1988). Rounding off, a TDI for 1080 was established using the BMDL of 0.10 mg kg^{-1} bw day^{-1} divided by the appropriate UF. Because 2994 is not meaningfully different from 3000, 2994 was rounded to 3000 in the final calculation.

Thus, the TDI would be

$$\text{TDI} = 0.10 \text{ mg kg}^{-1} \text{ bw day}^{-1} / 3000$$
$$= 0.033 \text{ ug kg}^{-1} \text{ bw day}^{-1}$$

For the purposes of this study, the TDI used in this study in estimating the risks from 1080 exposures is 0.03 ug kg^{-1} bw day^{-1} (Foronda *et al.* 2007b, see published article in Appendix 3). This value may be considered as conservative (i.e., protective) and errs on the side of caution due to the incomplete information currently available, as discussed earlier.

Acute/short-term exposure

Although acute exposure is outside the scope of this study, it is recognised that humans may be exposed to 1080 for only a short period of time. In this context, a "tolerable intake" was estimated using the NOAEL of 0.10 mg kg^{-1} bw day^{-1} derived from the teratogenic study conducted by Eason *et al.* (1998; 1999) (see Table 10). Applying an

UF of 300 (i.e., 10 for intraspecies variability, 10 for interspecies differences and 3 for incomplete database), the "tolerable intake" was estimated to be 0.33 ug kg^{-1} bw day^{-1}. This value was ten-fold higher than the TDI derived earlier of 0.03 ug kg^{-1} bw day^{-1} and could be used for health risk assessment purposes when appropriate.

5.1.1.5 Derivation of Provisional Maximum Acceptable Value (PMAV)

As a basic rule, unless there were good reasons to believe the contrary, the WHO Guidelines are usually accepted or adopted as MAVs in the DWS NZ (M. Taylor pers. comm. 2003). The current PMAV in the DWS NZ for 1080 is 0.0035 mg L^{-1} (3.5 ppb). The MAV is established for adults and to a limited extent for children (e.g., for DDT) and assumes that exposure occurs over the entire lifetime.

The WHO recommends that the standard human body weight of 60 kg be used in the calculation. However, a study conducted by the Ministry of Health concluded that the average human body weight in the New Zealand population is 75 kg (M. Turley pers. comm. 2004). The use of a 75 kg bw would not be appropriate for women as they generally weigh less than 75 kg. For the purposes of this study, 70 kg was used as the standard adult human body weight consistent with the DWS NZ 2005.

There were two calculations made:

"Scenario a" using 50% as the proportion of total daily intake allocatable to drinking water, if based on maximum concentrations so far found in various media (excluding milk, tea, air and soil) (Table 14); and

"Scenario b" using 80% as the proportion of total intake allocatable to drinking water, if based on the maximum allowable concentrations in various media, including the Ministry of Health's interim policy measure of 2 ppb for drinking water (Table 15).

The finally proposed PMAV was based on adults and via "scenario a" as derived using the formula:

Adult PMAV = (BMDL/UF * bw * proportion)/daily intake of drinking water

(a) PMAV = (0.10/3000) * 70 * 0.5)/2
= **0.00058 mg/L or 0.58 μg L^{-1}**

(b) = (0.10/3000) * 70 * 0.8)/2
= **0.00094 mg/L or 0.94 μg L^{-1}**

where: average weight of adult = 70 kg
average quantity of water consumed by an adult = 2 L day^{-1}
proportion of total intake allocated to drinking water = 0.50 for "scenario a" and 0.80 for "scenario b"
uncertainty factor = 3000 (for inter and intraspecies variation, subchronic study, and incompleteness of database)

It is common practice to use the data first, and then the relative source contribution defaults second (M. Dourson pers. comm. 2005). The data suggest 50% comes from drinking water, hence 50% was used as the proportion of total intake (refer Table 14). The maximal allowable 1080 concentrations (refer Table 15) in drinking water has accounted for 80% of the total intake. The difference was due to meat and milk contributing a significant proportion of the total intake, therefore reducing the proportion of drinking water in 50% of the total daily intake. It is acknowledged that contamination of meat and milk are considered to be rare incidents. In meat, the highest concentration was used while the concentration of 1080 after considerable dilution within the silo was used in milk (see 2.2.2.2).

The derived value of 0.58 μg L^{-1} (rounding off to 0.60 μg L^{-1}) is 6 fold lower than the current PMAV of 3.5 μg L^{-1} in drinking water for 1080. Using the maximal allowable concentration of 2 ppb, the derived PMAV of 0.94 μg L^{-1} is about 4 fold lower than the current PMAV. It should be noted that the analytical limit of detection for 1080 is 0.1 μg/L (Wright 2007).

PMAV using child parameter:

Child PMAV = (BMDL/UF * bw * proportion)/daily intake of drinking water

The proportion of total intake allocated was based on 4 ppb 1080 concentration present in drinking water in "scenario a" (refer Table 16) while the maximum allowable concentration of 1080 of 2 ppb (Ministry of Health's interim policy measure) was used in "scenario b" (refer Table 17).

Scenario a

PMAV = (0.10/3000) * 15 * 0.4)/0.87

= **0.00023 mg L^{-1} or 0.23 µg L^{-1}**

Scenario b

PMAV = (0.10/3000) * 15 * 0.7)/0.87

= **0.0004 mg L^{-1} or 0.4 µg L^{-1}**

where: average weight of child = 15 kg

average quantity of water consumed by a child = 0.87 L day^{-1}

proportion of total daily intake allocated to drinking water = 0.4 for "scenario a" (refer Table 16) and 0.7 for "scenario b" (refer Table 17)

uncertainty factor = 3000 (for inter and intraspecies variation, subchronic study, and incompleteness of database)

Table 19

Provisional Maximum Acceptable Value (PMAV) for 1080

	Scenario a, µg L^{-1}	**Scenario b, µg L^{-1}**
Adult, 70 kg	0.58	0.94
Child, 15 kg	0.23	0.40

The child PMAV of 0.23 µg L^{-1} is about 15 fold lower than the current PMAV of 3.5 µg L^{-1} in drinking water for 1080 using 4 ppb of 1080 and about 9 fold lower (PMAV

of 0.4 μg L^{-1}) when 2 ppb of 1080 was used as the concentration of 1080 in drinking water (Table 19). However, the use of a TDI for a child's exposure scenario is conservative unless the critical effect is based on toxicity in the young. This is because most critical effects occur after longer exposures, which exceed the childhood portion of the lifecycle.

WHO assigns an arbitrary (default) value of 10 % for drinking water when data are not available concerning the proportion of total intake ingested in drinking water in the derivation of WHO guideline values. This default value is, in most cases, sufficient to account for additional routes of intake (i.e., inhalation and dermal absorption) of contaminants in water (Ministry of Health 1995a). A value of 20% was assigned as the proportion of 1080 intake in the DWS NZ (Ministry of Health 1995). This value was subsequently revised to 50% in the DWS NZ 2005 (Ministry of Health 2005).

The Drinking Water Standards and Health Advisories published by the US EPA (2002) do not include 1080 on their list. The USA may not need a reference value for 1080 as it has limited use in that country, i.e., used only in livestock protection collars designed to kill coyotes when they bite the neck of a lamb or kid goat (Fagerstone *et al.* 1994), and the situation in New Zealand is extremely different from that of the USA. Similarly the WHO guidelines have no MAV for 1080 in drinking water (D. Ogilvie pers. comm. 2004).

5.1.1.6 Risk characterisation

Risk characterisation takes into account the quantitative considerations in risk assessment including dose-response assessment, exposure assessment (Beasley 1996), and uncertainty (Eaton and Klaassen 2001). The risk characterisation should convey that the risk assessment process is subject to scientific uncertainty and disagreement (Paustenbach 1995). Uncertainty can be defined as a lack of precise knowledge about the state of nature (Bailer *et al.* 1999). This creates practical problems in determining how to assess and deal with the uncertainty itself, and also in estimating the risk associated with 1080 exposure. It includes a policy based on science that underlies decisions throughout the risk assessment process (Ohanian *et al.* 1997) and discussion

of data gaps together with recommendations for improving the accuracy of the assessment (Barnard 1994).

The risks posed by exposure are primarily determined by the quantity used and types of 1080 exposure. In this case, the risk may be higher as opposed to other chemicals used in the environment because it is aerially applied. Compound 1080 is released to the environment from ground application but more particularly during aerial application. Estimating the likely absorbed dose of 1080 is a challenging task, especially if one considers all the potential sources of exposure such as food, water, and air. Available data upon which to base estimates of human exposure to 1080 are limited. However, based on exposure estimates drinking water is likely to be the principal source of exposure (Tables 14 and 16).

Exposure from other media, such as air and dermal absorption, appears to be negligible in comparison with that from drinking water. However, 1080 in contaminated feral meat and milk has contributed a significant proportion of 1080 intake because the concentrations of 1080 found in these media were well above the maximum residue limit in food. Since food contamination was considered to be a rare event, the focus of the human health risk characterisation is on the potential exposure of the general population to 1080 contaminated drinking water. Compound 1080 can be legally aerially applied to drinking water catchments provided permits have been obtained from relevant regulatory authorities. Hence, contamination of drinking water catchments cannot be ruled out (see Chapters 1 and 7). Tables 15 and 17 provide the maximal acceptable limits of 1080 in various media, with drinking water providing the likely principal source of exposure.

The primary concern is about the potential toxic effects in humans associated with possible exposures to 1080 long term and at low level of exposures. The magnitude, frequency, and duration of exposure may vary considerably in different situations. Modern toxicology contributes specifically to the assessment of human hazard from exposure to 1080. Ideally, laboratory and epidemiology studies are utilised. However, in this particular case the only information that is available is from laboratory animals and the challenge in health risk assessment lies in predicting what effects will occur in human. Also, the target area in the health risk assessment process is usually the risk at

low levels of exposure. This is where there is lack of data and where projections of effects and risks are most needed (Bailer *et al.* 1999).

Animal studies have demonstrated the adverse effects of 1080. Critical effects identified from the pivotal studies were testicular, teratogenic effects and cardiomyopathy. Since there are no human studies on the subchronic or long-term effects of 1080 in humans, the subchronic toxicity information is limited to laboratory animals. Whether or not the critical effects identified are relevant to humans is unknown. However, it would be prudent from a public health standpoint that with no valid reason to believe the contrary, it is reasonable to assume that these effects also occur in humans.

Noncancer risk assessment is currently based on the assumption that a biologic threshold dose must be exceeded before exposure to a chemical causes effects. Under this view, if a person is exposed to a dose below their threshold of response, no effect is experienced and thus no risk is involved. However, there is variability in the sensitivity of individuals to chemicals and in order to assess population risks, responses of sensitive individuals must be taken into account. Unfortunately, human environmental epidemiological data are rare and, even when available, the data may be inadequate to determine with any precision the threshold for particularly sensitive individuals. Hence, the human threshold dose is usually extrapolated from animal data. Animal test data provide an estimate of the subthreshold dose, or NOAEL. Because the true relationship between this animal threshold dose and the human threshold remains unknown, uncertainty is inherent in the extrapolation.

Two systemic toxicity mammalian studies in different species, one mammalian multigeneration reproductive study, and two mammalian developmental toxicity studies in different species comprise the criteria used to define a "complete database". There is a lack of toxicology studies relating to 1080 chronic exposure studies, and this hinders the determination of appropriate TDI for long-term exposure. Special attention is given to studies involving low-dose chronic exposures, since such exposures can elicit effects that may be considered of health concern.

In general, other studies did not meet these criteria, resulting in a higher UF with respect to the completeness of the database. The UFs can be reduced if additional studies are carried out to generate a "complete database" and better understanding of the interspecies and intraspecies variability of 1080. Testing in the past has focussed mostly on acute effects rather than long-term effects (Horrigan *et al.* 2002) and employing large doses of 1080 to elicit its toxic effects. In addition, it is difficult to interpret older studies they tended to not comply with current GLP standards. Risk assessors should be better placed to adjust UFs once the data gaps are resolved through the conducting of additional studies.

In reality, the majority of risk assessments are based on "imperfect or incomplete" data. An attempt to estimate population threshold for humans is fraught with uncertainty because toxicokinetics and toxicodynamics between the test species and humans have not been studied adequately, and because of the heterogeneity in these processes among human populations. In addition, the paucity of information with respect to toxicokinetics of 1080 in humans highlights the need to carefully limit and monitor occupational and environmental exposures to achieve a better understanding and management of human toxicity (Temple and Edwards 1985). Thus, estimates of the human population threshold will always involve uncertainty (Baird *et al.* 1996).

Since there are no reported adequate long term feeding studies on 1080, any TDI needs to be derived from subchronic studies and the utilisation of higher UFs than would be used when a full toxicology database is available and used in the estimation of the TDI. This short-term exposure scenario may, however, reasonably represent the picture in the case of some feral animals that have been exposed to 1080 entering the human food chain, as human dietary exposure is likely to be very different than average lifetime exposure. Estimating the risk to humans following chronic exposure to low doses can be particularly difficult since laboratory animals are usually exposed to concentrations which approach toxic levels, while humans are normally exposed to concentrations $1/100^{th}$ to $1/1000^{th}$ the NOEL in rodent bioassays (Paustenbach 1989).

For all critical end points a dose response trend was observed. The probit slope for testicular and cardiomyopathy were both steeper than the epididymis. The q1 slope for cardiomyopathy was much steeper for males than the females. The q1 slope for the

teratogenic end point was shallower compared with the other toxic effects (see Table 10).

A major difference was also observed with regard to the susceptibility of males and females to the myocardial toxicity of 1080, males being more susceptible. This was evident as 50% of males were affected at 0.25 mg/kg as opposed to 5% in females (see Table 5). Male rats are well known for their greater capacity to detoxify certain compound because of their higher activity of cytochrome P450-dependent monooxygenases. Therefore, they may demonstrate less toxicity to some compounds than females. However, if the metabolic product is more toxic than the parent compound, they may demonstrate higher sensitivity than females (Hodgson *et al.* 2001). The male specific cytochrome P450s in rat are CYP2A2, CYP2C11, CYP2C13, CYP3A2, CYP3A18 and CYP4A2 while the female specific cytochrome P450 is CYP2C12 (Waxman and Chang 2005). It might be predicted that the differences in the susceptibility of male and female rats to the toxic effects of 1080 could be associated to a large degree with differences in their liver miscrosomal enzymes.

In the case of continuous end points, a statistically significant ($p \leq 0.01$) 15% decrease in fetal weight between animals receiving the highest dose vs control group was observed for both males and females (Table 6). In relation to sperm concentration, the BMDL was defined as the lower 95% confidence limit on the dose that produced a mean sperm count in exposed animals that was 10% less than the mean sperm count in control animals (Pease *et al.* 1991). The sperm concentration was severely affected by this compound, producing a 74% reduction when exposed at 0.25 mg/kg ($2.22 * 10^8 g^{-1}$) (Table 6) and significantly different from the control group ($P < 0.01$).

The pivotal studies utilised that established NOAELs were more recently conducted and complied with GLP standards. The NOAELs established for critical end points were 0.075 mg kg^{-1} bw day^{-1} for the testicular and cardiomyopathy and 0.10 mg kg^{-1} bw day^{-1} for teratogenicity. Six different mathematical models (i.e., three each for quantal and continuous end points) were considered. The BMD was defined as a 10% increase in risk response. The BMDL of 0.10 mg kg^{-1} bw day^{-1} was utilised to estimate the TDI for 1080.

Characterisation of the risk of human exposure to 1080 focussed on the levels of exposure that might occur in the general population with 1080 contamination of environmental media including food and drinking water. The total estimated 1080 intake from various sources of exposure pathways (Table 14 and Table 16) under these conditions was compared with the estimated TDI of 0.03 μg kg^{-1} bw day^{-1}. The estimated total potential intake from 1080 sources was 0.22 μg kg^{-1} bw day^{-1} or 16 μg 70 kg^{-1} adult and 0.55 μg kg^{-1} bw day^{-1} or 8.3 μg 15 kg^{-1} child. These values are seven and 18 times the estimated TDI of 0.03 μg kg^{-1} bw day^{-1} for adults and children, respectively. The exposure assessments were based on an estimate of daily consumption of 2 L and 0.87 L for adults and children, respectively of drinking water contaminated with 4 ppb of 1080 that is likely to be without appreciable risk of deleterious effects occurring during a lifetime.

The emphasis on the so-called "worst case scenarios" appears to be the major shortcoming of exposure assessments, although such an approach may be a reasonable "screening assessment" used to dismiss insignificant hazards (Paustenbach 1989). Predictably, worst-case assessments will usually not describe the bulk of the exposed population and will often overestimate even the most exposed person. Hence, exposure assessment was also provided using maximum acceptable limits of 1080 content in relevant media (Tables 15 and 17). The value of 0.07 μg kg^{-1} bw/day^{-1} is over twice the estimated TDI of 0.03 μg kg^{-1} bw day^{-1}. In children, 0.16 μg kg^{-1} bw/day^{-1} is five times the estimated TDI of 0.03 μg kg^{-1} bw day^{-1}. The exposure assessments were based on daily consumption of 2 L and 0.87 L of drinking water contaminated with 2 ppb of 1080 for adults and children, respectively that is likely to be without appreciable risk of deleterious effects during a lifetime.

For the purposes of this study, exposure of the general population has been estimated based on 4 μg L^{-1} (the value is just over the DWS NZ PMAV of 3.5 μg L^{-1}). Assuming that adult humans drink on average 2 L of water each day, the exposure would be 8 μg 70 kg^{-1} adult day^{-1} or about 0.11 μg kg^{-1} bw day^{-1} for a 70 kg adult. This exposure level is almost four times the TDI of 0.03 μg kg^{-1} bw day^{-1} which demonstrates that it may be possible for a person who consumes drinking water that

has been contaminated with 4 μg L^{-1} to receive an exposure dose above the estimated TDI.

Assuming that adult humans drink on average 2 L of water each day and applying the Ministry of Health's interim recommendation of 2 μg L^{-1} in drinking water (Durham 1998b), the exposure would be 4 μg 70 kg^{-1} adult day^{-1} or about 0.06 μg kg^{-1} bw day^{-1} for a 70 kg adult. This exposure level is twice the TDI of 0.03 μg kg^{-1} bw day^{-1} which demonstrates that it may be possible for a person who consumes drinking water that meets the Ministry of Health's recommendation of 2 μg L^{-1} in the DWS NZ to exceed the TDI, i.e., the PMAV is not adequately protective of public health[6] . Also, **this estimate represents intake of only less than 1 L of water per day so as not to exceed the estimated TDI of 0.03 μg kg^{-1} bw day^{-1}**. This demonstrates that more than 1 L daily water consumption might be a health concern.

Estimating the child intake using 1080 concentration of 4 μg L^{-1}, the exposure would be 3.5 μg 15 kg child day^{-1} (4 * 0.87 L) or 0.23 μg kg^{-1} bw day^{-1} for a 15 kg child. This value is about eight times higher than the TDI of 0.03 μg kg^{-1} bw day^{-1}. For the purpose of the child intake estimate using the maximum acceptable 1080 intake is 15 kg * 0.03 μg kg^{-1} bw day^{-1}/2 μg L^{-1} = 0.22 L. Therefore, if 1080 in drinking water was at the maximum acceptable level (in terms of the Ministry of Health's interim recommendation of 2 μg L^{-1}), a child weighing 15 kg would need to be limited to no more than 0.22 L (220 ml) of water per day, if the TDI is not to be exceeded. This volume is almost four fold less than the drinking water intake allocated to this particular age group. This estimate shows that a child weighing 15 kg gets the same dose of 1080, on a body weight basis, with one-fourth the water intake of a 70 kg adult. This is clearly a small amount of drinking water and is likely to represent a health concern, illustrating that children are likely to be at greater risk of being exposed to toxic effects of 1080 than adults.

[6] The exposure assessment was based on an estimate of daily consumption of 2 L of drinking water contaminated with 2 ppb of 1080 that is likely to be without appreciable risk of deleterious effects during a lifetime of exposure.

Estimates made on various contaminated drinking water scenarios indicated that:

- **Scenario a** - 1,400 L of water contaminated with 4.5 g of 1080 would only need 0.65 ml of drinking water to reach the TDI of 0.03 $\mu g\ kg^{-1}$ bw day^{-1}.
- **Scenario b** - 250,000 L of water contaminated with 4.5 g of 1080 would only need 120 ml of drinking water to reach the TDI of 0.03 $\mu g\ kg^{-1}$ bw day^{-1}.
- **Scenario c** - 1,000,000 L of water contaminated with 4.5 g of 1080 would only need 466 ml of drinking water to reach the TDI of 0.03 $\mu g\ kg^{-1}$ bw day^{-1}.

Comparing all the exposure scenarios modelled, it appears that those who source their drinking water from a tank according to "scenario a" was considered likely to be at most risk from the overt effects of 1080. In the event of such contamination occurring, exposure of the general public becomes a public health issue.

The concentrations of 1080 estimated in the three scenarios modelled was compared with the proposed PMAV of 0.60 $\mu g\ L^{-1}$ and the current Ministry of Health's interim policy measure of 2 $\mu g\ L^{-1}$ (Table 20). To summarise:

Table 20

Comparisons of various Provisional Maximum Acceptable Values (PMAVs)

	Scenario a *	**Scenario b ***	**Scenario c ***
Proposed PMAV of 0.60 µg/L	5357	30	7.5
MoH interim policy of 2 µg/L	1607	9	2.25

* X fold higher than PMAV

The estimates made showed that the volume of water was a significant contributing factor in lowering the level of 1080 present because of the water dilution factor involved.

As there have been isolated cases in the past concerning 1080 contamination of milk and meat, the following analysis illustrates the risk that may arise from these sources. Assuming the recommended amount of milk consumed by an adult (500 ml equivalent to 2 standard glasses) and 1080 content in the contaminated milk was 0.004 mg kg^{-1} (J. Sim pers. comm. 1998), this exposure was estimated to be 2 µg 1080 or 0.03 mg $kg^{-1}bw\ day^{-1}$ in a 70 kg person. The highest concentration of 1080 found in contaminated feral meat from samples that have been taken for testing was 0.028 mg kg^{-1} (J. Sim pers. comm. 1998). The recommended intake for adults is about 200 g = 5.6 µg 1080 or equivalent to 0.08 mg $kg^{-1}bw\ day^{-1}$ in a 70 kg person. Comparing these exposure estimates with the TDI of 2 µg in a 70 kg adult, 1080 intake via contaminated meat intake is almost three fold higher than the TDI. Therefore, it is possible for an adult eating highly contaminated feral meat to be affected and this could be of public health significance.

As shown earlier, children have a greater potential for exposure to 1080. The exposure estimate for milk was 2 µg 1080/15kg = 0.13 µg kg^{-1} bw. This value is four fold higher than the TDI. Meat intake is 2.8 µg 1080/15 kg = 0.18 µg kg^{-1} bw, which is six fold higher than the TDI. Exposures to contaminated meat and milk only constituted minor pathways for 1080 exposure when maximum residue limits were employed in risk assessment. However, when these media were highly contaminated, such as in these scenarios, a single exposure to these sources may likely be of health concern, particularly in children.

Owing to the high biodegradability of 1080, exposures to high concentrations of 1080 over long periods of time appear to be unlikely. However, short-term exposures at high concentrations cannot be ruled out and is particularly relevant in case of women of child-bearing age exposed during the vulnerable periods of organogenesis. These findings have implications for humans exposed to 1080, particularly during the susceptible periods of early development. Approximately 3% of newborn children have one or more significant congenital malformations at birth, and by the end of the first postnatal year about 3% more are recognised to have serious developmental effects (Bracken and Holford 1981). Of these, it is estimated that 20% are of known

genetic transmission, 10% are attributable to known environmental factors, and the remaining 70% result from unknown causes (Wilson 1977). Furthermore, the study of Eisler (1995) demonstrated that it is possible to elicit toxic effects of 1080 even with a relatively short exposure period. A "tolerable intake" based on short-term exposure was estimated, although outside the scope of this study, and could be used as appropriate (see page 127).

The margin of exposure (MOE) is the ratio of the NOAEL or BMDL determined in animals and expressed as mg kg^{-1} $day^{-1}$to the calculated human exposure (Faustmann and Omen 2001; US EPA 2003). Therefore, 0.10 mg kg^{-1} bw day^{-1}/0.22 µg kg^{-1} bw day^{-1}= 454 (adult MOE) (see 5.1.1.3.1 and Table 14) while the MOE for a 15 kg child = 0.1 mg kg^{-1} bw day^{-1}/0.55 µg kg^{-1} bw day^{-1}= 180 (see section 5.1.1.3.1 and Table 16). Using maximum acceptable values would yield an MOE of 1430 for adults (0.10 mg kg^{-1} bw day^{-1}/ 0.07 µg kg^{-1} bw day^{-1}) (see 5.1.1.3.1 and Table 15) and for children, the estimated MOE was 625 (0.10 mg kg^{-1} bw day^{-1}/0.16 µg kg^{-1} bw day^{-1}) (see 5.1.1.3.1 and Table 17). Table 21 summarises the MOEs for the four scenarios described above for easy reference.

Table 21

Margin of exposure (MOE) at various exposure scenarios

	Highest concentration	Maximum acceptable limits
Adult, 70 kg*	454	1430
Child, 15 kg**	180	625

* highest concentration, excluding milk, tea, soil, air

** highest concentration, excluding milk, soil and air

Low values of MOE indicate that the human levels of exposure are close to levels for the NOAEL or BMDL in animals. There is usually no factor included in this calculation for differences in human or animal susceptibility or animal-to-human extrapolation. Based on a NOAEL determined in laboratory animals, MOEs greater than 100 would generally be considered adequate for protection against the potential toxicity of a chemical that has a complete toxicity database (Dourson and Stara 1983; Davidson *et al.* 1986; Burin and Saunders 1999). The assumption that an MOE of 100

or more is acceptable assumes that humans could be 10 times more sensitive to a chemical than the most sensitive laboratory animal tested, and some individuals could be 10 times more sensitive than others within the human population. In this case since the MOEs for both adults and children are higher than 100, these would represent lower levels of risk. However, the toxicity database is not complete for 1080 and thus a MOE higher than 100 is needed for appropriate comparisons of safety.

Although it was acknowledged that 1080 is highly biodegradable, evidence showed that smaller doses of 1080 given at regular intervals produced cumulative effects, such as myocardial damage in sheep (Annison *et al.* 1960). Whether this finding is relevant to humans is unknown. It appears, therefore, that low doses may produce adverse effects and would be of public health concern. The key questions here are whether humans are susceptible to the toxic effects of 1080 at low doses, and if so, at what level of environmental exposure would toxic effects manifest.

Chapter 6

General Discussion

6.1.1 Key findings

The primary concern of this investigation is to develop a model for assessing the public health risk using 1080 as an example. Based on a comprehensive review of the literature considered to be relevant to human health risk assessment, this study found that the critical effects of 1080 exposure in animal experiments were teratogenicity, testicular/epididymis and myocardial toxicity. The BMD approach utilised in the study demonstrated that the BMDLs for both the quantal and continuous end points were generally slightly higher (but comparable) to the corresponding NOAELs for those same endpoints. The pursuit of an appropriate UF was also investigated, which resulted in a statistically derived UF in preference to the use of a conventional default set of UFs.

This study also showed that the most likely source of 1080 exposure would be from contaminated drinking water. Hence, this route of exposure was the main focus of risk characterisation. The proposed PMAV of 0.60 μg L^{-1} for 1080 in drinking water is six-fold lower than the current PMAV of 3.5 μg L^{-1} in the DWS NZ. The current PMAV of 3.5 μg L^{-1} may not be protective of public health, particularly in areas where their drinking water sources are collected from small water supplies or from personal reservoirs where the water dilution would not be so great (see exposure scenarios in 5.1.1.3.1). These findings suggest that the PMAV for 1080 in the DWS NZ estimated based on an adult human being would be of particular health concern if this amount was taken by a 15 kg child.

6.2 Health hazards

There is little reliable information on 1080's action and toxicity in larger animals (Annison *et al.* 1960). The acute health effects of 1080 are well studied in animals, particularly by the oral route, but there is a paucity of data in humans by any route of

exposure. Information on the oral toxicity of 1080 in humans is limited to acute symptoms in a few reported cases of individuals who ingested a single dose of the compound. As pointed out by Bailer *et al.* (1999), there is generally a lack of human data at low levels of exposure. Unfortunately, many substances of toxicological concern do not have human exposure data available. Therefore, in this particular instance only animal model studies were utilised to predict potential human responses. In so far as the availability of data is concerned, rats were the test animals used in the pivotal studies and were therefore used in carrying out the health risk assessment.

The potential health risks of 1080 reflect the identification of the critical end points of toxicity as being reproductive and myocardial toxicity and teratogenicity. The studies commissioned by the DoC and AHB regarding the short term developmental (teratogenesis) and the 90-day sub chronic studies were not robust enough due to lack of, for example, another species for the teratogenic testing and the absence of a chronic study. However, these have been the most useful studies that have been carried out on the potential adverse effects of 1080. Frequently, older studies do not meet current protocol standards. In the case of 1080, older studies were found not to be suitable for the purposes of this study as test animals were subjected to a single lethal dose or only a single duration of exposure. The likely chronic effects of 1080 cannot be accurately ascertained from the test animals as only subchronic studies have been conducted so far. For the critical end points identified (other than the teratogenic effects), the absence of chronic studies is a critical weakness in the health risk assessment of 1080.

Some may argue that a chronic study may not be necessary as 1080 is not likely to be carcinogenic, since genotoxic studies are negative. However, authors such as Kroes (1995) supported the concept that subchronic 90-day rodent tests have limitations with regard to human health hazard assessment since exposure takes place for only approximately 10% of the lifetime. Hence, the substance may produce different toxic responses when repeatedly administered over a long period of time, as the time frame may not be long enough to reveal chronic effects. Moreover, the ageing process may alter sensitivity, metabolism or physiological capability. This study, therefore, agrees with Beck and co-workers' (2001) definition on what would constitute a "complete database", where a chronic study is a main component.

The absence of human exposure information constitutes a critical source of uncertainty for risk-based regulatory decision making. In the absence of 1080 human exposure data, policy makers, regulators, risk assessors, and others must rely on estimates. This approach is limited in identifying health risks because it relies on assumptions about potential 1080 exposures, thus introducing uncertainty in the risk estimates and ensuing policies necessary to protect public health.

Values derived from human studies are preferred, if available, for comparison with estimates of exposure to characterise risk, despite the uncertainties in using epidemiological data (Paustenbach 1995). However, human studies should be at least of comparable quality to an animal study that might be used to determine a risk value (Dourson *et al.* 1996). [Quality here refers to the quality of the study for the purposes of conducting a human risk assessment. Obviously, a well conducted study that monitors an effect in rats that has no counterpart in humans would not be a high quality study for a human risk assessment]. The concept of using human data was not supported by Rall (1979), however, as epidemiological studies are difficult to use to predict or assure safety for several reasons, such as the difficulty of detecting adverse health effects at low exposure levels.

6.3 Toxicokinetics

Metabolism is an important source of species differences in toxicokinetics (IPCS 2000b). Small animals tend to metabolise chemicals more rapidly than humans because their relative liver weight is generally greater, liver perfusion is higher, and the activity of most mammalian hepatic metabolising enzymes, for instance, cytochrome P-450, increases relatively with decreasing body weight (IPCS 2000b). This implies that humans may metabolise 1080 at a much slower rate than rats due to the difference in body size, and therefore may be at greater risk from the toxicological effects of 1080. Schaefer and Machleidt (1971) suggested that fluorocitrate was found in small amounts (as little as 2.5% of ^{14}C fluoroacetate was converted to fluorocitrate) and it is not as toxic as 1080 after oral ingestion in mouse. This finding was supported by Gal *et al.* (1961) who reported that after administration of ^{14}C labelled fluoroacetate, fluorocitrate only accounted for 3% radioactivity in rats. This finding appears to

indicate that fluoroacetate may be more of concern than its metabolite fluorocitrate. Therefore, a slower metabolism may not necessarily to be beneficial.

There is no toxicokinetic and toxicodynamic information suggesting that rat and human metabolism is very similar for 1080, but in the absence of information to the contrary, the assumption should be made that 1080 may manifest the same adverse toxic effects in other species, including humans.

The toxicity of many chemicals requires metabolic activation to reactive compounds, which can cause adverse effects. The major metabolic pathways of 1080 result in a metabolite that is of high toxicity and appears to be readily excreted. Human acute toxicity data were estimated based on only a few observations (Chenoweth 1949). Among the larger animals tested, sheep and human have similar acute toxicities and these were also based on few observations (Chenoweth 1949). As there are no human data to determine the nature or dose-response pattern of the critical effects, it is not possible to determine how 1080 behaves in the body. Whether it is comparable to sheep is unknown.

Incorporation of biological half-life data into risk assessments can have substantial benefits for improving the understanding on potential exposures and risks (Travis *et al.* 1983) associated with 1080 exposures. As shown in Table 2, the elimination half-lives of the different species tested vary (Eason *et al.* 1994b). The results showed that in sheep both the plasma and the muscle elimination half-lives were longer than those of other animal species tested. This may explain the difference in the overall toxicity of 1080 to various animal species investigated. It was also noted that based on their LD_{50s}, rats were more susceptible to the toxic effects of 1080 than mice (Table 3). However, whether their rate of elimination is the same is not known, as there were no specific data for rats.

On the assumption that the elimination half-life of the rats is similar to that of the mouse could be a possible reason why sheep continue to exhibit myocardial toxicity, because their rate of elimination could be longer than the rats. Therefore, it is likely that they are exposed longer to the toxic effects of 1080 due to slow elimination rate. Oral gavage was the route of administration used in both studies. A direct comparison

cannot be made as the dosing regimes were different but it can be assumed that toxic effects may be likely to occur at doses below the 0.075 mg kg^{-1} bw day^{-1} NOAEL derived from Eason *et al.* (2001) and Eason and Turck (2002). Wolfe (1988) obtained a slightly lower NOEL of 0.05 mg kg^{-1} bw day^{-1} for the heart, testes/epididymides and spleen effects. Rats were the test animals used and oral gavage was the route of administration chosen.

In an investigation carried out by Whittem and Murray (1963) in sheep, the myocardium was affected even at the lowest dose of 0.055 mg $kg^{-1}day^{-1}$ applied. Sheep were exposed to multiple doses (0.055, 0.11, 0.22 mg $kg^{-1}day^{-1}$) of 1080. The findings from this study concur with those of Eason *et al.* (2001) and Eason and Turck (2002) which demonstrated that the heart is a critical organ affected by the toxic effects of 1080. The dose of 0.055 mg $kg^{-1}day^{-1}$ was clearly below the NOAEL established by Eason *et al.* (2001) and Eason and Turck (2002) of 0.075 mg kg^{-1} bw day^{-1} and similar to that of Wolfe (1988). It appears that the true lowest effect level may possibly be even lower than 0.05 mg kg^{-1} bw^{-1} day^{-1}.

In an experiment carried out by Annison *et al.* (1960), administration of 0.4 mg kg^{-1} bw of 1080 intravenously to sheep proved lethal within 4 to 6 hours of exposure. However, it was observed that doses of 0.2 to 0.3 mg kg^{-1} bw demonstrated only slight hypersensitivity reactions, irrespective of the route of administration. Interestingly, after recovery from a sublethal dose the animals showed an increased susceptibility to 1080. This finding demonstrated that despite the high biodegradability of 1080, a cumulative effect may still occur. The opposite is true in rats where a non-fatal dose seems to provide a protective effect towards further doses for 24 to 36 hours (Chenoweth 1949) which demonstrated that rats are more tolerant to the adverse effects of 1080 at lower levels of exposure than sheep even though they were exposed for a relatively short period of time. Supporting this notion was the statement made by Eason (2002) that while 1080 itself does not accumulate in the body, repeated exposure to large sub-lethal doses may result in cumulative damage to the heart.

Fluoroacetate has also the ability to cause a reduction in the levels of reduced glutathione in the liver necessary for detoxification as demonstrated by the reduction of liver glutathione levels in skinks exposed for up to 14 days (Twigg 1986). It would

appear therefore that depletion of glutathione may enhance susceptibility to the overt toxic effects of 1080. Whether this finding is relevant to humans is unknown.

6.4 Interspecies variability

Examination of the toxicology data suggested that there were differences between species in susceptibility to the mortality and subchronic toxicity of 1080. Compound 1080 is not selective and it could be toxic to all mammals that ingest the 1080 baits. Dogs are particularly susceptible to both the primary poisoning (direct ingestion of bait) and secondary poisoning (consumption of an animal killed by primary poisoning (Rammel and Fleming 1978)). Development of a tolerance is not a characteristic feature of 1080's action in dogs (Chenoweth 1949). They eventually die when exposed to minute quantities of 1080 (LD_{50} = 0.06 mg kg^{-1} or LD_{100} = 0.10 mg kg^{-1}). Fish, amphibians, and reptiles were usually less sensitive to 1080 than warm-blooded animals (Atzert 1971; Twigg *et al.* 1986).

6.5 NOAEL and BMD approaches

It is well known that the NOAEL does not necessarily identify a zero risk below a threshold dose (Gaylor *et al.* 1998). In this study, the BMD approach, which involves fitting a mathematical model to toxicological dose-response data, was examined as an alternative to the use of a NOAEL. In the pivotal studies, test animals were exposed via the oral route and NOAELs were established for all the critical toxicity end points. All of the studies have at least one dose level above the NOAEL. Model performance (Table 8) was analysed and the AIC values obtained for the three models were comparable.

Gephart *et al.* (2001) suggested that the strength of the BMD methodology is that different models that properly fit the data should give similar BMD estimates for the same data set. The findings from this study generally concur with this notion, as the choice of dose response model had little effect on the estimated BMD. There was a little difference in BMD results between models with a similar fit. Furthermore, the same authors claimed that if models were of equally good fit, then different models should give similar BMD estimates for both the continuous and quantal data. Again,

this notion was supported by this study (Tables 9 and 11). In this sense, the results of this investigation support the argument made by Crump (1984) that model choice is not a critical factor for BMD estimation because model-based extrapolation to low doses is not required.

In comparing the three quantal models (Table 7), all models passed the goodness of fit test although in most cases the Weibull and probit models generally provided a better fit to the data. A difference noted between the first two models and that of quantal linear was with the latter usually producing the more conservative BMD/BMDL, i.e., two to four fold lower in all end points investigated. The probit model provided the best fit to testicular and male cardiomyopathy data and was chosen in estimating the BMDL for the determination of TDI. The quantal linear model was not chosen, although it provided the lowest BMDL, because it provided the worst fit among the models tested (Table 9). The epididymal effects provided the lowest BMDL but this value was not chosen as the point of departure because relevant research studies have concluded that the most critical effects arising from 1080 exposures were the testicular and myocardial effects. In addition, testicular effects and male cardiomyopathy have lower AIC values than epididymal effects (Table 8) and *p*-values of 1.0 and 0.3213 were observed (Table 7), respectively. All continuous dose response models provided reasonable fits to all of the data except for the female fetal weight using the linear model (Table 7). The BMDs for the three continuous models were consistently similar (Table 12), supporting Crump's principle (1984) regarding model choice.

Gaylor *et al.* (1998) pointed out that when no clear dose response is obtained and/or the BMD is calculated to be above the highest experimental dose level, use of the NOAEL might be more appropriate for setting a TDI. The BMD for female cardiomyopathy was higher than the LOAEL, 0.89 mg kg^{-1} bw and 0.25 mg kg^{-1} bw, respectively so it may be more appropriate to use the NOAEL as a point of departure in this particular situation (Table 10). Fowles *et al.* (1999) and Gaylor (1996) suggested that the BMD should be below the observable LOAEL if it is to represent a point of departure for health risk assessment. The BMDL was 0.21 mg kg^{-1} bw which is lower than the LOAEL. The BMD for teratogenicity (0.45 mg kg^{-1} bw) was higher than the LOAEL in the study (0.33 mg kg^{-1} bw) (Table 10). Although the BMD exceeds the LOAEL for female cardiomyopathy, the BMDLs are consistently below

the LOAELs for the other toxic end points, and the BMDL is recommended in deriving the TDI for health risk assessment. Also, Barnes *et al.* (1995) suggested that it was not realistic to assume that implementation of the BMD approach would end the use of the NOAEL approach because there will always data sets that cannot be evaluated using the BMD approach. Hence, the NOAEL approach should be used where appropriate.

For effects that have the same NOAEL, the effect with the steeper dose-response will have a higher BMD (Gephart *et al.* 2001) is generally true for slopes of dose response curves for populations because such slopes reflect population variability, by definition. Thus, steeper slopes indicate more homogeneity in the population and higher BMDLs, other items being equal. Given that the data have the same NOAEL and different slopes, the BMD is likely smallest with shallower slope (M. Dourson pers. comm. 2005). This statement is particularly true in relation to effects on the epididymis, exhibiting a shallower slope and a lower BMD compared with testicular effects and male cardiomyopathy with steeper slopes and higher BMDs (Table 10).

However, the statement conflicts with the observation that the slopes of the dose-response curves for cardiomyopathy in females are shallower than that of cardiomyopathy in males and testicular effects, but the BMDs for cardiomyopathy in males and testicular effects are smaller than those for cardiomyopathy in females. The reason for this apparent discrepancy is that the relationship between the slopes and BMDs for different effects with similar NOAELs depends on the location of the BMR. If the BMR is below the response at the LOAELs, then the effect with the steepest slope will likely have a higher BMD, while if the BMR is above the response at the LOAEL, the shallower slope will likely yield a higher BMD.

Fetal weight changes are often a very sensitive measure of effect of developmental toxicity studies, thus making it an important endpoint in the risk assessment process. Female and male fetal weights have the same slopes but they have different BMDs (Table 12) which could be due to difference in background and power parameters. This was consistent with the suggestion made by Gephart *et al.* (2001). The NOAEL for this end point was at 0.33 mg kg^{-1} and, compared with sperm count, was less affected by 1080 toxicity exhibiting 15% reduction in fetal weight (Table 6).

Compared with many other species, human males produce fewer sperm relative to the number of sperm required for fertility. Since most test animal species produce many more sperm than do humans, negative results in an animal study that is limited to fertility endpoint do not prove that the compound poses no reproductive hazard for men (Obasanjo and Hughes 1997). Therefore men may be at risk of reproductive effects of 1080 and this could be of public health concern. Environmental effects on male fecundity have been reported in a few studies (Mattison *et al.* 1990; Kaur 1988; Stachel *et al.* 1989; Thomas 1981). However, whether these examples are relevant in case of 1080 exposures is unknown.

A gender-related difference was observed in myocardial toxicity, in which male animals were found to be more susceptible than the females at 0.25 mg kg^{-1} bw^{-1} (50% vs 5% of the animals tested, respectively) (Table 5).

6.6 Uncertainty factor

It is known that there is variability in the sensitivity of individuals to chemicals and thus in order to assess population risks the responses of sensitive individuals must be taken into account. Unfortunately, human environmental epidemiologic data are very rare, and even when they are available, the data may be inadequate to determine with any precision the threshold for particularly sensitive individuals. Epidemiological studies are less often available and are sometimes of reduced value because of the lack of quantitative information on the concentrations to which the people have been exposed or to what else the populations have been simultaneously exposed (Ministry of Health 1995a). Hence, the human threshold dose is typically extrapolated from animal data. Animal test data provide an estimate of the subthreshold dose, or NOAEL. Because we do not know the true relationship between this animal threshold dose and the human threshold, uncertainty is inherent in the extrapolation.

The derivation of the TDI for 1080 was based on subchronic studies due to the absence of chronic studies. Higher UFs were utilised to take into account the uncertainties involved in the inter and intraspecies differences, the use of subchronic studies and the incompleteness of the overall database. In addition, critical information on the

conditions of human exposure is lacking. Exposures to the general population are less well documented than occupational exposures due to limited availability of systems capable of measuring the exposures to specific risk agents actually experienced by people (Covello and Merkhoffer 1993).

6.7 Derivation of TDI

The statistically derived UF of 2994 (rounded to 3000 in the final calculation) proposed in this study represents a viable alternative to the use of a product of default factors to establish the TDI. The UF provides a known level of confidence in health protection, without unnecessarily compounding the conservatism built into each individual factor. The same UF of 2994 was used for the BMD approach to make the resulting TDIs comparable, on average, to those calculated using the NOAEL approach. The BMD can provide a more consistent approach that avoids the extreme behaviour of the NOAEL, such as it does not use all of the dose response data; highly dependent on the number of animals used; and constrained to one of the experimental dose (Gaylor *et al.* 1998).

The NOAEL of 0.075 mg kg^{-1} bw day^{-1} for testicular and cardiomyopathy from Eason *et al.* (2001) and Eason and Turck (2002) might provide the most appropriate and relevant basis for 1080 TDI. A complementary study was also carried out with a NOAEL of 0.10 mg kg^{-1} bw day^{-1} based on malformations as the toxic end point (Eason *et al.* 1998, 1999).

Six different mathematical models (i.e., three each for quantal and continuous end points) were considered at 95% confidence limit at 10% risk response. However, the BMDLs generated by the probit models arising from the most critical end points, i.e., male cardiomyopathy and testicular effects of 0.10 mg kg^{-1} bw day^{-1} was ultimately chosen to estimate the TDI, because the use of these models was able to capture more of the available data. TDI of 0.03 ug kg^{-1} bw day^{-1} is proposed to be used for 1080 health risk assessment until additional studies are carried out since these studies may likely reduce the UF in deriving the TDI and thereby likely raise the value of the TDI.

The exposure estimate may be considered conservative, as the general population may not be exposed to 1080 throughout their entire life. However, it can be argued that most risk estimates are based on lifetime exposure possibly due to difficulties in estimating the frequency and length of time an individual has been exposed. This methodology has been widely used to develop TDIs based on the assumption that the general population may be exposed to the chemical in question for lifetime. The PMAV has also been estimated using a similar concept (Ministry of Health 2005). The health risk assessment carried out in this study was based on this rationale.

6.8 Risk characterisation

In characterising the risk for 1080, the potential total intake from 1080 sources was estimated to be 15.62 μg 70 kg adult^{-1} or 0.22 μg kg $^{-1}$ bw/day $^{-1}$ (Table 14). As can be seen, this value is seven-fold the estimated TDI of 0.03 μg kg^{-1} bw day^{-1}.

In 1998, the Ministry of Health recommended an interim level of 1080 in drinking water of 2 μg L^{-1} to be acceptable for human consumption (Durham 1998b). However, the results from this study demonstrated that 4 μg 1080 (2 L * 2 μg L^{-1}) which equates to 0.057 μg kg^{-1} bw day^{-1} for a 70 kg adult is almost two-fold higher than the derived TDI of 0.03 μg kg^{-1} bw day^{-1}. It appears, therefore, that it may be possible for an adult person who consumes 2 L of contaminated drinking water at this level to exceed the TDI. This may pose a health risk to the general population.

By convention, risk assessments are based on adults weighing 70 kg. However, results from this study show that children are likely to be more susceptible than adults to the adverse affects of 1080 based on the parameters used in this study. Children have been shown to be more at risk than adults as the recommended drinking water intake of 0.87L equates to 3.48 μg 1080 (0.87 L * 4 μg L^{-1}) or 0.232 μg kg^{-1} bw day^{-1} for a 15 kg child which is about eight fold higher than the derived TDI of 0.03 μg kg^{-1} bw day^{-1}. Using the Ministry of Health's interim recommendation of 2 μg L^{-1} equates to 1.74 μg 1080 (0.87 L * 2 μg L^{-1}) or 0.12 μg kg^{-1} bw day^{-1}, which is four fold higher than the derived TDI of 0.03 μg kg^{-1} bw day^{-1}. Based on this health risk assessment, children would only need 220 ml of drinking water per day in order to reach the TDI. A 15 kg

child drinking 1 L of water with 2 ppb of 1080 receives 2.2 times the dose per kg bodyweight of a 70 kg adult drinking 2 L of water day^{-1}. Also, children of all ages are still developing so they may be at greater risk than of adults (Scheuplein *et al.* 2002). In general, early life exposures in some instances can lead to adverse health outcomes later in life (Needham 2005). Low level environmental exposures do not cause obvious or immediate illness and their impacts on the society receives less attention. There is a paucity of child exposure information for most chemicals (Hubal *et al.* 2000; Morford *et al.* 2004).

In considering toxic effects at various dose levels, the dose range of interest is generally the low dose range, since it usually reflects the human exposure situation. However, in most cases data for dose responses are available for high doses only and are often derived from animal experiments only. Therefore, the uncertainty in dose response assessment is large. Gavage exposures are expected to result in significant effects since laboratory animals are exposed to higher doses of the chemical administered and the overt effects are seen at short periods of exposure as opposed to continuous low level of exposures where the harmful effects may only manifest over a relatively long period of time. This additional uncertainty justifies a conservative TDI.

The use of the UF for within-human variability (10-fold) and incomplete database (3-fold) which together represent a 30-fold reduction in the TDI to account for sensitivity or the lack of a two generation study that monitored younger animals justified the application of a higher UF. Proponents of the theory that children are at higher risk of adverse effects following exposure to environmental chemicals, including pesticides, advocate an increase for children in the margin of safety that is used when setting exposure limits. In practice, this means an additional safety factor for children that would translate into smaller permissible exposures to children. In considering this point, the NAS panel recommended that an additional UF up to the 10-fold factor should be considered when there is evidence of postnatal developmental toxicity and when data from toxicity testing to children are incomplete.

The additional factor under the FQPA is largely policy-based and not driven by scientific reason (Scheuplein 2000). Furthermore, technical evaluation of the uncertainty factors for both human variability and database completeness show that

these two factors are sufficient to address any children's sensitivity issues (Dourson *et al.* 2002). Based on this rationale, no additional UF was incorporated for children's potential increased susceptibility, but it was incorporated within human variability as discussed earlier (and a separate assessment was made for children, which incorporated the higher exposure considerations).

The environmental fate of a chemical can dramatically influence the degree of human exposure (Paustenbach 1995). Davis *et al.* (1993) has also supported the importance of incorporating information on the fate of chemicals in the environment in their exposure estimates, whenever possible. This is particularly relevant in the case of 1080 as it tends to degrade rapidly. Influencing factors include soil and water microbes, weather and temperature. The resultant change may alter the exposure assessment. If exposure occurs through a water source, then exposure assessment must consider how 1080 is altered over time as 1080 generally becomes diluted and degrades after release. This was the main reason why the interim level recommended by the Ministry of Health of 2 ppb was also used in this risk assessment. In addition, a separate health risk assessment was carried out using the actual concentrations of 1080 found in drinking water.

As 1080 is rapidly biodegraded, it is unlikely that the general population exposed to detectable concentrations of 1080 over relatively long periods of time. However, women of childbearing age may be exposed for short periods of time and it is possible that this may occur during the vulnerable developmental periods and could be of public health significance. In risk assessment, the appropriate application of UF is complicated in the case of teratogenic effects because of the assumption that a single exposure during development may produce an effect, and the recognition that multiple exposures may result in effects at lower doses in many cases (US EPA 1991).

Compound 1080 is an established teratogenic agent in rats. The period of organogenesis (from day 18 through about day 40 postconception in the human) is the period of greatest sensitivity to teratogenic insults and the period when most gross anatomic malformations can be induced. Most major malformations occur before the 36^{th} day of gestation in human (Scialli and Colie 1997). For exposures of limited duration, the time-in-life during which the exposure occurred may be more critically

important in determining whether exposure occurred while the child was developing in utero and possibly on which days of gestation. This is particularly important to women of child-bearing age who may be pregnant, and may be exposed to 1080.

The question posed for the present investigation is whether the adverse toxic effects found in laboratory test animals are relevant to the human population. The establishment of the TDI is complicated by the fact that there are no chronic studies, multigeneration toxicity studies or relevant human data available to help in ascertaining the toxic effects of 1080. A further complicating factor is the lack of information on the amount of 1080 to which the public may be exposed. A low dose extrapolation was required to the dose range most relevant to the general public. However, it should be noted that the degree to which the dose may be below the population threshold is unknown (Dourson *et al.* 2001).

No scientific evidence is presently available on the long-term effects of 1080. However, this is probably due to low occupational and environmental exposures, which has never made the collection of data on 1080 of enough relevance to elicit epidemiological studies.

When limited data are available, and in the absence of empirical data to the contrary, it is generally assumed that a chemical will be absorbed in humans to approximately the same extent as it occurs in laboratory animals. This should take into account that the same conditions of exposure were applied and recognising the differences between species, such as dermal exposure where absorption is often lower in humans than in the common laboratory species (IPCS 2000b).

It is recognised that well documented human data with respect to environmental exposures occur rarely. Intraspecies extrapolation must be performed when no data on sensitive human subpopulations exist (Kalberlah *et al.* 2003). To evaluate critically the adverse effects of 1080, it is necessary to compare data derived from experiments with laboratory animals, the results of epidemiological studies (if any), as well as the effects observed in acute human exposures. These factors are critically important to minimise the uncertainties identified in conducting the risk assessment process.

6.9 Conclusion

The use of BMD methodology to provide a more quantitative dose response evaluation from all available data was investigated with the aim of improving human health risk assessment and compared with the traditional NOAEL approach. Generally, for both the quantal and continuous end points, the BMDLs generated were generally slightly higher but comparable point of departure to the NOAEL approach. The BMD approach has the advantage of using all the data points, resulting in better quantification of the effect level. This study has provided evidence that the BMD approach is useful for improving the scientific basis of the human health risk assessment for 1080.

Available data upon which to base estimates of human exposure to 1080 are limited. However drinking water is likely to be the principal source of exposure (Tables 14 and 16). This statement was supported by Eason (1995) who concluded that the most significant potential exposure route for the general public is likely to be the contamination of surface water in water supply catchments. Exposure from other media, such as air and dermal absorption appears to be negligible in comparison with that from drinking water. Based on exposure estimates derived using the highest recorded concentrations of 1080 in meat and drinking water (excluding milk, air and soil) and the acceptable limits of 1080 in various exposure pathways, intake for the general population would be primarily from drinking water. The focus of the human health risk characterisation is, therefore, the general population exposed to contaminated drinking water.

The adult PMAV derived from the study was found to be much lower than the current PMAV in the DWS NZ (Table 19), suggesting the value may need to be reviewed in light of the findings from this study. At present, the maximum acceptable value is categorised as 'provisional', as it is acknowledged that relevant studies are still missing for the purposes of human health risk assessment. The PMAV can be reviewed and revised when adequate additional information becomes available.

Although not a common practice in setting standards in New Zealand, the increased exposure potential of children may need to be examined with a view to setting a standard that is protective of all the population. It is well recognised that children are more susceptible to the toxic effects of many environmental pollutants. This has been acknowledged in developed countries, such as the USA, where special legislation for the US FDA and US EPA was drawn up to specifically monitor whether existing measures were adequate to protect children. That said, specific examples of standards that have been revised to accommodate extra susceptibility of infants or children are not yet available.

It is worth exploring the option of having additional toxicology and epidemiology studies (if possible) conducted to increase the confidence in the TDI, as this would have significant health policy implications and health risk management approaches.

The recommended PMAV was based on findings from this study. It is up to the relevant regulatory authority to make the final decision on what guideline value should be set in New Zealand. The following chapter discusses health risk management approaches relevant to this study which may serve as the basis in developing policy options taking into account political, cost-benefit analyses, and so on.

Chapter 7

Health Risk Management

7.1 Health Risk management

Health risk management deals with associated health risks so as to protect public health from the toxic potential of 1080 including the management of public health concerns and relevant processes. For the purposes of this study, risk management generally focuses on public health. For simplicity, the term risk management was used throughout this document.

Before health risks can be managed, they have to be assessed and characterised (see Chapter 5). Once risk characterisation has been completed, the focus turns to risk management (van Leeuwen 1995). In reality, health risk assessment and risk management are inextricably linked as shown by the overlapping circles in Figure 12. Risk characterisation (see sections 5.1.1.6 and 6.8), the last step in health risk assessment, is the starting point for risk management considerations (Paustenbach 1995). The risk characterisation showed that drinking water is likely to be the principal source of exposure (Tables 14 and 16). Hence, the risk management for the purposes of this study focuses mainly on drinking water.

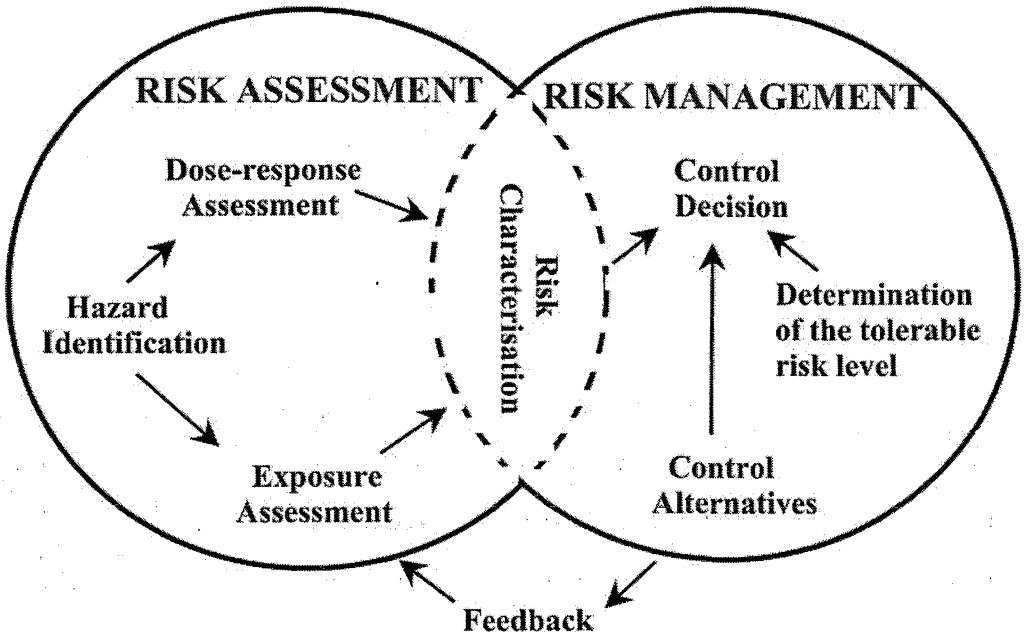

Figure 12

Relationship between health risk assessment and health risk management

Risk management refers to the process of reducing the risks to a level deemed to be tolerable by society and to assure control, monitoring, and public communication (Morgan 1990). It also includes decisions concerning the need for regulatory schemes and the type of scheme that should be implemented. Such schemes may include specifying the PMAV of 1080 in the DWS NZ or setting a TDI. These are called 'intake' standards, i.e., concentration standards based on measurements on ambient medium from which absorption takes place, such as in drinking water or food (Illing 2001). Toxicologists are often concerned with defining the highest amount that can be present in the body without significant ill–health occurring.

Done well, risk management is inherently precautionary in the sense that it should make use of effective health risk assessment to predict, anticipate, and prevent harm, rather than merely reacting when harm arises (Hrudey and Leiss 2003). The book *Silent Spring* (Carson 1962) had a profound effect on the way in which pesticides were viewed by the general public (Wilkinson 1990). This book found a voice in the political and legislative realm (Stark *et al.* 2004). For instance, the Food Quality and

Protection Act in the USA was enacted restricting the use of many pesticides in a wide range of uses. This piece of legislation particularly protects the consumers, especially children, illustrating the increasing public concern about the dangers of environmental contaminants to public health.

Regulation is perhaps the most visible aspect of risk management (Hood *et al.* 1992).

7.2 Statutory framework relating to the use of 1080

There are a number of legislative frameworks relevant to the use of 1080 in New Zealand. These are summarised below:

7.2.1 Hazardous Substances and New Organisms Act 1996 (HSNO Act)

The Hazardous Substances and New Organisms Act 1996 aims to protect the environment, and the health and safety of people and communities by preventing or managing the adverse effects of hazardous substances and new organisms. Section 97 of the HSNO Act sets out the responsibilities for enforcement of the Act and associated regulations. Under this Act, the Director-General (Chief Executive) of the Ministry of Health must ensure that the provisions of this Act are enforced where it is necessary to protect public health which covers all locations in which public health is put at risk.

The HSNO Act repealed a number of statutes in New Zealand, including the Pesticides Act 1979 and the Toxic Substances Act 1979 which were relevant to the use of 1080. The hazardous substances part of the HSNO Act came into force on 2 July 2001. The Pesticides (Vertebrate Pest Control) Regulations 1983 (Pesticides (VPC) Regulations) and the Toxic Substances Regulations 1983 continued in force as transitional HSNO regulations by virtue of section 174 of the HSNO Act. The effect of section 174(4) and (5) of the HSNO Act was to preserve the powers of the functions exercised by the Medical Officers of Health under these regulations and continued until 30 June 2005.

The HSNO transfer process involved the assessment of the intrinsic hazardous properties of 1080 and assignment or a classification to it that was based on the criteria specified in the Hazardous Substances (Classification) Regulations 2001 make the treatment of 1080 consistent with the regulations of other vertebrate toxic agents, such as cyanide. The Hazardous Substances (Sodium Fluoroacetate) Gazette Notice 2005 came into effect on 1 July 2005 and completed the transfer of the risk management of 1080 to the HSNO regime. As a consequence, 1080 is now subject to the HSNO suite of controls which cover the full life cycle of 1080 from import or manufacture through to final disposal. Labelling, packaging, emergency management, tracking and disposal are also covered in the HSNO controls. Under the HSNO Act, all hazardous properties of 1080 are considered and controls are assigned by the Environmental Risk Management Authority (ERMA) in accordance with the appropriate hazard classifications. The default controls may be varied by the ERMA so as to maintain the existing requirements under the previous legislation. The HSNO Act is administered by the MfE and the ERMA.

7.2.2 Resource Management Act 1991 (RMA)

The MfE administers the RMA. There are requirements under the RMA that provide restrictions on discharges of contaminants into the environment. These include discharges to soil, water and air where actual or potential 1080 contamination may occur. In cases where regional plans have classified water as for human uses, discharge of "contaminants" to water either requires a consent or it must be a permitted activity (an activity that is allowed by a plan without a resource consent if it complies in all respects with any conditions specified in the plan) under the RMA. "Contaminant" is defined under the RMA as includes any substance ...

> (a) when discharged into water, changes or is likely to change the physical, chemical or biological condition of water: or
> (b) when discharged onto or into land or into air, changes or is likely to change the physical, chemical, or biological condition of the land or in air onto or into which it is discharged.

Discharges to air may largely be determined by the nature of the discharge activities, such as where 1080 is discharged to air as dust. A resource consent is required for any discharge activities that have actual or potential effects on the environment. Discharge of 1080 to land such as in ground bait applications or for baits that dropped aerially onto land would only require a discharge permit if the activity is restricted by rules or plans. It should be noted that the requirement to obtain a resource consent is only one of the approvals that are required before 1080 aerial operation can be undertaken.

7.2.3 Health Act 1956

The administration of the Health Act falls within the responsibility of the Ministry of Health. The purpose of the Health Act is to improve, promote and protect public health. Local authorities are empowered under the Act to abate nuisances which are offensive or likely to be injurious to health. The functions and powers of Medical Officers of Health, such as the protection of water supplies are set out in this Act.

The nuisance provisions of the Health Act can be used to protect public health. "Nuisance" entails either damage to private property or infringement of a public right which causes "injury" to the public. However, because this provision can only be applied once a nuisance has already occurred, not before its occurrence, it may not be useful in most respects. The Ministry of Health is currently reviewing the Health Act. In 2001, Cabinet approved proposals for the Public Health Bill (CAB Min (01) 29/15).

7.2.4 Food Act 1979

The New Zealand Food Safety Authority (NZFSA) administers the Food Act 1979. All food produced for sale in New Zealand must comply with the New Zealand (Maximum Residue Limits of Agricultural Compounds) Food Standards 2004. These standards are mandatory standards under the Food Act. The MRL for 1080 is 0.001 mg kg^{-1} (default value) or at about the limits of detection.

7.2.5 Agricultural Compounds and Veterinary Medicines Act 1996 (ACVM Act)

The NZFSA is accountable for the implementation of the ACVM Act. The purpose of the Act is to prevent or manage the risk associated with the use of agricultural compounds and veterinary medicines (formerly called animal remedies under the repealed Pesticides Act), such as risks associated with 1080 to the trade in primary produce, animal welfare, and domestic food standards.

7.2.6 Health and Safety in Employment Act 1992 (HSE Act)

The HSE Act is administered by the Department of Labour (Workplace Services). The purpose of the Act relates to the health and safety of employees, and other people at work or affected by the work of other people. The minimisation of worker's exposure to the use of 1080 is covered by the requirements of the HSE Act.

7.2.7 Drinking Water Standards for New Zealand 2005 (DWS NZ 2005)

The Ministry of Health sets the quality standards for drinking water in New Zealand. The DWS NZ 2005 (Ministry of Health 2005) provides a yardstick for assessing how safe the water is to drink. The DWS NZ is considered to be a safety or quality standard, which is another approach to 1080 control. Such a standard is set with the intention to protect human health.

The DWS NZ specifies the Maximum Acceptable Value (MAV) for drinking–water constituents or properties (determinands) of concern to public health. The MAV in drinking water represents the concentration of a determinand which, on the basis of present knowledge, is not considered to cause a significant risk to the health of the consumer over a lifetime of consumption of water. The current Provisional Maximum Acceptable Value (PMAV) for 1080 is 0.0035 mg L^{-1} (3.5 ppb). It is a requirement under the DWS NZ for Priority 2 determinands, such as 1080, that monitoring be carried out if the level of 1080 in drinking-water exceeds 50 % of the PMAV as discussed in sections 5.1.1.3.1 and 5.1.1.5.

7.3 1080 reassessment

The DoC and the Animal Health Board (AHB) are the main users of 1080 for possum control. These two government agencies have applied for reassessment of 1080 in the light of updated scientific research information into the adverse effects of 1080 and the benefits and risks of its use. The ERMA has decided that there are grounds for reassessment of 1080 as new significant information has become available relating to the toxic effects of 1080 since it was initially registered under the Pesticides Act in 1964, and that there is information relating to a significant change in the quantity of substance used (ERMA New Zealand 2002).

The initial target date for reassessment of 1080 in 2002 was postponed due to the inability of the HSNO Act to deal with local issues, such as addressing the need to impose additional conditions to suit local needs. In particular, DoC and the AHB were concerned about whether the new legislation enabled the Medical Officers of Health to retain their former role under the Pesticides (VPC) Regulations which enabled them to impose additional controls on 1080 operations in order to address local needs. These two agencies recognised the concerns raised by the general public being driven by the potential human health risks that may arise from the use of 1080 and they saw the role of the Medical Officer of Health as critical in addressing these public health concerns (N. Hancox pers. comm. 2002). The action taken by the two agencies has acknowledged the importance of public health specialists in dealing with such issues. It is worth noting that the Ministry of Health has raised similar concerns to ERMA on how local issues should be dealt with when 1080 is applied in areas where public health may likely be at risk (S. Gilbert pers. comm. 2002).

The HSNO Act was later amended (Hazardous Substances and New Organisms (Transitional Provisions and Controls) Amendment Act 2004) to give the ERMA the power to delegate the decision for any application for any permits or revocation as specified in the legislation. The power may be delegated to individuals, such as the Medical Officer of Health, or a HSNO enforcement officer, or an employee of the Ministry of Health (see section 5.4). This has been a great improvement to the workability of the HSNO Act in so far as addressing local issues in a similar manner to the previous legislative regime.

On 13 August 2007, the ERMA has announced that the reassessment for 1080 has been completed and highlighted the fact that tighter management regime on the use of 1080 is to be imposed. From 1 January 2008 all aerial operations using 1080 will be actively monitored by the ERMA New Zealand (ERMA NZ 2007).

7.4 Implications for the Medical Officers of Health

Prior to the HSNO Act coming into force, the approval and method of application of 1080 was governed by the Pesticides (VPC) Regulations 1983 (now repealed). Permission from a number of authorities, including the Medical Officer of Health at the local public health unit was required prior to 1080 being used. The role of the Medical Officer of Health is to ensure that public health is not at risk. If the Medical Officer of Health is satisfied that the application or use 1080 to which it relates will not contravene the Health Act and the Pesticides (VPC) Regulations, the regulations require that the Medical Officer of Health give permission to the use or application of 1080. The legislative power to grant 1080 permits is mandatory provided the relevant legislation is not contravened. The Medical Officer of Health may, however, impose additional conditions as he/she thinks fit to protect public health consistent with local needs.

To promote national consistency in setting any such conditions, the Ministry of Health published the Model Permit Conditions for the Use of Sodium Monofluoroacetate (1080) (Ministry of Health 1995b, see Appendix 6) to assist Medical Officers of Health to identify and develop conditions for 1080 use. The Medical Officers of Health use their discretion in applying additional conditions to 1080 permits on a case-by-case basis in light of the toxicology findings.

Under the Pesticides (VPC) Regulations, the Medical Officer of Health may grant a permit to apply 1080 in restricted areas specified in the regulations including on a public road, in any other place to which the public are entitled to have access, within a certain distance of any such road or place, or in any catchment area from which water is drawn for human consumption.

The Hazardous Substances (Sodium Fluoroacetate) Transfer Notice 2005 provides that a permit to use 1080 is required from a person who has been delegated for the purpose by the ERMA. The ERMA has delegated specific functions to Medical Officers of Health and Health Protection Officers (the delegated officers) who are warranted HSNO-enforcement officers and who have obtained a Certificate of Completion of a Ministry of Health risk management course or Health Impact Assessment course, any University of Otago summer school course on risk management or attendance at other Ministry of Health training such as professional development, resource management and emergency management, a Diploma in Public Health, or a Master in Public Health. The delegation under the HSNO Act includes the power to decide an application for a permission; and/or to add, delete or otherwise vary any condition on a permission; and/or to revoke a permission for the use of 1080 in a catchment area from which water is drawn for human consumption or in any other area where a risk to public health may be created by such application.

The Medical Officer of Health's role in ensuring that public health is not compromised during 1080 operations is illustrated in the following example (M. Broughton-Webb pers. comm. 1998). In April 1998, residents of Wairarapa expressed concerns about a proposed 1080 drop in the catchment of the Waihora stream due to the low rainfall and the Wellington Regional Council (WRC) decided to postpone the operation until normal rainfall returned. When the Medical Officer of Health met with the local residents, it was agreed that if the operation were to continue during the abnormally dry weather then WRC would be required to provide the local residents with alternative drinking water. The provision of the drinking water would need to continue until testing showed that the Waihora stream was not contaminated with 1080. Because of the abnormally dry weather and the minimal flow in the Waihora stream, the Medical Officer of Health agreed that the WRC would need to consult with and obtain the agreement of all users of drinking water drawn from the Waihora stream as to when the testing of the stream would take place. As a result of this meeting, the WRC indicated that they did not intend to proceed with the operation until rainfall occurred and the flow of the Waihora stream returned.

7.5 Model 1080 permit conditions

The Ministry of Health's model permit conditions (Ministry of Health 1995b) provide guidance to Medical Officers of Health. These model permit conditions (Appendix 6) are the Ministry's expectations but are only best practice guidelines in that they have no statutory status. However, the conditions become legal requirements if they are included by the Medical Officer of Health as part of their permit conditions.

The model 1080 permit conditions were developed by the Ministry of Health after rigorous consultation with affected parties. The model conditions were finalised taking into consideration the views expressed by the District Health Boards (then Crown Health Enterprises), regional councils, DoC, Ministry of Agriculture and Fisheries (MAF), PCE, National Pest Control Agencies (NPCA) and the National Beekeepers Association. Furthermore, considerable discussion took place between relevant agencies, such as DoC, AHB, NPCA, and representatives from the regional councils, in particular on whether the additional conditions were achievable and reasonable prior to finalising and printing the model permit conditions (M. Taylor pers. comm. 1995).

The Medical Officer of Health has the statutory authority to apply the conditions to the permits for the 1080 applications, but may vary the conditions from the Ministry of Health's model permit conditions in some circumstances to meet local needs. For instance, the requirement for water sampling may be waived if historical results are available from the same area and have demonstrated that 1080 concentration in the water will be less than 2 ppb of 1080 and the same conditions are proposed with the application, such as the strength and rate of application. However, these would be at the discretion of the Medical Officer of Health and additional precautions may be required due to unforeseen circumstances and may compromise public health.

Special emphasis was given in relation to drinking water catchments because of the controversy over this area. For the purposes of the permission required from the Medical Officer of Health, the restriction applies to any drinking-water catchment from which water is drawn for human consumption. As a guideline to the Medical

Officer of Health, the Ministry of Health has defined this to mean that a "catchment area from which water is drawn for human consumption", is simply "a water catchment that is used as a source of human drinking water". However, there were difficulties encountered in the above definition, in particular, Northland where over 90% of the area is probably a water catchment (J. Jarman pers. comm. 1996). The definition was revised by the Ministry of Health in 1998 for the purposes of regulation 12(1)(f) of the Pesticides (VPC) Regulations (now repealed) only as "Any area from which rainfall flows into a body of water, that is proximate enough to an abstraction point which supplies water for human consumption, such that it can be said that the water is drawn from that area." (Durham 1998c).

Drinking water catchment is not defined in the HSNO Act. The same definition was adopted for the purposes of Hazardous Substances (Sodium Fluoroacetate) Gazette Notice 2005 only and this definition was included in the approved application form (Appendix 4). However, this is not a statutory definition and should be applied cautiously. It is considered essential to take into account the potential threat to human health of application/use of 1080 in relation to the abstraction point supplying water for human consumption.

7.6 Concerns/problems surrounding the 1080 national application form and permit conditions

In 2000, the Medical Officers of Health agreed to use standard application and permission forms for the use of 1080 taking into account the model permit conditions and incorporating the ability to carry out a health impact assessment. The forms were formally adopted by the Medical Officers of Health in November 2000 but it was acknowledged that the individual Medical Officer of Health may adapt and vary the forms as they think fit. The revised application and permission forms were subsequently amended to take into account the HSNO requirements and the comments from all public health units. The forms were then approved by the ERMA for use by a delegated person[7] from 1 July 2005. These forms were subsequently amended and approved by the ERMA New Zealand in June 2007 and required to be used from 1

[7] Person acting under a delegation from the ERMA.

July 2007 (Appendices 2 and 3). It should be noted that the delegated persons have no power to modify the application form but it can be amended if a new approval is obtained from the ERMA New Zealand. However the conditions set in the permit form may be modified or waived by the delegated person as she/he sees fit to suit local circumstances. The permit form also specified the fact that the HSNO requirements are minimum requirements and that stricter conditions may be imposed by the delegated person.

The health impact assessment component of the application form should be carried out by the agency conducting the operation and that any potential public health risks that have been identified and the proposed measures in mitigating those risks should be advised to delegated persons. In this way, delegated persons would be in a better position to set conditions in 1080 permits. There is also some confusion as to what would constitute a "drinking water catchment". A definition was provided in the application form for the purposes of the Hazardous Substances (Fluoroacetate) Gazette Notice only (see section 7.5 and Appendix 4)

Because most of the 1080 operations are now being contracted out, the agency conducting the operation is considered to be "responsible" for all poisoning operations where permits have been granted under their names because in most cases delegated persons would not even know the contractors and/or subcontractors.

The need for a shorter version of the application form was also raised by users of 1080 to PHUs when the application form was initially reviewed in 2005 because others found the form too complex from a user's point of view. On balance, this was found to be acceptable by others as contractors would only need to mark any item "not applicable" if it was not relevant to their application.

It is known that risk can never be entirely eliminated from life, and risk reductions come at a price (Zeckhauser and Viscusi 1990). To put this statement in the context of using 1080, in 1999 the Wellington Regional Council (WRC) raised concerns with the then Minister of Health regarding the burden that tighter controls on 1080 use placed on them in terms of the financial impact and the potential alarm these additional conditions may raise in the general public (G. Durham pers. comm. 1999). For

instance, the WRC raised concerns in 1999 about the "excessive" water sampling regime and cost with additional water sampling costs around $25,000 for a period of six months. In addition, it was claimed that testing increases public concern generated by the requirement to notify affected households of the application of 1080 in their drinking water catchment and providing alternative drinking-water (G. Durham pers. comm. 1999). WRC stated that the concerns outlined in their letter to the Minister of Health were a reflection of national concerns and were not confined to the Wellington region.

However, the Ministry of Health does not view this cost of water sampling and monitoring to be excessive, when considered within the overall Council budget of $5 million for pest control operations. For example, New Zealand spent over $30 million in 1993/94 (since increased) and $14 million has been allocated for possum research in 1995 (G. Durham pers. comm. 1999). The price indicated by the WRC was indeed not onerous and the findings from this study have shown that water monitoring is crucial in 1080 operations.

WRC advised that other councils were canvassed about their concerns, and asked what permit conditions were applied in their regions, and whether they were consistent. Regional councils were seeking consistency in the approach and procedures of Medical Officers' of Health nationally. Fundamental inconsistencies identified were the Medical Officers of Health interpretation of risks with water supplies, application of ground laying and interpretation of regulations to territorial authorities.

The MAF have also expressed concerns about the effect any restrictions on 1080 use may have in jeopardising the existing possum control programme and subsequent impact this may have on the incidence of bovine tuberculosis, export markets and viability of agriculture (G. Durham pers. comm. 1999). Addressing the concerns raised by MAF, the permit conditions do not restrict the use of 1080 *per se*, but merely ensure that adequate monitoring of environmental conditions and quality control standards are followed. In addition, it should be noted that excessive levels of 1080 in dairy milk, as occurred in Carterton where nine dairy cows died (J. Sim pers. comm. 1998), may be of concern from the perspectives of both consumers and damage to export markets.

Despite these two major issues, the permit conditions have been applied throughout the country because the conditions can be modified to suit local needs.

7.7 Tolerable level of risk

Zero risk and absolute safety is unlikely to be achieved or proven. Hence, the major question is the tolerability. A good approach to risk management should achieve a tolerable risk. The terms "tolerable" and "acceptable" have the same intent (similar to ADI and TDI as discussed in section 5.1.1.2) but the term "tolerable" is chosen, for the purposes of this study, because it connotes a level of intake that could be tolerated by an individual. It does not imply acceptability of that level in any other sense. The term "acceptable" is retained if the original author has used this word on the original text.

What constitutes a tolerable risk is an important decision that will vary according to a large number of circumstances. It is basically a policy decision that must carefully weigh a number of factors. It should be noted that what is tolerable for risk assessors may not necessarily be tolerable to communities who are susceptible to threats.

For carcinogens, the DWS NZ presents concentrations in drinking water that are equivalent to lifetime cancer risks of one in 10 000 (10^{-4}) to one in a 100 000 (10^{-5}). Risk estimates are determined by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure through drinking water. This provides a low-dose estimate cancer risk to humans that are considered unlikely to pose a carcinogenic risk in excess of the stated values (US EPA 1989).

For non-carcinogenic pesticides such as 1080, a common way to derive an equivalent value is with the MOE. It should be noted, however, that this is not actually a measure of risk but an exposure. However, the MOE has been used as a surrogate for an acceptable risk level (R. Howd pers. comm. 2005).

With the BMD modelling approach, the actual level of risk at low dose levels can be extrapolated. This is frequently achieved using the 5% effect level (an effect in 5% of

the population) (R. Howd pers. comm. 2005). For the purposes of this study, the probit model was employed and the same parameters were applied as in deriving the $BMDL_{10}$ for 1080 (see Chapter 5) but the 5% effect level was used instead of the 10% effect level. The $BMDL_{05}$ for 1080 for male cardiomyopathy and testicular effects were estimated to be 0.07 mg kg^{-1} bw^{-1} day^{-1} and the statistically derived UF of 2994 (rounded to 3000) was used in deriving the tolerable level of risk. The tolerable risk level was estimated to be 0.024 µg kg^{-1} bw^{-1} day^{-1}.

7.8 Policy involvement

Attempts to estimate population threshold for humans based on studies of toxicity in laboratory animals are fraught with uncertainty. The uncertainty is compounded by the absence of chronic animal studies and availability of information on the incidence of adverse chronic health effects in humans. The sensible approach is to use the best scientific understanding of relevant risks and adopting sensible default assumptions in the face of uncertainty (Ellman and Sunstein 2004). Any approach for deriving, for instance, a TDI or PMAV, inherently involves both scientific assessment and policy judgement. This mixture of science and policy causes difficulty for decision-makers because the relative impacts of scientific assessment and policy judgment, respectively are not readily evident.

When there is substantial scientific uncertainty about the risks, policy decisions should be made that err on the side of caution with respect to the health of the public (Kriebel *et al.* 2001). Existing 1080 data do not permit comprehensive health risk assessments of all possible exposure situations. Therefore, a certain amount of scientific uncertainty is by necessity inherent in most situations (Johnston and Simmons 1990).

Risks cannot be evaluated solely on the basis of scientific considerations alone, but evaluation involves a decision on what risk is 'tolerable'. What constitutes 'tolerable' is a societal judgement and depended on how the public perceives the risk (Illing 2001). This would also include taking into account residual risks, such as those not evaluated because they have not been identified. Providing that the health risk has been fully assessed, the residual risk remaining after implementation of the appropriate

management procedures should be at least 'tolerable'. The major question is ascertaining what is 'tolerable'. This area is where policy decisions are made.

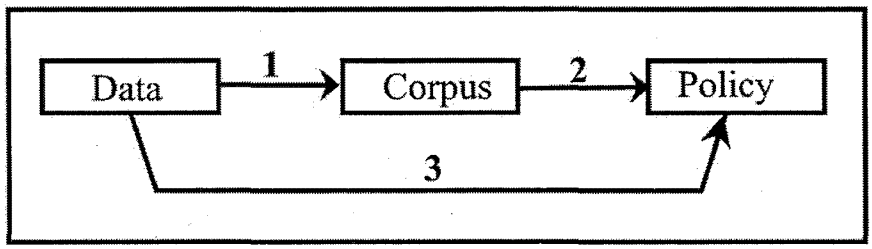

Figure 13

Use of scientific data for policy purposes

Figure 13 illustrates the use of scientific data for policy purposes (Hansson 2002). Data originating in toxicological experiments and other observations give rise to scientific corpus of information, e.g., complete database for 1080 (arrow 1). In developing policy, sufficient scientific corpus of information is normally used (arrow 2). In the context of protecting public health, however, exclusive reliance on sufficient scientific information may have unwanted consequences. The thalidomide incident is a classic example, in which several thousand children were born with serious birth defects. When thalidomide was initially tested, no teratogenic effects in rats and mice at 4,000 mg/kg were observed. Due to the negative finding, thalidomide was allowed to be continuously taken by pregnant women. It was later discovered that limb malformations could be produced in certain strains of white rabbits if they were exposed during the 8^{th}-16^{th} days of gestation. Several strains of monkeys were also found to be susceptible and gave similar malformations to those seen in humans (Timbrell 2000).

In this study, due to incomplete data currently available on 1080, the evidence would not be sufficient to warrant its use solely for the purpose of influencing policies in the "standard" way (arrows 1 and 2). However, if toxicological evidence suggests that a precautionary approach is warranted, a direct route from scientific data to policies (arrow 3) should be applied (called a science-based precaution by Hansson and Ruden

2002). This precautionary approach was adopted for the purposes of this study. The National Radiological Protection Board (2004) defines "precautionary approach" as a scientific term used to describe the cautious process that scientists use when converting experimental data into advice on acceptable levels of public exposure to any agent. Where data cannot provide a reliable estimate, it is customary to use the most conservative estimate of the risk when setting standards.

The scientific research community and policy decision makers have viewed responses to the uncertainty of risk estimations, and its consequences differently (McMichael 1989). Determining an "acceptable" level of risk entails a complex interaction of science, perceptions, values and priorities of different social interests (Steensberg 1989). "Acceptability" varies with time and place. This can be demonstrated by the following scenarios:

- What was tolerable in the past may no longer be tolerable in the future or vice versa. In 1995, the PMAV for 1080 in the DWS NZ was 5 ppb but this was subsequently reduced to 3.5 ppb in the 2000 and 2005 editions of the DWS NZ in light of the results from the latest teratology study commissioned by DoC and AHB.

- What may be acceptable in one country may be totally unacceptable in another. In the USA, the use of 1080 is limited to livestock protection collars while it is legally allowed to be aerially applied in New Zealand. Use of 1080 is restricted in many countries, such as the USA because of its effects on native mammals and predators during poisoning operations. However possums have no natural predators in New Zealand and there are only two native mammals (both bats) (NPCA 1994).

7.8.1 Recommendations made by the Ministry of Health

The Ministry of Health has encouraged health officials to adopt a precautionary approach and use tighter controls on permit conditions governing the use of 1080 (Durham 1998a, 1998b). This was as a result of toxicology studies commissioned by

the DoC and the AHB which indicated that potential risks from exposure to 1080 were higher than previously thought, as discussed in previous chapters.

This precautionary approach included recommending to Medical Officers of Health that they apply the specific model permit conditions relating to drinking-water supplies when granting permits for 1080 use in drinking water catchment areas. In addition, the Ministry advised Medical Officers of Health to require water sampling for 1080 in those affected areas to ensure that contamination levels were below 50% of the PMAV set in the DWS NZ. The Ministry of Health has further advised that 1080 concentrations above 50% of the PMAV (i.e., 2 ppb) should not be recommended as permissible for human consumption (Durham 1998b).

The Ministry of Health has made two recommendations to the Medical Officers of Health that could be applied to water catchments used for drinking water. These were for alternative situations, to be part of the permit conditions as a precautionary measure and that the following conditions given below be part of a 1080 permit. However, these conditions were not applied consistently in all localities because they were at the discretion of the local Medical Officer of Health (Durham 1998b).

- A permit exemption should not be granted when applying 1080 in any catchment area from which water is drawn for human consumption, unless it is possible to avoid use of water from that catchment until the chemical analysis of the water demonstrates a level of less than 2 ppb and for affected residents to be provided with an alternative drinking water source. For example, if there are multiple sources of water supply, one source could be segregated from 1080 applications and used until the level of 1080 in the water source affected by the 1080 application is less than 2 ppb.

- If 1080 is applied in a catchment area which is the only source of drinking water, mandatory monitoring of the water supply, to the satisfaction of the Medical Officers of Health, is required until tests show that the concentration is below 2 ppb. Depending on the circumstances (e.g., the extent to which water from the treated water catchment is diluted by other sources), health officials may require that an alternative temporary drinking-water supply be available, such as bottled water or storage of uncontaminated water by households. This could involve notices being issued by regional councils to the households in the area prior to 1080 being laid so that water can be stored and the public make informed choices.

7.8.2 Proposed actions

The preliminary collection of information provided by the public health units on the way 1080 was used in their region (see Appendix 7) demonstrated that all public health units grant permits to drop 1080 onto drinking water catchments and appropriate conditions are imposed when such permits are granted. In addition, there were occasions where 1080 baits were inadvertently dropped onto drinking water catchments. Key 1080 issues/incidents brought to the attention of the Ministry of Health by the local PHU that were of public health significance are summarised below:

- The anti-1080 lobby have attempted to provide evidence of the biological plausibility validating the linkage between the alleged cluster of miscarriages and the aerial application of 1080 in the Tararua ranges. They implied that exposure to trace levels of 1080 in drinking water below the detectable limit or to 1080 dust led to miscarriages and malformed babies.

- A 1080 mishap had occurred sometime in 2001. 1080 baits accidentally dropped in an area where Takaka residents sourced their drinking water supply, resulting in residents being very concerned about the possible contamination of their drinking water supply. The 1080 baits were discovered by chance after a resident had gone for a walk.

- An off-target drop of 1080 near Westport was reported to the Ministry of Health in 2001. The target area was near Westport but the actual drop occurred within the Westport drinking water catchment. Calculations of the worst-case scenario suggested that the maximum number of pellets which may have entered the water supply was less than 20. Monitoring of the water supply was immediately undertaken. In this particular scenario, the results showed no detectable levels of 1080 in the water supply as the dilution may have been too great for the concentration of 1080 to be analytically measured, i.e., below the limit of detection.

In view of the likely contamination of drinking water, adequate precautionary measures should be taken to ensure that health of the general public would not be put

at risk. The proposed conditions are similar to those previously recommended (see section 7.7.1) and support the precautionary approach adopted by the Ministry of Health. The only difference is the suggested maximum allowable concentration of 1080, i.e., from 2 to 0.60 μgL^{-1}. The conditions proposed will be at the discretion of the delegated person as he/she sees fit to meet **local** needs.

In some circumstances, it may be appropriate for the delegated person to apply discretion and have less stringent requirements. This could depend, for instance, on,

- the extent to which drinking-water source area in the catchment has been diluted by other sources;
- the distance between the treatment area and the draw-off point for the water supply;
- water test results from previous operations covering the same catchment at the same or greater application rate;
- method of application of 1080 (ground laying and the use of bait stations are likely to involve lower risk of contamination of surface water than aerial application).

7.8.3 Ground application

1080 aerial application has been a focus of controversy and has been recognised as posing greater risk than ground application because the latter is likely to involve lower risk of contamination because of the better control of the location of the bait drops. There are limited data to assess the effect of ground based 1080 poisoning application. WRC (2000) has concluded in its report that following hand broadcasting of 1080 baits, water samples contained no detectable levels of 1080 and therefore ground-based application appears not to have a measurable effect on the quality of drinking water. This may likely be due to less quantities of bait entering water courses and thus, less stringent requirements may be required for ground application than for aerial

application. For example, if a locality has a 1080 water monitoring data available from previous treatments, this information could be used to ascertain whether or not the level of 1080 may be likely to exceed the proposed PMAV of 0.60 μgL^{-1} and further water testing may not be required or the numbers and frequency of samples collected may be reduced. Any additional requirement would depend on local circumstances and will be at the discretion of the delegated person.

However, it was recognised that ground application was not always appropriate in some areas and aerial application may still be the best option to take by the agency conducting the operation (Ministry of Health 1995b). Thomas (1994) suggested that effective and safer control of possums could be achieved using bait stations containing 1080. Several advantages of using bait stations include, but are not limited to,

- the actual amount of 1080 used can be reduced by over 90% from the amounts currently used in aerial application;

- baits can be placed at selected locations so that waterways and public-use areas such as roads can be avoided;

- bait stations are designed specifically for possums, making it difficult for non-target species to eat toxic bait by placing bait stations in trees out of their reach;

- unused toxic baits can be removed from the forest.

7.9 Monitoring

Water tests

The agency conducting the operation is responsible for ensuring that water intended for human consumption has been tested by a reputable laboratory, such as a laboratory recognised by the Ministry of Health for the purposes of examining whether drinking water complies with the DWS NZ. This requirement should be included as a condition of the permit.

The Landcare Research Ltd has prepared a set of guidelines for water sample collection and handling (Wright 2007) and it is recommended that these guidelines be consulted for demonstration of compliance with the DWS NZ. In addition, NIWA has published a report (Suren and Lambert 2004) stating that water samples should be collected within 8-12 hours after 1080 operation.

Because the possibility of run-off into drinking water supply could not be eliminated, monitoring would need to be repeated following rainfall. If the level in the water supply exceeds the proposed PMAV of 0.60 μgL^{-1}, an alternative supply may be required to be provided. The agency conducting the operation may need to address levels of concern from the general public in such circumstances. For example, the public should be advised of any forthcoming 1080 operation and that they should store drinking water for their use or (free) bottled water could be provided until the monitoring results are available to demonstrate the safety of the drinking water supply. These requirements would be at the discretion of the delegated person to suit local circumstances.

Figure 14 illustrates the decision flowchart when water sampling would be required. However, water sampling would be at the discretion of the delegated person after assessing the situation.

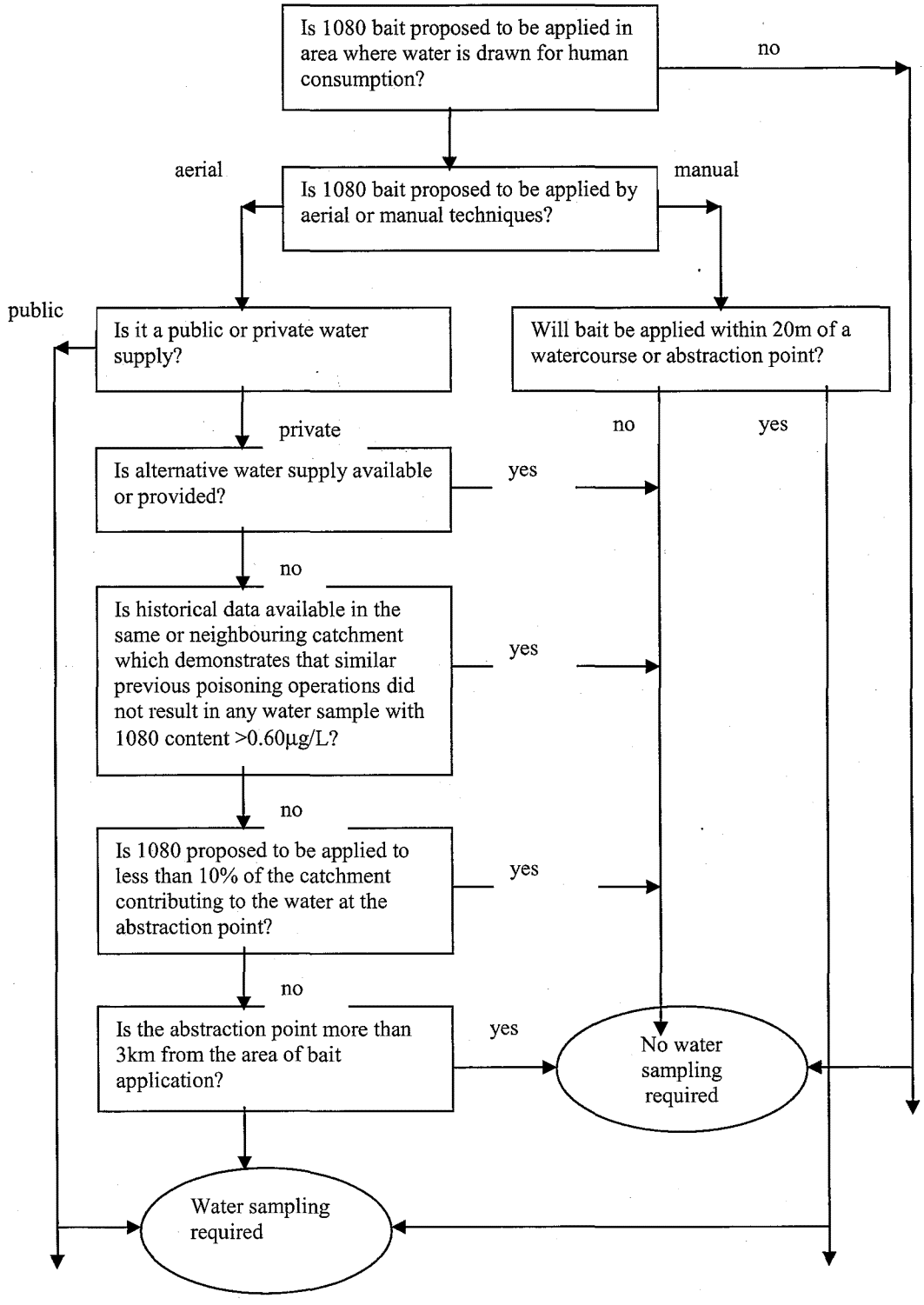

Figure 14

Guide to water sampling requirements where 1080 is proposed to be applied

Source: Modified from Ministry of Health 2006

The water sampling protocol prepared by Wright (2007) is still recommended for use. The protocol states that "samples should be taken immediately after 1080 poisoning operations and continue daily until after the first significant rainfall water reaches the sampling site. Samples may also be taken before poisoning and from adjacent sites, to provide a check on the sampling process."

The recent study carried out by Suren and Lambert (2004) suggested that water should be collected within 8-12 hours after 1080 poisoning operations to detect the presence of 1080. This has implications for water sampling programmes that commonly sample water 24 hours after an operation. The study showed that the 1080 concentrations detected during a fish experiment were "within" the 2 ppb recommended by the Ministry of Health. Data extrapolation demonstrated that all the 1080 would have leached from the baits by 18 hours (Suren and Lambert 2004). Based from this information and on the assumption that drinking water has been contaminated with 1080, it can be assumed that the 1080 peak concentration occurred is within 24 hours. It was also reported by Suren (2006) that the potential number of baits falling into a stream cannot be calculated from the bait application rate and the stream size. Furthermore, the distribution of baits in most of the stream was non-uniform. Therefore, assessing 1080 water contamination should be done on a case by case basis.

The findings from previous monitoring programmes (Wright 2007) showed that water samples above 1 ppb have occurred in the first two days (48 hours) of sampling which appeared to be inconsistent with the findings by Suren and Lambert (2004) which stated that water samples should be collected within 8-12 hours for 1080 to be detectable. It is emphasised that advice should be sought from the local regional council hydrologist or a water quality scientist with respect to the choice of water sampling times when designing the water monitoring programme.

Others (meat and milk)

Contaminated samples would be tested and monitored (if required) as the need arises.

7.10 Future research

From the gaps in information identified, it is considered that additional toxicology studies are required to meet the definition of a 'complete database' (Beck *et al.* 2001) (see section 5.1.1.4) to provide a more sound basis for reviewing or updating the health risk assessment as discussed in chapter 5 of this study. This would provide more comprehensive data and be the basis of a review of the PMAV of 1080 in the DWS NZ and provide a more defensible TDI. These studies should include two systemic mammalian studies in two different species, one mammalian multigeneration reproductive study and two mammalian developmental toxicity studies in two different species. A 14-day teratogenic study has already been carried out by Eason *et al.* (1998, 1999), and it is proposed that another species be tested since two species are required for standard toxicology tests.

An epidemiological study also appears to be warranted to ascertain whether or not humans are susceptible to the toxic effects of 1080 at environmental exposure levels. An important limitation of epidemiological studies is the difficulty in both detecting adverse health effects at low level of exposures and characterising the general population. The difficulty in conducting such epidemiological studies is acknowledged.

Laboratory animal data may still be the only available data for extrapolation to calculate the human threshold, since a policy that is based on evidence alone, such as epidemiological studies, may take decades to be established. Both animal and human data (if available) should be carefully analysed and both sets of data may need to be used where appropriate.

The need for additional studies has been supported by Fleury (1995) who has suggested that longitudinal studies of any long-term impact of 1080 on communities are uncommon despite the fact that this has been an area of public concern voiced by protesters and others. If repeated and robust studies can demonstrate that 1080 does not give rise to a public health risk, current restrictions imposed by Health authorities, for example, may be able to be relaxed. Although the views expressed in the Fluery

article have in part been overtaken by events in that additional toxicology studies have already been carried out which confirmed that 1080 is a teratogenic, testicular/epididymis and myocardial toxin (Eason *et al.* 2001; Eason and Turck 2002), the recommendations remain valid because additional studies are indeed required.

The challenge in this context is to enable the design of policies that would protect the general population, specifically children, against environmental exposures to 1080, to improve research and other initiatives whose purpose is to protect children, and to ensure that new safeguards consider special risks to children.

7.11 Discussion

7.11.1 Key Findings

The study found that the adult PMAV for 1080 in drinking water is 0.60 μg L^{-1} which is 6-fold lower than the current PMAV in the DWS NZ (in children the derived PMAV was 0.23 μg L^{-1} which is 15-fold lower than the current PMAV in the DWS NZ). The Ministry of Health previously recommended that if 1080 is present at 50% of the PMAV then continuous monitoring should be carried out until the level of 1080 meets 2 ppb from drinking water to be considered as permissible for human consumption at this concentration (Durham 1998b). Since the database for 1080 is incomplete, it is not possible to develop a policy directly using the available scientific information, i.e., arrows 1 and 2. Therefore, it is suggested that the development of policy will be derived from the model developed by Hansson (2002), i.e., from scientific data to policy (arrow 3) as illustrated in Figure 13.

Based on the adult PMAV derived from the actual 1080 present (see section 5.1.1.3), the proposed PMAV is 0.60 μg L^{-1} and 50% of the proposed PMAV equates to 0.30 μg L^{-1}. It would be prudent for the Ministry of Health's earlier interim policy to be reviewed in light of the findings from this study and utilise 0.30 μg L^{-1} as the trigger requirement for the monitoring for 1080 in drinking water source that may have been contaminated. Although it is recognised that exposure to drinking water contaminated with 1080 is extremely unlikely to be lifetime (see "tolerable intake" for short-term

exposure on page 126), this should be treated with caution due to the fact that teratogens exert their biologic damage after only short durations of exposure and also on the assumption that it could manifest even after a single exposure (US EPA 1991), and that the health effects can be lasting and serious. In addition, since the derivation of the TDI and PMAV were based from an incomplete database it is of utmost importance that this factor should be accounted for in the risk management process.

It would be prudent to apply a risk management process that will minimise the exposure of the susceptible population. The risk management should always include the precautionary approach, which is well recognised by a number of authors, such as Bodansky (1991), Kriebel *et al.* (2001), Raffensperger and Tickner (2001) and Harremoes *et al.* (2001). At present, it is hardly possible to estimate accurately the risk to humans from the data that are currently available on 1080. Case studies by Harremoes *et al.* (2001) have demonstrated that there are valid reasons to adopt the precautionary approach and acknowledge and respond to the uncertainty and potential risk that may result. In this case, these are the adverse toxic effects of 1080, which should be taken into account in policy decision-making process.

It would appear, therefore, that the findings from this study might have implications for public health since the PMAV estimated was 6-fold lower than the current PMAV in the DWS NZ. The findings may also have significant impact in relation to the risk management process in the context of a lower permissible level of 1080. However, it appears that only a small proportion of the population may be affected by this finding. People whose drinking water source comes from a reticulated water supply or in any drinking water supply where, historically, no detectable levels of 1080 were measured because of significant water dilution that has occurred may not be affected and this group accounts for the majority of the population.

However, it is acknowledged that there are some rural households that draw drinking water from local streams or personal reservoirs, and are not connected to domestic reticulated systems. People on unreticulated surface water, e.g., personal reservoirs will need to be accounted for since they could potentially access higher concentrations than any other group, because the water dilution factor would be much lower (see exposure scenarios in 5.1.1.2).

The risk management process proposed in this study was not considered onerous and is, in fact, very similar to the risk management protocols currently in place as recommended by the Ministry of Health (see sections 7.7.2 and 7.8). Mandatory water sampling may need to be required after 1080 aerial application or in any 1080 operation where drinking water may have been contaminated. The monitoring should continue until the 1080 concentrations found from the water tests are below the requirement for Priority 2 determinands in the DWS NZ. The recommendations are consistent with the Ministry of Health's precautionary approach until additional information is made available and further health risk assessment is carried out and the proposed PMAV can later be reviewed. The proposed actions are already in place (with minor modifications) at the discretion of the delegated person.

7.11.2 Water monitoring

Fisher and Eason (2003) reported that previous water monitoring programmes carried out in New Zealand between 1990 and 2003 after 1080 aerial applications showed that 1080 concentrations complied with the 2 ppb recommended by the Ministry of Health as suitable for human consumption. No detectable levels of 1080 were found in reticulated water while significant and prolonged 1080 contamination was not evident in surface waters. Only five percent of over 1450 water samples tested found 1080 close to the limit of detection (Eason 2002a; He Korero Paihama 2001) and these levels were transient and associated with the visible presence of baits in small streams. The 1080 levels ranged from 0.2 to 9 $\mu g\ L^{-1}$ (see Appendix 1).

In certain areas, 1080 levels were above the 2 ppb, such as, in Marlborough Sounds, Erua State Forest, Te Whaiau Spillway, Toko, and Te Kopia Scenic Reserve (Appendix 1). The report did not specify which water samples (if any) were collected from drinking water catchments. It appears that since there were water samples where 1080 residues were higher than others, it would not be appropriate to use the mean level in the exposure assessment, because using the mean value would underestimate the likely exposure of those who live in areas where 1080 water levels were high. Hence in line with the precautionary approach, 4 ppb was used in the exposure assessment.

The number of samples taken in each operational area was unclear (Appendix 1). For example, there were 125 water samples taken in 1993 in Mt. Taranaki resulting in 15 samples that contained 1080 residues but only four samples taken in 1995 in the Waimakariri with only one sample showing 1080 residues at 0.2 ppb; and four water samples in the Waitohu Stream taken in 1996 with no detectable levels of 1080. It appeared that from the water data, the limited number of water samples taken in some areas as described above may not provide sufficient data to establish conclusively that a specific drinking water catchment had historical water 1080 data that meet the Ministry of Health's interim policy measure of 2 ppb. It should be borne in mind that water contamination should be assessed on a case by case basis.

In the early 1990s, the analytical limit of detection for 1080 was 0.3 ppb (this value is 50% of the proposed PMAV) which means that some of the water samples tested may have had levels of 1080 that may have required monitoring as required for Priority 2 determinands had the proposed PMAV of 0.60 ppb from this study been the basis of such a requirement. The limit of detection improved to 0.1 ppb from 1995 when advances in instrumentation provided much improved sensitivity (G.Wright pers. comm. 2005).

The water sampling from 1990 to 2002 may have also been based on a 24-hour sampling period according to the protocol written by Wright (1998). Suren and Lambert (2004) reported that water sampling should be carried out within 8-12 hours after 1080 operation but not later than 24 hours to be able to test for the presence of 1080. Therefore, the time difference may explain the reason why 95% of the water samples showed no detectable levels of 1080.

It can be argued that despite the fact that water samples were tested within the 24-hour period, 1080 levels were still detected. The highest level found in surface water was 4 ppb (Fisher and Eason 2003) suggesting that 1080 does not biodegrade within such a short period of time as suggested by Suren and Lambert (2004). In fact, Wright (1998) stated that water samples containing above 1 ppb occurred during the first two days (i.e., 48 hrs) of sampling.

Results of water testing could be used to reassure the public of the safety of the programme, as well as individual householders of the safety of their water supply. Monitoring 1080 in water supplies also provides benefits for regional councils and other agencies, particularly from a public risk perception approach. Appendix 9 shows the survey carried out by this author (NF) in relation to public perception of risk from the use of pesticides and 1080. Over time, the monitoring records can be used to evaluate whether there needs to be the same level of ongoing monitoring in the future (G. Durham pers. comm. 1999).

To demonstrate compliance, the agency conducting the operation must provide the delegated person with water monitoring data showing compliance with the Ministry of Health's interim policy measure on 1080 of 2 ppb. Samples must have been analysed by a laboratory recognised by the Ministry of Health for the purposes of examining drinking water. Compliance can be demonstrated by the following factors and it would be at the discretion of the delegated person.

- continued monitoring[8] is required if the level of 1080 is more than 50% of the PMAV;

- water dilution is so great that the level of 1080 is at or below the limits of detection;

- based on historical information of a particular water supply as complying with the Ministry of Health's interim policy measure of 2 ppb.

The PCE report (1994) considered that 1080 was a contaminant. However, DoC has taken the view that the scientific evidence of the effects of 1080 when it enters water does not support classifying 1080 as a "contaminant" for the purpose of RMA because the impact is so minimal as to be outside the scope of the definition (PCE 1994). Based on the assumption that the PCE's interpretation is correct, then discharge permits must be obtained if 1080 could enter water sources unless there are rules made

[8] Continuous compliance monitoring is defined as the process of measuring and recording a defined chemical property by taking frequent measurements, using an electronic monitoring device specifically designed for the purpose, to prove the values of the measured property meet the requirements of the DWS NZ.

under the regional plans classifying the use of 1080 as a permitted activity. This activity is particularly relevant in cases where 1080 baits are aerially applied. However, if 1080 aerial application is a permitted activity in the resource consent of a local authority, then this poisoning operation is not notifiable. This non-notifiable activity has raised concerns to the general public living in the vicinity of 1080 aerial application (M. Molloy pers. comm. 2003).

Definition of Water Supplies

Public water supply

The working definition of public water supplies for the purposes of the Hazardous Substances (Vertebrate Toxic Agents) Transfer Notice 2004 and Hazardous Substances (Sodium Fluoroacetate) Transfer Notice 2004, is:

"all water supplies that are not to self-supplied buildings are classed as public water supplies".

According to the Water Supply Protection Regulations 1961, a "public water supply" means any mode, system, or works for the collection, supply, and distribution of wholesome drinking water in any district by a local authority or by any person or persons authorised by any enactment to undertake the supply of such water to the public. The WSP Regulations definition effectively means that the only water supplies that are public supplies are ones owned by local authorities. However, using the WSP Regulations definition would leave a significant portion of the population unprotected by the provisions of the vertebrate toxic agent consent conditions. It is suggested that a public drinking-water supply serving 25 people or more should give written permission/s. However this is up to the discretion of the delegated person/s.

Private water supply

A private water supply is simply one that is privately owned (i.e., it is not used for profit). The Ministry understands that identifying private water supply sources is standard practice for more rural operations.

7.11.3 1080 model permit conditions

The Ministry of Health published the model permit conditions (Appendix 6) initially to provide assistance to the Medical Officers of Health. The Ministry of Health has not established rigid guidelines for the conditions applied by the Medical Officers of Health as such conditions need to take account of the local situations relating to use of the land and surface water in the area, the nature and control of the operations and consultation with interested parties locally. There are many factors affecting the concentrations of 1080 along the pathway to the consumer which will reduce the likelihood of 1080 reaching drinking water or will reduce the final concentration of 1080 in drinking water. Some of these factors could depend, for example on its water solubility or biodegradation, significant water dilution, and weather conditions.

It is recognised in the 1080 model permit conditions (Ministry of Health 1995b, Appendix 6) that during wet and warm conditions the bait may disintegrate rapidly. Bait breakdown is dependent on the amount of rainfall as 1080 is highly soluble in water. Biodegradation takes longer under dry and cold conditions because there will be little biological activity to breakdown the structure of the bait. Since 1080 operations are carried out during the winter months, 1080 baits may disintegrate at a slower rate especially during dry conditions.

Delegated persons are expected to use their specialist professional judgment and local community knowledge in deciding what conditions are appropriate for each individual application. The model permit conditions are still applicable and can be used as appropriate (Appendix 6). The requirements under the Pesticides (VPC) Regulations were deleted as they have been superseded by the requirements under the HSNO Act.

There is still considerable concern regarding potential danger to non-target species, either directly or through secondary poisoning. It is known that secondary poisoning occurs with 1080 but it remains a poorly understood problem, largely because of lack of an appropriate laboratory analysis for 1080 or its toxic metabolites in animal tissue where background fluoride readings may be high (Calver and King 1986). To reduce secondary poisoning, the model permit conditions require that the agency conducting the operation is required to inspect all rural/domestic water supply streams and

publicly visible sites in the area of the operation and where feasible collect all carcasses from places where they may put public health at risk.

7.11.4 Implications for the Medical Officer of Health

Under the HSNO Act, the Medical Officers of Health retain their role in granting 1080 permits. In addition, the delegation has been extended to include qualified Health Protection Officers. However, in addition to granting permits when 1080 is applied in drinking water catchments the Medical Officers of Health's role has been broadened covering "any other area where public health risk may be created". This requirement applies whether or not the land is being managed by DoC[9]. As a guiding principle, "any other area where public health risk may be created" may include those restricted areas specified under the Pesticides (VPC) Regulations such as a public road, or places where the public are entitled to have access. The delegated person would have to use their professional judgment to establish what other areas would fall under this category.

Given that the delegated person is empowered to amend, add or waive conditions to a permit that has been previously granted, any problems or issues that may have been encountered by them during 1080 operations can be dealt with by incorporating additional or modify existing conditions to protect public health. In addition, this power also gives them the flexibility to address local needs.

Amending the HSNO Act giving the ERMA the power to delegate certain functions to Medical Officers of Health and qualified Health Protection Officers was an important step towards improving the workability of the HSNO Act.

7.11.5 Susceptible population

Living in areas where dilution of water is not so great, pregnant women or women of childbearing age, or the general public, including children because of their unique susceptibility may be potentially exposed to the adverse effects of 1080. Children may

[9] DoC was also delegated by the ERMA to grant 1080 permits on DoC land.

also be at greater risk of accidental poisoning despite warning signs because they are still unable to read and understand the hazards of 1080. Parents or caregivers need to be vigilant in not letting children gain access in areas where 1080 baits have been applied. Regular washing of children's hands is also important. Contamination of surfaces or toys may arise from parents or any member of the household handling 1080, e.g., in preparation of baits or directly involved in 1080 operations.

7.11.6 Exposure due to contaminated meat and milk

Exposures from contaminated meat and milk were rare events but may still be considered as a public health issue especially in situations where exposures of animals concerned were unknown. In New Zealand where the use of 1080 is extensive, there is need for strict supervision during its use, and livestock should not be allowed access to grazing land known to contain 1080 baits. Responsible management is necessary to reduce risks likely to arise from 1080 poisoning.

The risks which milk may impose would be manifested in areas where cows, for instance were milked and consumed by the general public. In this scenario, the milk remains undiluted and the concentration of 1080 would be high and may be of public health significance. This exposure pathway must also be taken into account although it may not affect a significant number of the population. Farmers must be notified and their consent be sought if their farm would be affected by the poisoning operation. If the owner agreed that such operation could take place, adequate precautionary measures should be taken to avoid any poisoning taking place.

To avoid residues in food, it would be prudent to impose a minimum withholding period of five days to achieve an adequate margin of safety. In cases of death attributed to 1080, the withholding period should be doubled to ten days for the surviving stock and the livestock be moved to pasture that has not been treated with 1080 (Rammell 1993). Similarly, it would appropriate to ensure that residues are not present in meat harvested for human consumption (Eason *et al.* 1996) and that a similar margin of safety of at least ten days applies. This source of exposure could be

relevant to hunters and other members of their household who sourced their meat from hunting and others to whom they may have given the meat.

NZFSA (2005a) has also advised that wild or game estate animals should not be taken from an area where 1080 has been laid until four months after 1080 aerial poisoning operation or two months after the operation has completed and after 100 mm of rain.

7.12 Conclusion

Policy makers should consider developing and implementing strategies to manage and protect public health from the potential adverse effects of 1080. If public health strategies can be designed and implemented to reduce overt exposure to 1080 to a level that is tolerable for most vulnerable subgroups in a population, the entire population will be protected. Through these means, health risk assessment can reduce, although not entirely eliminate, the uncertainties involved and it can aid decision makers in identifying those areas where research is most needed. The data gaps identified in this study represent the main barrier to the advancement of the common understanding of the consequences of 1080 to human health. Hence, filling these data gaps is crucial to be able to develop sound policy advice.

There are currently regulatory systems and guidelines in place but New Zealand is not yet in a position to confidently conclude that there is negligible risk involved and that the health effects described by concerned members of the public, such as fetal malformations, increase in miscarriages (see Appendix 7) are not in any way related to 1080 exposures.

The PMAV for 1080 in the DWS NZ is currently 3.5 ppb and from the findings of this study it could be considered that a lower PMAV is appropriate, reflecting concerns about the causal link between 1080 and teratogenicity, testicular/epididymis and myocardial effects in toxicological studies. Because there are no epidemiological studies to date and the toxicology data are inadequate, as discussed in previous chapters, a lower PMAV appears to be warranted as a precautionary approach. The PMAV may be revised in the future based on findings that decrease uncertainties in quantifying risk for the drinking water route of exposure.

This precautionary measure may involve compliance costs as the agency conducting the operation is required to sample water catchments that have been contaminated with 1080. However, this requirement is already in place, and hence there are no additional/new costs to the agencies involved. Hood *et al.* (1992) stated that forecasts would only be of relevance if they can be communicated to those who are in a position to take action to avoid or mitigate the risk.

The findings from this study do not suggest the complete restriction of 1080 use as it recognises the importance to agricultural and environment sectors of the need for sustained efforts in controlling possums in New Zealand. However, the protection of the health and safety of the general public must be of paramount importance in light of the adverse effects of this compound. In the absence of data to the contrary, it is prudent to assume that humans and animals are equally sensitive to 1080.

7.13 Recommendation

- Since the Provisional Maximum Acceptable Value for 1080 found in this study is lower than the current Provisional Maximum Acceptable Value in the Drinking Water Standards New Zealand 2005, it would be prudent for the Provisional Maximum Acceptable Value for 1080 in drinking water to be reviewed. This study does not recommend that the Provisional Maximum Acceptable Value should be derived from child parameters data without carrying out any further investigation.

- The precautionary approach should be adopted until a more comprehensive data set are made available and in turn, to reduce the uncertainties in developing the Tolerable Daily Intake and consequently the Provisional Maximum Acceptable Value. The difficulty in conducting proper epidemiology studies is acknowledged. However, it is inappropriate to conclude that such adverse effects may be irrelevant to humans as no such study has been carried out to refute the conclusions made in animal toxicology studies.

- A national geocoded record of drinking-water catchments treated with 1080 should be developed. To accomplish this, the local public health units should keep a record of all the drinking-water catchments where a permit has been granted and this information collected at the national level by the Ministry of Health. This information would be important, for any future enquiry concerning 1080 drinking-water contamination.

- Further research should be carried out with respect to 8-12 hours sampling as suggested by Suren and Lambert (2004) as their results are inconsistent with the findings of Wright (1998) where water samples above 1 ppb 1080 were detected in the first two days (48 hours) of sampling.

- The use of Digital Global Positioning System should be made mandatory as part of permit conditions.

- The water sampling criteria should be clearly defined in the water protocol, e.g., the number of water samples that should be collected for analyses. In addition, Digital Global Positioning System readings should be recorded where water samples were taken.

- Modelling studies, similar to Wright *et al.* (2002) would be useful in estimating 1080 contamination arising from bait laying operations and could therefore provide information with respect to reducing 1080 contamination for future 1080 operations.

- It has been found that 1080 workers contain urine 1080 levels exceeding the Biological Exposure Index and this finding was supported by the postal survey conducted by this author (NF) that vehicle contamination may potentially be a likely route of exposure (see Appendix 8a). Monitoring could include wipe samples of the vehicles. Because members of their household could be potentially exposed to 1080 they should also be included as part of the biological monitoring. The biological monitoring could be incorporated as part of the Department of Labour's study on 1080.

- An epidemiological study examining health parameters including reproductive and cardiac effects of 1080 in workers and their families would be useful in adding to the human health profile of 1080.

- There has been an inconsistency between the Parliamentary Commissioner for the Environment's and the Department of Conservation's interpretation on what would constitute a "contaminant" with respect to 1080 aerial application under the Rerource Management Act. The Ministry for the Environment should clarify this situation to avoid any dispute in future.

References

Abernathy, C.H., Donohue, J.M., Cicmanec, J., Poirier, K.A. Reference doses (RfDs): Factors in the selection of human intraspecies uncertainty factor (Ufh) when using human data. *Undated report from the 2003 Society of Toxicology meeting*, USA.

Agricultural Compounds and Veterinary Medicines Act 1996. New Zealand.

Alexeeff, G.V., Broadwin, R., Liaw, J. Dawson, S.V. (2002). Characterisation of the LOAEL-to-NOAEL uncertainty factor for mild adverse effects from acute inhalation exposures. *Regulatory Toxicology and Pharmacology* 36: 96-105.

Al-Juburi, A.Z., Clarkson, T.W., Cockett, A.T.K. (1989). Vasocystostomy: A model for studying male reproductive toxicity in the rat. *Reproductive Toxicology* 3: 181-186.

Allen, B.C., Kavlock, R.J., Kimmel, C.A., Faustman, E.M. (1994). Dose response assessments for developmental toxicity: II. Comparison of generic benchmark dose estimates with NOAELs. *Fundamental and Applied Toxicology* 23: 487-495.

Allen, B.C., Strong, P.L., Price, C.J., Hubbard, S.A., Daston, G.P. (1996). Benchmark dose analysis of developmental toxicity in rats exposed to boric acid. *Fundamental and Applied Toxicology* 32: 194-204.

Annison, E.F., Hill, K.J., Lindsay, D.B., Peters, R.A. (1960). Fluoroacetate poisoning in sheep. *Journal of Comparative Pathology* 70: 145-155.

Aplin, T. E. H. (1971). Poison plants of Western Australia: The toxic species of *Gastrolobium* and *Oxylobium*. *Western Australian Department Agriculture Bulletin* No. 3772: Pp. 1-66.

Atzert, S.P. (1971). A review of sodium monofluoroacetate (compound 1080), its properties, toxicology, and use in predator and rodent control. United States

Department of the Interior Fish and Wildlife Services Special Scientific report – *Wildlife* No. 146, 34 pp.

Aulerich, R.J., Ringer, R.K., Safronoff, J. (1987). Primary and secondary toxicity of warfarin, sodium monofluoroacetate, and methyl parathion in mink. *Archives of Environmental Contamination and Toxicology* 16: 357-366.

Auton, T.R. (1994). Calculation of benchmark doses from teratology data. *Regulatory Toxicology and Pharmacology* 19: 152-167.

Aylward, L.L., Hays, S.M., Karch, N.J., Paustenbach, D.J. (1996). Relative susceptibility of animals and humans to the cancer hazard caused by 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin using internal measures of dose. *Environmental Science and Technology* 30(12): 3534-3543.

Bailer, A.J., Maltoni, C., Ballar, J.C. III., Belpoggi, F., Brazier, J.V., Soffriti, M., eds. (1999). Uncertainty in the risk assessment of environmental and occupational hazards. *Annals of New York Academy of Sciences* 895:1-377.

Baird, S.J.S., Cohen, J.T., Graham, J.D., Shlyakhter, A.I., Evans, J.S. (1996). Non-cancer risk assessment: a probabilistic alternative to current practice. *Human and Ecological Risk Assessment* 2: 79-102.

Balcomb, R., Bowen, C.A., Williamson, H.A. (1983). Acute and sublethal effects of 1080 on starlings. *Bulletin of Environmental Contamination and Toxicology* 31: 692-698.

Baltrop, D. (1966). The prevalence of pica. *American Journal of Diseases of Children* 112(2): 116-123.

Barnard, R.C. (1994). Scientific method and risk assessment. *Regulatory Toxicology and Pharmacology* 19: 211-218.

Barnes, D.G., Daston, G.P., Evans, J.S., Jarabek, A.M., Kavlock, R.J., Kimmel, C.A., Park, C. Spitzer, H.L. (1995). Benchmark dose workshop: Criteria for use of a benchmark dose to estimate a reference dose. *Regulatory Toxicology and Pharmacology* 21: 296-306.

Barnes, D.G., Dourson, M. (1988). Reference dose (RfD): Description and use in health risk assessments. *Regulatory Toxicology and Pharmacology* 8: 471-486.

Batcheler, C.L. (1978). A report to the Minister of Forests and the Minister of Agriculture on: Compound 1080, its properties, effectiveness, dangers and use. Wellington, *N.Z. Forest Service*. 68 pp.

Beasley, M. (1996). 1080-overview of toxicology issues. In: *Improving conventional control of possums*. The Royal Society of New Zealand Miscellaneous Series 35: 15-17.

Beck, B.D., Blayton, T.M., Calabrese, E.J., Baldwin, L., Rudel, R. (2001). The use of toxicology in the regulatory process. In: Hayes, AW., ed. *Principles and Methods of Toxicology*, Fourth Edition, Taylor and Francis, Philadelphia. Pp. 23-75.

Bell, J. (1972). The acute toxicity of four common poisons to the opossum, *Trichosurus vulpecula*. *New Zealand Veterinary Journal* 20(1): 212-214.

Bell, A.T., Newton, L.G., Everist, S.L., Legg, J. (1955). *Acacia georginae* poisoning of cattle and sheep. *Australian Veterinary Journal* 31: 249-257.

Bender, J. (2002). The use of noncancer endpoints as a basis for establishing a reference concentration for formaldehyde. *Regulatory Toxicology and Pharmacology* 35: 23-31.

Bodansky, D. (1991). Scientific uncertainty and the precautionary principle. *Environment* 33(7): 4-5 and 43-44.

Bong, C.L., Cole, A.L.J., Walker, J.R.L. (1979). Effect of sodium monofluoroacetate (compound 1080) on the soil microflora. *Soil Biology and Biochemistry* 11: 13-18.

Booth, L.H., Ogilvie, S.C., Wright, G.R., Eason, C.T. (1997). Water quality monitoring after 1080 pest control operations. *Water and Wastes* 96: 22.

Booth, L.H., Ogilvie, S.C., Wright, G.R., Eason, C.T. (1999). Degradation of sodium monofluoroacetate (1080) and fluorocitrate in water. *Bulletin of Environmental Contamination and Toxicology* 62: 34-39.

Bowen, L., Morgan, D.R., Eason, C.T. (1995). Persistence of sodium monofluoroacetate (1080) in baits under simulated rainfall. *New Zealand Journal of Agricultural Research* 38: 529-531.

Bowsakowski, T., Levin, A.A. (1986). Serum citrate as a peripheral indicator of fluorocitrate toxicity in rats and dogs. *Toxicology and Applied Pharmacology* 85: 428-436.

Bracken, M.B., Holford, T.R. (1981). Exposure to prescribed drugs in pregnancy and association with congenital malformations. *Obstetrics and Gynecology* 58: 336-344.

Brockmann, J.L., McDowell, A.V., Leeds, W.G. (1955). Fatal poisoning with sodium fluoroacetate: Report of a case. *Journal of American Medical Association* 159: 1529-1532.

Bromley, A.M. (1996). "Monitoring atmospheric air quality during a 1080 poison airdrop near Featherston", April 1996. NIWA Contract Report (unpublished). 5 pp.

Buffa, P., Guarriero-Bobyleva, V., Costa-Tiozzo, R. (1973). Metabolic effects of fluoroacetate poisoning in animals. *Fluoride* 6(4): 224-247.

Buffa, P., Peters, R.A. (1950). The *in vivo* formation of citrate induced by fluoroacetate poisoning and its significance. *Journal of Physiology*. (London) 110: 488-500.

Burin, G.J., Sunders, D.R. (1999). Addressing the human variability in risk assessment - The robustness of the intraspecies uncertainty factor. *Regulatory Toxicology and Pharmacology* 30: 209-216.

Burns, R.J., Connoly, G.E., Okuno, I. (1986). Secondary toxicity of coyotes killed by 1080 single dose baits. In: Salmon, T.P., ed. *Proceedings Twelfth Vertebrate Pest Conference*. University of California, Davis. Pp 324-329.

Burns, R.J., Tietjen, H., Connolly, G.E. (1991). Secondary hazard of livestock protection collars to skunks and eagles. *Journal of Wildlife Management* 55: 701-704.

Calabrese, E.J. (1985). Uncertainty factors and interindividual variation. *Regulatory Toxicology and Pharmacology* 17: 44-51

Calabrese, E.J. (1991). *Multiple Chemical Interactions*. Lewis Publishers, Chelsea, MI. P 704.

Calabrese, E.J., Beck, B.D., Chapell, W.R. (1992). Does the animal-to-human uncertainty factor incorporate differences in surface area? *Regulatory Pharmacology and Toxicology* 15: 172-179.

Calabrese, E.J., Stanek, E. (1992). What proportion of household dust is derived from outdoor soil? *Journal of Soil Contamination* 1: 253-263.

Calver, M.C., King, D.R. (1986). Controlling vertebrate pests with fluoroacetate: lessons in wildlife management, bioethics, and co-evolution. *Journal of Biological Education* 20: 257-262.

Carrell, H., Glusker, J.P., Villafranca, J.J., Mildvan, A.S., Dummell, R.J., Kunn, E. (1970). Fluorocitrate inhibition of aconitase; relative configuration of inhibitory isomer by X-ray crystallography. *Science* 170: 1412-1414.

Carson, R. (1962). *Silent Spring*. Houghton Mifflin, Boston. p 378.

Casper, H.H., Mount, M.E., Marsh, R.E., Schmidt, R.H. (1986). Fluoroacetate residues in ground squirrel and coyote tissues due to primary or secondary 1080 poisoning. *Journal of the Association of Official Analytical Chemists* 69: 441-442.

Castorina, R., Woodruff, T.J. (2003). Assessment of potential risk levels associated with U.S. Environmental Protection Agency reference values. *Environmental Health Perspectives* 111: 1318-1325.

Cater, D.B., Peters, R.A. (1961). The occurrence of renal changes resembling nephrosis in rats poisoned with fluorocitrate. *British Journal of Experimental Pathology* 42: 278-289.

Chenoweth, M.B. (1949). Monofluoroacetic acid and related compounds. *Pharmacological Reviews* 1: 383-424.

Chung, H.M. (1984). Acute renal failure caused by acute monofluoroacetate poisoning. *Veterinary and Human Toxicology* 26(2): 29-32.

Clarke, M.L., Harvey, D.G., Humphreys, D.J. (1981). *Veterinary Toxicology*. Second Edition. London: Bailliere Tindal, P 162.

Committee on Advances in Assessing Human Exposure to Airborne Pollutants (CAAHEAP). (1991). Human exposure assessment for airborne pollutants. *National Research Council Board of Environmental Studies and Toxicology*, National Academy of Science. Washington, DC: National Academy Press. 344 pp.

Covello, V.T. (1989). Communicating right-to-know information on chemical risks. *Environmental Science and Technology* 23: 1444-1449.

Covello, V. T., Merkhofer, M. W. (1993). *Risk Assessment Methods: Approaches for Assessing Health and Environmental Risks*. Plenum, New York. 319 pp.

Crisp, M.D., Weston, P.H. (1987). Cladistics and legume systematics, with an analysis of the Bossiaeeae, Brongniartieae and Mirbelieae. In: Stirton, C.H., ed. *Advances in Legume Systematics*, Part 3. Kew: Royal Botanic Gardens. Pp 65-130.

Crump, K.S. (1984). A new method for determining allowable daily intakes. *Fundamental and Applied Toxicology* 4: 854-871.

Crump, K.S. (1995). Calculation of benchmark doses from continuous data. *Risk Analysis* 15(1): 79-89.

Crump, K.S., Howe, R.B. (1985). A review of methods for calculating statistical confidence limits in low dose extrapolation. In: *Toxicological Risk Assessment.* Clayson, D.B., Krewski, D., Munro, I., eds. Boca Raton: CRC Press, Inc. Pp 197-203.

David, W.A.L., Gardiner, B.O.C. (1966). Persistence of fluoroacetate and fluoroacetamide in soil. *Nature* 26: 1367-1368.

Davidson, I.W.F., Parker, J.C., Beliles, R.P. (1986). Biological basis for extrapolation across mammalian species. *Regulatory Toxicology and Pharmacology* 6: 211-237.

Davis, A., Drexter, J.W., Ruby, M.V., Nicholson, A. (1993). Micromineralogy of mine waste in relation to lead bioavailability, Butte, Montana. *Environmental Science and Technology* 27: 1415-1425.

De Meyer, R., De Plaen, J. (1964). An approach to the biochemical study of teratogenic substances in isolated rat embryos. *Life Sciences* 3: 709-713.

Department of Conservation (DoC). (1994). *Possum Control in Native Forests.* Department of Conservation, Wellington. 12 pp.

Department of Conservation and Animal Health Board (DoC and AHB). (2003). *The use of 1080 to control possums and other pests: A resource document.* Department of Conservation and Animal Health Board, Wellington. 49 pp.

Department of Conservation, Animal Health Board and Ministry of Agriculture and Forestry (DoC, AHB and MAF). (1994). *Possum control and the use of 1080 in New Zealand.* Department of Conservation, Animal Health Board and Ministry of Agriculture and Forestry, Wellington. 16 pp.

Dourson, M.L. (1994). Methods for establishing oral reference doses (RfDs). In Mertz, W., Abernathy, C.O., Olin, S.S., eds. *Risk Assessment of Essential Elements*. ILSI Press, Washington, D.C. Pp 51-61.

Dourson, M.L., Andersen, M.E., Erdreich, L.S., MacGregor, J.A. (2001). Using human data to protect the public's health. *Regulatory Toxicology and Pharmacology* 33: 234-256.

Dourson, M.L., Charnley, G., Scheuplein, R. (2002). Differential sensitivity of children and adults to chemical toxicity: II. Risk and regulation. *Regulatory Toxicology and Pharmacology* 35: 448-467.

Dourson, M.L., DeRosa, C.T. (1991). The use of uncertainty factors in establishing safe levels of exposure. In: Krewski D., Franklin, C., eds. *Statistics in Toxicology*. New York: Gordon and Breach, Pp 613-627.

Dourson, M.L., Felter, S.P., Robinson, D. (1996). Evolution of science-based uncertainty factors in noncancer risk assessment. *Regulatory Toxicology and Pharmacology* 24: 108-120.

Dourson, M.L., Knauf, L, Swartout, J. (1992). On reference dose (RfD) and its underlying toxicity data base. *Toxicology and Industrial Health* 8(3): 171-189.

Dourson, M.L., Stara, J.F. (1983). Regulatory history and experimental support of uncertainty (safety) factors. *Regulatory Toxicology and Pharmacology* 3: 224-238.

Durham, G. (1998a). *Memorandum to Medical Officers of Health*, 27 March 1998. Ministry of Health, Wellington.

Durham, G. (1998b). *Memorandum to Managers, Public Health Services, Medical Officers of Health and Health Protection Officers*, 27 April 1998. Ministry of Health, Wellington.

Durham, G. (1998c). *Memorandum to Managers, Public Health Services, Medical Officers of Health and Health Protection Officers*, 25 May 1998. Ministry of Health, Wellington.

Eason, C.T. (1993). Persistence of 1080. *Surveillance* 20(2): 7-8.

Eason, C.T. (1995). Sodium monofluoroacetate (1080): An update on recent environmental toxicology data and community concerns. *Proceedings 10th Australian Vertebrate Pest Conference*, Pp 39-43.

Eason, C.T. (1996). Vertebrate pesticides, old and new. What will influence their future development and use? In: *Improving conventional control of possums*. The Royal Society of New Zealand Miscellaneous Series 35. Pp 46-50.

Eason, C.T. (1997). Sodium monofluoroacetate toxicology in relation to its use in New Zealand. *Australasian Journal of Ecotoxicology* 3: 57-64.

Eason, C.T. (2002a). Sodium monofluoroacetate (1080) risk assessment and risk communication. *Toxicology* 181-182; 523-530.

Eason, C.T. (2002b). *Technical Review of Sodium Monofluoroacetate (1080)*. Animal Health Board (Inc), Wellington. 25 pp.

Eason, C.T., Frampton, C.C. (1991). Acute toxicity of sodium monofluoroacetate (1080) baits to feral cats. *Australian Wildlife Research* 18: 459-462.

Eason, C.T., Frampton, C.M., Henderson, R., Thomas M.D., Morgan, D.R. (1993a). Sodium monofluoroacetate and alternative toxins for possum control. *New Zealand Journal of Zoology* 20: 329-334.

Eason, C.T, Gooneratne, R. (1993b). An evaluation of the risk to man of secondary poisoning with sodium monofluoroacetate (1080). *New Zealand Medical Journal* 106: 41.

Eason, C.T., Gooneratne, R., Fitzgerald, H., Wright, G., Frampton, C. (1994a). Persistence of sodium monofluoroacetate in livestock animals and risk to humans. *Human and Experimental Toxicology* 13: 119-122.

Eason, C.T.; Gooneratne, R.; Rammell, C.G. (1994b). A review of the toxicokinetics and toxicodynamics of sodium monofluoroacetate in animals. In: Seawright, A.A., Eason, C.T., eds. *Proceedings of the Science Workshop on 1080.* Royal Society of New Zealand Miscellaneous Series 28: 82-89.

Eason, C.T., Gooneratne, R., Wright, G.R., Pierce, R., Frampton, C.M. (1993b). The fate of sodium monofluoroacetate (1080) in water, mammals, and invertebrates. In: *Proceedings of the 46th New Zealand Plant Protection Conference*, Pp 297-301.

Eason, C.T., Turck, P. (2002). A 90-day toxicological evaluation of compound 1080 (sodium monofluoroacetate) in Sprague-Dawley Rats. *Toxicological Sciences* 69: 439-447.

Eason, C.T., Turck, P., Fountain, J. (2001). "A 90-day oral (gavage) study of compound 1080 (sodium monofluoroacetate) with a 56-day recovery period in rats, and its implications for human health". Landcare Research Contract Report LC0001/39 (unpublished). 91 pp.

Eason, C.T., Wickstrom, M., Turck, P. (1998). "Interim report regulatory and environmental studies on 1080: Results and implications". Landcare Research Contract Report LC9798/94 (unpublished). 16 pp.

Eason, C.T., Wickstrom, M., Turck, P., Wright, G.R.G. (1999). A review of recent regulatory and environmental toxicology studies on 1080: Results and implications. *New Zealand Journal of Ecology* 23 (2): 129-137.

Eason, C.T., Wright, G. (2001). Water monitoring for contamination after aerial 1080 pest control operations: An update. *He Korero: Possum Research News* 16: 10-11.

Eason, C.T., Wright, G.R., Fitzgerald, H. (1992). Sodium monofluoroacetate (1080) water residue analysis after large scale possum control. *New Zealand Journal of Ecology* 16(1): 47-49.

Eason, C.T., Wright, G.R., Meikle, L., Elder, P. (1996). The persistence of secondary poisoning risks of sodium monofluoroacetate (1080), brodifacoum, and cholecalciferol in possums. In: Timm, R.M., A.C. Crabb., eds. *Proceedings of the 17th Vertebrate Pest Conference*. Pp 54-58.

Eastland, W.G., Beasom, S.L. (1986). Effects of ambient temperature on the 1080-LD_{50} of raccoons. *Wildlife Society Bulletin* 14: 234-235.

Eaton, D.L., Klaassen, C.D. (2001). *Principles of Toxicology*. In: Klaassen. C.D., ed. Casarett and Doull's Toxicology, Sixth Edition. McGraw-Hill Medical Publishing Division, New York, Pp 11-34.

Ecobichon, D.J. (2001). *Toxicity of Pesticides*. In: Klaassen, C.D., ed. Casarett and Doull's Toxicology, Sixth Edition. McGraw-Hill Medical Publishing Division, New York, p 801.

Egekeze, J.O., Oehme, F.W. (1979). Sodium monofluoroacetate (SMFA, Compound 1080): A literature review. *Veterinary and Human Toxicology* 21: 411-416.

Eisler, R. (1995). Sodium monofluoroacetate (1080) hazards to fish, wildlife, and invertebrates: A synoptic review. *US Department of the Interior Biological Report* 27. 47 pp.

Ellman, L.M., Sunstein, C.R. (2004). Hormesis, the precautionary principle, and the legal implications. *Human and Experimental Toxicology* 23: 601-611.

ERMA New Zealand (ERMA NZ) (2007). *Environmental Risk Management Authority Decision: Application for reassessment of a hazardous substance under section 63 of the Hazardous Substances and New Organisms Act.* Available from New Zealand Government Online http://www.ermanz.govt.nz/news-ents/1080/Decision%20(2007.08.13)%20FINAL.pdf Accessed on 15 August 2007.

ERMA New Zealand (ERMA NZ) (2006). *Environmental Risk Management Authority Decision on Grounds for Reassessment of a Substance.* Available from New Zealand Government Online http://www.ermanz.govt.nz/consultations/consult-apps.cfm. Accessed on 2 December 2006.

ERMA New Zealand (ERMA NZ) (2002). *Grounds for Reassessment of 1080.* Available from New Zealand Government Online http://www.ermanz.govt.nz/news-events/archives/media-releases/2002/mr-20020319.asp. Accessed on 9 July 2004.

Fabian, N. (1998). The issue of children's environmental health. *Journal of Environmental Health.* January/February 1998, Pp 53-55.

Fagerstone, K.A., Savarie, P.J., Elias, D.J., Schafer, W. (1994). Recent regulatory requirements for pesticide registration and the status of compound 1080 studies conducted to meet EPA requirements. In: Seawright, A.A., Eason, C.T., eds. *Proceedings of the Science Workshop on 1080.* Royal Society of New Zealand Miscellaneous Series 28: 33-39.

Faustman, E.M., Omenn, G.S. (2001). *Risk Assessment.* In: Klaassen, C.D., ed: Casarett and Doull's Toxicology, Fifth Edition. McGraw-Hill Medical Publishing Division, New York, Pp 83-104.

Fawaz, G., Fawaz, E.N. (1953). *Proceedings of the Society of Experimental Biology and Medicine* 84: 680.

Fenner-Crisp, P. (2001). The FQPA 10x safety factor-How much is science? How much is sociology? *Human and Ecological Risk Assessment* 7(1): 107-116.

Fisher, P., Eason, C.T. (2003). "Review of the regulatory toxicology of sodium fluoroacetate (1080)". Landcare Research contract report: LC0203/086. Animal Health Board. (unpublished). 114 pp.

Fleming, P.J.S., Parker, R.W. (1991). Temporal decline of 1080 within meat baits used for control of wild dogs in New South Wales, *Wildlife Research* 18: 729-40.

Fleury, B. (1995). A Department of Conservation perspective. In: *Improving Conventional Control of Possums*. The Royal Society of New Zealand Miscellaneous Series 35: 40-41.

Food Act 1979. New Zealand.

Foronda, N.M., Fowles, J., Smith, N., Taylor, M., Temple, W. (2007a). A benchmark dose analysis for sodium monofluorocetate (1080) using dichotomous toxicity data. *Regulatory Toxicology and Pharmacology* 47(1): 84-89.

Foronda, N.M., Fowles, J., Smith, N., Taylor, M., Temple, W., Darlington, C. (2007b). The use of myocardial and testicular end points as a basis for estimating a proposed tolerable daily intake for sodium monofluoroacetate (1080). *Regulatory Toxicology and Pharmacology* 47(1): 29-36.

Fowles, J.R., Alexeeff, G.V., Dodge, D. (1999). The use of benchmark dose methodology with acute inhalation lethality data. *Regulatory Toxicology and Pharmacology* 29: 262-278.

Fruton, J.S. (1972). *Molecules and Life: Historical Essays on the Interplay of Chemistry and Biology*. Wiley-Interscience, New York. 579 pp.

Gajdusek, D.C., Luther, G. (1950). Fluoroacetate poisoning: A review and report of a case. *American Journal of Diseases of Children* 79: 310-320.

Gal, E.M., Drewes, P.A., Taylor, N.F. (1961). Metabolism of fluoroacetic acid-2-C^{14} on the intact rat. *Archives of Biochemistry and Biophysics* 93: 1-4.

Gaylor, D.W. (1992). Incidence of developmental defects at the no observed adverse effect level (NOAEL). *Regulatory Toxicology and Pharmacology* 15: 151-160.

Gaylor, D.W. (1996). Quantalization of continuous data for benchmark dose estimation. *Regulatory Toxicology and Pharmacology* 24: 246-250.

Gaylor, D.W., Aylward, L.L. (2004). An evaluation of benchmark dose methodology for non-cancer continuous data health effects in animals due to exposure to dioxin (TCDD). *Regulatory Toxicology and Pharmacology* 28: 150-164.

Gaylor, D.W., Ryan, L., Krewski, D., Zhu, Y. (1998). Procedures for calculating benchmark doses for health risk assessment. *Regulatory Toxicology and Pharmacology* 40: 9-17.

Gaylor, D.W., Slikker, W., Jr. (1990). Risk assessment for neurotoxic effects. *Neurotoxicology* 11: 211-218.

Gephart, L.A., Salminen, W.F., Nicolich, M.J., Pelekis, M. (2001). Evaluation of subchronic toxicity data using benchmark dose approach. *Regulatory Toxicology and Pharmacology* 33(1): 37-59.

Golden, R.M. (2000). Statistical tests for comparing possibly misspecified and nonnested models. *Journal of Biological Chemistry* 44: 153-170.

Goldman, P. (1965). The enzymatic cleavage of the carbon-fluorine bond in fluoroacetate. *Journal of Biological Chemistry* 240: 3434-3438.

Goldman, P., Milne, G.W.A., Keister, D.B. (1968). Carbon-halogen bond cleavage-III. Studies on bacterial halidohydrolases. *Journal of Biological Chemistry* 243: 428-438.

Gooneratne, R., Dickson, C., Wallace, D., Eason, C.T., Fitzgerald, H., Wright, G. (1994). Plasma and tissue 1080 in rabbits after lethal and sublethal doses. In: Seawright, A.A., Eason, C.T., eds. *Proceedings of the Science Workshop on 1080.* Royal Society of New Zealand Miscellaneous Series 28: 67-73.

Gosselin, R.E., Smith, R.P., Hodge, H.C. (1984). *Clinical Toxicology of Commercial Products*. Fifth Edition. Baltimore: Williams and Wilkins, Pp 111-194.

Grant, W.M. (1986). *Toxicology of the Eye*. Third Edition. Springfield, IL: Charles C. Thomas Publisher, Pp 438-439.

Haber, L.T., Dollarhide, J.S., Maier, A., Dourson, M.L. (2001). Noncancer risk assessment: Principles and practice in environmental and occupational settings. In: *Patty's Toxicology*, Fifth edition. Bingham, E., Cohrssen, B., Powell, C.H., eds. Wiley and Sons, Pp 169-232.

Hagan, E.C., Ramsey, L.L., Woodward, G. (1950). Absorption, distribution, and excretion of sodium fluoroacetate (1080) in rats. *Journal of Pharmacology and Experimental Therapeutics* 99: 432-434.

Hamilton, D.J., Eason, C.T. (1994). Monitoring for 1080 residues in waterways after a rabbit poisoning operation in Central Otago. *New Zealand Journal of Agriculture* 37: 195-198.

Hansson, S.O. (2002). Philosophical perspectives on risks. *Keynote Address, Research in Ethics and Engineering*, Delft, 25-27 April. Available on line www.infra.kth.se. Accessed 21 July 2003.

Hansson, S.O., Ruden, C. (2004). A science-based strategy for chemical control. *UNEP Industry and Environment* 27(2-3): 12-18.

Harremoes P., Gee, D., MacGarvin, M., Stirling, A., Keys, J., Wynne, B., Guedes Vaz, S. (2001). Late lessons from early warnings: The precautionary principle 1896-2000.

Environmental Issue Report No. 22. European Environment Agency Copenhagen. Pp 11-16.

Harrisson, J.W.E., Ambrus, C.M., Rees, E.W., Peters, R.H., Reese, L.C., Baker, T. (1952). Acute poisoning with sodium fluoroacetate (compound 1080). *Journal of American Medical Association* 149: 1520-1522.

Hattis, D. (1998). Strategies for assessing human variability in susceptibility, and using variability to infer human risks. In: Neumann, D., Kimmel, C., eds. *Human Variability in Response to Chemical Exposures: Measures, Modelling, and Risk Assessment*. ILSI Press, Washington, DC. Pp 27-57.

Hattis, D., Banati, P., Goble, R. (1999a). Distributions of individual susceptibility among humans for toxic effects: How much protection does the traditional tenfold factor provide for what fraction of which kinds of chemicals and effects? *Annals of the New York Academy of Sciences* 895: 286-316.

Hattis, D., Banati, P., Goble, R., Burmaster, D.E. (1999b). Human interindividual variability in parameters related to health risks. *Risk Analysis* 19: 711-726.

Hattis, D., Goble, R., Russ, A., Banati, P., Chu, M. (2001). Human interindividual variability in susceptibility to airborne particles. *Risk Analysis* 21(4): 585-599.

Hayes, A.W. (2001). *Principles and Methods of Toxicology*. Taylor and Francis, Philadelphia. Pp 1272-1277.

Hazardous Substances and New Organisms Act 1996. New Zealand.

Hazardous Substances and New Organisms (Transitional Provisions and Controls) Amendment Act 2004. New Zealand.

Hazardous Substances (Classification) Regulations 2001. New Zealand.

Hazardous Substances (Sodium Fluoroacetate) Gazette Notice 2005. New Zealand.

Hazardous Substances (Vertebrate Toxic Agents) Transfer Notice 2004. New Zealand.

Health Act 1956. New Zealand.

Health and Safety in Employment Act 1992. New Zealand.

Hegdal, P.L., Fagerstone, K.A., Gatz, T.A., Glahn, J.E., Matschke, G.H. (1986). Hazards to wildlife associated with 1080 baiting for California ground squirrels. *Wildlife Society Bulletin* 14: 11-21.

Hertz-Picciotto, I. (1995). Epidemiology and risk assessment: A bridge from science to policy. *American Journal of Public Health* 85: 484-491.

Hodgson, E., Silver, I.S., Butler, L.E., Lawton, M.P., Lovi, P.E. (2001). Metabolism. In: Hayes, A.W., eds. *Principles and Methods of Toxicology*, Fourth Edition, Taylor and Francis, Philadelphia. Pp 107-167.

Hood, G.G., Jones, D.K.G., Pidgeon, N.F., Turner, B.A., Gibson, R. (1992). Risk management. In: *Risk Analysis, Perception and Management: Report of a Royal Society Study Group*. London: Royal Society: 135-201.

Hornshaw, T.C., Ringer, R.K., Aulerich, R.J. (1986). Toxicity of sodium monofluoroacetate (compound 1080) to mink and European ferrets. *Environmental Toxicology and Chemistry* 5: 213-223.

Horrigan, L., Lawrence, R.S., Walker, P. (2002). How sustainable agriculture can address the environmental and human health harms of industrial agriculture. *Environmental Health Perspectives* 110(5): 445-456.

Hrudey, S.E., Leiss, W. (2003). Risk management and precaution: Insights on the cautious use of evidence. *Environmental Health Perspectives* 111: 1557-1581.

Hubal, E.A.C., Sheldon, L.S., Burke, J.M., McCurdy, T.R., Berry, M.R., Rigas, M.L., Zartarian, V.G., Freeman, N.C.G. (2000). Children's exposure assessment: A review of factors influencing children's exposure, and the data available to characterise and assess that exposure. *Environmental Health Perspectives* 108: 475-486.

Hudson, E.J., Tucker, R.K., Haegele, M.A. (1984). *Handbook of Toxicity of Pesticides to Wildlife*. Second Edition. United States Department of Interior. Fish and Wildlife Service. Resource Publication 153. Washington DC: US Government Printing Office. Pp 83-84.

Huggins, E.J., Casper, H.H., Ward, C.D. (1988). Tissue fluoroacetate residues in prairie dogs dosed with low level sodium monofluoroacetate. *Journal of the Association of Official Analytical Chemists* 71: 579-581.

Illing, P. (2001). *Toxicity and Risk*. London, Taylor and Francis Ltd., p 154.

International Agency for Research on Cancer (IARC). (1994). Volume 59. *Hepatitis Viruses*. Lyon, World Health Organization, IARC. Pp 17-37.

International Agency for Research on Cancer (IARC). (2000). Volume 76. *Some Antiviral and Antineoplastic Drugs, and the Pharmaceutical Agents*. Lyon, World Health Organization, IARC. Pp 9-31.

International Programme on Chemical Safety (IPCS). (1986). *Environmental Health Criteria 60: Principles and Methods for the Assessment of Neurotoxicity Associated with Exposure to Chemicals*. Geneva, World Health Organization, International Programme on Chemical Safety. 180 pp.

International Programme on Chemical Safety (IPCS). (1990). Environmental Health Criteria 104: *Principles for the Toxicological Assessment of Pesticide Residues in*

Food. Geneva, World Health Organization, International Programme on Chemical Safety. 113 pp.

International Programme on Chemical Safety (IPCS). (1992). Chemical safety. *Fundamentals of Applied Toxicology*. Geneva, World Health Organization, International Programme on Chemical Safety. 122 pp.

International Programme on Chemical Safety (IPCS). (1994). Environmental Health Criteria 170: *Assessing Human Health Risks of Chemicals: Derivation of Guidance Values for Health-Based Exposure Limits*. Geneva, World Health Organization, International Programme on Chemical Safety. 73 pp.

International Programme on Chemical Safety (IPCS). (1999). Environmental Health Criteria 210: *Principles for the Assessment of Risks to Human Health from Exposure to Chemicals*. Geneva, World Health Organization, International Programme on Chemical Safety. 110 pp.

International Programme on Chemical Safety (IPCS). (2000a). Environmental Health Criteria 214: *Human Exposure Assessment*. Geneva, World Health Organization, International Programme on Chemical Safety. 375 pp.

International Programme on Chemical Safety (IPCS). (2000b). *General Scientific Principles of Chemical Safety*. Geneva, World Health Organization, International Programme on Chemical Safety. 205 pp.

International Programme on Chemical Safety (IPCS). (2002). Environmental Health Criteria 227: *Fluorides*. Geneva, World Health Organization, International Programme on Chemical Safety. 268 pp.

Jacobson, J.L., Janisse, J., Banerjee, M., Jester, J., Jacobson, S., Ager, J.W. (2002). A benchmark dose analysis of prenatal exposure to polychlorinated biphenyls. *Environmental Health Perspectives* 110(4): 393-398.

Johnston, P., Simmons, M. (1990). Precautionary Principle (Letter). *Marine Pollution Bulletin* 21: 402.

Kalberlah, F., Schneider, K. (1998). Quantification of extrapolation factors. *Federal Institute of Occupational Safety and Health*, Fb 797, Wirtschaftsverlag NW, Bremerhaven.

Kalberlah, F., Schneider, K., Schuhmacher-Wolz, U. (2003). Uncertainty in toxicological risk assessment for non-carcinogenic health effects. *Regulatory Toxicology and Pharmacology* 37: 92-104

Kalmbach, E.R. (1945). "Ten-eighty", a war-produced rodenticide. *Science* 102: 232-233.

Kaur, S. (1988). Effect of environmental pollutants on human semen. *Environmental Contamination and Toxicology* 40: 102-104.

Kavlock, R.J., Allen, B.C., Kimmel, C.A., Faustman, E.M. (1995). Dose response assessment for developmental toxicity: IV. Benchmark doses for fetal weight changes. *Fundamental and Applied Toxicology* 26: 211-222.

Kelly, M. (1965). Isolation of bacteria able to metabolise fluoroacetate or fluoroacetamide. *Nature* (London) 208: 809-810.

Kimmel, C.A. (1990). Quantitative approaches to human risk assessment for noncancer health effects. *Neurotoxicology* 11: 189-198.

King, D.R., Wong, D.H., Kirkpatrick, W.E., Kinnnear, J.E. (1994). Degradation of 1080 in Australian soils. In: Seawright, A.A., Eason, C.T., eds. *Proceedings of the Science Workshop on 1080*. Royal Society of New Zealand Miscellaneous Series 28: 45-49.

Klaassen, C.D., Doull, J. (1980). Evaluation of safety. In: Klaassen, C.D., Doull, J, Amdur, M.O., eds. *Casarett and Doull's Toxicology*. New York: McMillan Publishing Co., Inc., p 12.

Kodell, R.L., Gaylor, D.W. (1999). Combining uncertainty factors in deriving human exposure levels of noncarcinogenic toxicants. *Annals of the New York Academy of Sciences* 895:188-195.

Kopecky, E.A., Koren, G. (1998). Maternal drug abuse: Effects on the fetus and neonate. In: Polin, R.A., Fox, W.F., eds. *Fetal and Neonatal Physiology*, 2nd edition, Volume 1: 203-220. Saunders, Philadelphia.

Kostyniak, P.J. (1979). Defluorination: A possible mechanism of detoxification in rats exposed to fluoroacetate. *Toxicology Letters* 3: 225.

Kostyniak, P.J., Bosmaan, H.B., Smith, F.A. (1978). Defluorination of fluoroacetate in vitro by rat liver subcellular fractions. *Toxicology and Applied Pharmacology* 44: 89.

Kriebel, D., Tickner, J., Epstein, P., Lemons, J., Levins, R., Loechler, E., Quinn, M., Rudel, R., Schettler, T., Stoto, M. (2001). The precautionary principle in environmental science. *Environmental Health Perspectives* 109: 871-876.

Kroes, R. (1995). Toxicity testing and human health. In: Van Leeuwen, C.J., Hermens, J.L.M., eds. *Risk Assessment of Chemicals: An Introduction*, Kluwer Academic Publishers, Dordrecht, Pp 147-174.

Lauble, H., Kennedy, M.C., Emptage, M.H., Beinert, H., Stout, C.D. (1996). The reaction of fluorocitrate with aconitase and the crystal structure of the enzyme-inhibitor complex. *Biochemistry* 93: 13699-13703.

Lehman, A.J. and Fitzhugh, O.G. (1954). 100-Fold margin of safety. Assoc. Food Drug Office. *U.S.Q. Bulletin*. 13:51-58.

Leisenring, W., Ryan, L. (1992). Statistical properties of the NOAEL. *Regulatory Toxicology and Pharmacology* 15: 161-171.

Livingstone, P.G. (1994). The use of 1080 in New Zealand. In: Seawright, A.A., Eason, C.T., eds. *Proceedings of the Science Workshop on 1080.* Royal Society of New Zealand Miscellaneous Series 28: 1-9.

Livingstone, P.G., Nelson, P.C. (1994). *Possum Control and the Use of 1080 in New Zealand.* Animal Health Board, Wellington. 16 pp.

Lu, F.C. (1983). Toxicological evaluations of carcinogens and noncarcinogens: Pros and cons of different approaches. *Regulatory Toxicology and Pharmacology* 3: 121-132.

Lu, F.C. (1996). *Basic Toxicology: Fundamentals, Target Organs, and Risk Assessment*, Third Edition. Philadelphia: Taylor and Francis Ltd. 376 pp.

Marsh, R.E., Schmidt, R.H., Howard, W.E. (1987). Secondary hazards to coyotes of ground squirrels poisoned with 1080 or strychnine. *Wildlife Society Bulletin* 15:380-385.

Matsumura, F., O'Brien, R.D. (1963). A comparative study of the modes of action of fluoroacetamide and fluoroacetate in the mouse and American cockroach. *Biochemical Pharmacology* 12: 1201-1205.

Mattison, D. R., Working, P. K., Blazak, W. F., Hughes, Jr C. L., Killinger, J. M., Olive, D. L., Rao, K. S. (1990). Criteria for identifying and listing substances known to cause reproductive toxicity under California's proposition 65. *Reproductive Toxicology* 4:163–175.

Mazzanti, L., Lopez, M., Berte, M.G. (1965). Atrophy of the testis produced by sodium monofluoroacetate in albino rats. *Experientia* 21: 446-447.

McDowell, E.M. (1972a). Light- and electron-microscopic studies of the rat kidney after administration of inhibitors of the citric acid cycle in vivo. Changes in the proximal convoluted tubule during fluorocitrate poisoning. *Journal of Pathology* 108: 303-318.

McDowell, E.M. (1972b). Light- and electron-microscopic studies of the rat kidney after administration of inhibitors of the citric acid cycle in vivo. Effects of sodium monofluoroacetate on the proximal convoluted tubule. *American Journal of Pathology* 66: 513-530.

McIlroy, J.C. (1981a). The sensitivity of Australian animals to 1080 poison. I. Intraspecific variation and factors affecting acute toxicity. *Australian Wildlife Research* 8: 369-383.

McIlroy, J.C. (1981b). The sensitivity of Australian animals to 1080 poison. II. Marsupials and eutherian carnivores. *Australian Wildlife Research* 8: 369-383.

McIlroy, J.C. (1982). The sensitivity of Australian animals to 1080 poison. III. Marsupials and eutherian carnivores. *Australian Wildlife Research* 9: 487-503.

McIlroy, J.C. (1983). The sensitivity of Australian animals to 1080 poison. V. The sensitivity of feral pigs, *Sus scrofa*, to 1080 and its implications for poisoning campaigns. *Australian Wildlife Research* 10: 139-148.

McIlroy, J.C. (1984). The sensitivity of Australian animals to 1080 poison. VII. Native and introduced birds. *Australian Wildlife Research* 11: 373-385.

McIlroy, J.C. (1986). The sensitivity of Australian animals to 1080 poison. IX. Comparisons between the major groups of animals and the potential danger non-target species face from 1080 poisoning campaigns. *Australian Wildlife Research* 13: 39-48.

McIlroy, J.C., Gifford, E.J. (1992). Secondary poisoning hazards associated with 1080 related carrot-baiting campaigns against rabbits, *Oryctolagus cuniculus*. *Wildlife Research* 19: 629-641.

McMichael, A.J. (1989). Setting environmental exposure standards: The role of the epidemiologist. *International Journal of Epidemiology* 18: 10-16.

McTaggart, D.R. (1970). Poisoning due to fluoroacetate (1080). *The Medical Journal of Australia* 2: 641-642.

Mead, R.J., Moulden, D.L., Twigg, T.E. (1985). Significance of sulfhydryl compounds in the manifestation of fluoroacetate toxicity in the rat, brush-tailed possum, woylie, and western grey kangaroo. *Australian Journal of Biological Sciences* 38: 139-149.

Mead, R.J., Oliver, A.J., King, D.R. (1979). Metabolism and defluorination of fluoroacetate in the brush-tailed possum. *Australian Journal of Biological Sciences* 32: 15-26.

Meenken, D.R. (1993). "*Effects on water quality of an aerial 1080 possum poisoning operation*", Wairarapa, June 1993. Wairarapa Report No. 94/1 (unpublished). 15 pp.

Meenken, D.R., Booth, L. (1997). The risk of dogs of poisoning from sodium monofluoroacetate (1080) residues in possum (*Trichosorus vulpecula*). *New Zealand Journal of Agricultural Research* 40: 573-576.

Meenken, D.R., Eason, C.T. (1995). Effects on water quality of a possum poisoning operation using toxin 1080 (sodium monofluoroacetate). *New Zealand Journal of Marine and Freshwater Research* 29: 25-28.

Ministry for the Environment and Ministry of Health (MfE and MoH). (1997). *Health and Environmental Guidelines for Selected Timber Treatment Chemicals*. Ministry for the Environment and Ministry of Health: Wellington. 5-1 to 5-58 pp.

Miller, R.F., Phillips, P.H. (1955). Effect of feeding fluoroacetate to the rat. *Proceedings of the Society for Experimental Biology and Medicine* 89: 411-413.

Ministry of Health. (1995a). *Drinking Water Standards for New Zealand.* Ministry of Health, Wellington. 130 pp.

Ministry of Health (1995b). *Model Permit Conditions for the Use of Sodium Monofluoroacetate (1080).* Ministry of Health, Wellington. 12 pp.

Ministry of Health. (2000). *Healthy Eating for Adult New Zealanders.* Ministry of Health, Wellington. 12 pp.

Ministry of Health. (2002). *Eating for Healthy Children Aged 2 to 12.* Ministry of Health, Wellington. 10 pp.

Ministry of Health. (2006). Hazardous substances. In: *Environmental Health Protection Manual.* Ministry of Health, Wellington. 165 pp.

Ministry of Health. (2005). *Drinking Water Standards for New Zealand.* Ministry of Health, Wellington. 171 pp.

Morford, L.L., Henck, J.W., Breslin, W.J., DeSesso, J.M. (2004). Hazard identification and predictability of children's health risk from animal data. *Environmental Health Perspectives* 112(2): 266-271.

Morgan, M.G. (1990). Choosing and managing technology-induced risks. In: Readings in Risk. Glickman, T.S., Gough, M., eds. *Resources for the Future*, Washington, D.C., Pp 5-15.

Morgan, D.R. Eason, C.T. (2004). 1080: a review of its properties, lethal and sub-lethal effects, and primary and secondary non-target poisoning risks. In: Feare, C.J., Cowan, D.P., eds. *Advances in Vertebrate Pest Management III*, Filander Verlag, Fürth. Pp 123–150.

Morgan, D.R., Thomas, M.D., Meenken, D. (1996). Optimising the aerial delivery of possum baits. In: *Improving Conventional Control of Possums.* The Royal Society of New Zealand Miscellaneous Series 35: 15-17.

Morrison, J.F., Peters, R.A. (1954). Biochemistry of fluroacetate poisoning: The effect of fluorocitrate on purified aconitase. *Biochemical Journal* 58: 473-479.

Morselli, P.L., Garattini, S., Marucci, F., Mussinni, E., Rewersky, W., Valzelli, L., Peters, R.A. (1968). The effect of injections of fluorocitrate into the brains of rats. *Biochemical Pharmacology* 17: 195-202.

Murgueytion, A., Evans, R., Roberts, D., Moehr, T. (1996). Prevalence of childhood lead poisoning in a lead-mining area. *Journal of Environmental Health* 58(10): 12-17.

Murphy, S.D. (1986). Toxic effects of pesticides. In: Klaassen, C.D., Amdur, M.O. Doull, J., eds. *Cassarett and Doull's Toxicology*. Third Edition, New York: McMillan Publishing Co., Inc., Pp 519-581.

National Possum Control Agencies (NPCA). (1994). *1080: Some Questions and Answers*. National Possum Control Agencies, Wellington. 6 pp.

National Radiological Protection Board. (2004). In terms of risk: Report of a seminar to help define important terms used in communicating about risk to the public. *National Radiological Protection Board* 15(4): 14 pp.

National Research Council (NRC). (1983). *Risk Assessment in the Federal Government: Managing the Process*. National Academy Press, Washington, D.C. Available on line http://www.nap.edu/books/0309033497/html/. Accessed on 2 July 2002.

National Research Council (NRC). (1993). *Pesticides in the Diets of Infants and Children*. National Academy Press, Washington, DC. 386 pp.

National Research Council (NRC). (1994). *Science and Judgement in Risk Assessment*. National Academy Press, Washington, D.C. 652 pp.

Needham, L.L. (2005). *Using CDC Biomonitoring Data for Assessing Children's Exposures to Environmental Chemicals*. Abstract No. 1340. 2005 Itinerary Planner. New Orleans, LA: Society of Toxicology.

New Zealand Food Safety Authority (NZFSA). (2005a). *Hunting Poison-Free Wild and Game Estate Animal*. New Zealand Food Safety Authority: Wellington. Available on line http://www.nzfsa.govt.nz. Accessed on 1 December 2006.

New Zealand Food Safety Authority (NZFSA). (2005b). *Toxic Residues in Wild Animals*. New Zealand Food Safety Authority: Wellington. Available on line http://www.nzfsa.govt.nz. Accessed on 1 December 2006.

New Zealand (Maximum Residue Limits of Agricultural Compounds) Food Standards 2004. New Zealand.

Obasanjo, I.O., Hughes, C.L. (1997). Biology of reproduction and methods in assessing reproductive and developmental toxicity in humans. In: Massaro, E.J., ed. *Handbook of Human Toxicology*. CRC Press LLC, Boca Raton, pp. 927-959.

O'Brien, P.H. (1988). The toxicity of sodium monofluroacetate (compound 1080) to captive feral pigs, *Sus scrofa*. *Australian Wildlife Research* 15: 163-170.

O'Brien, P.H., Kleba, R.E., Beck, J.A., Baker, P.J. (1986). Vomiting by feral pigs after 1080 intoxication: nontarget hazard and influence of anti-emetics. *Wildlife Society Bulletin* 14: 425-432.

O'Connor, C.E., Eason, C.T., Fountain, J.S. (2000). "Assessing exposure risks to 1080 workers in New Zealand". Landcare Research Contract Report LC9900/98 (unpublished), prepared for the Department of Conservation and the Animal Health Board. 19 pp.

O'Connor, C.E., Fountain, J.S., Eason, C.T. (2001). "1080 worker exposure". Landcare Research Contract Report LC0001/56 (unpublished), prepared for the Department of Conservation and the Animal Health Board. 9 pp.

Oelrichs, P.H., McEwan, T. (1961). Isolation of the toxic principle of *Acacia georginae*. *Nature* 190: 808.

Ohanian, E.V. (2000). Improving risk characterisation at the U.S. Environmental Protection Agency. In: *Toxicology in Risk Assessment.* Salem, H., Olajos, E.J., eds. Taylor and Francis, Philadelphia. pp. 51-56.

Ohanian, E.V., Moore, J.A., Fowle III, J.R., Omenn, G.S., Lewis, S.C., Gray, G.M. (1997). Risk characterisation: A bridge to informed decision making. *Fundamental and Applied Toxicology* 39: 81-88.

Oliviera, M.M. de (1963). Chromatographic isolation of monofluoroacetic acid from *Palicourea marcgraviii* (St Hill). *Experientia* 19: 586-587.

Organisation for Economic Co-operation and Development (OECD). (1989). *OECD Principles of Good Laboratory Practice.* Paris: Organisation for Economic Co-operation and Development. 41 pp.

Organisation for Economic Co-operation and Development (OECD). (1998). *Harmonised Integrated Hazard Classification System for Human Health and Environmental Effects of Chemical Substances*. Paris: Organisation for Economic Co-operation and Development. 247 pp.

Organisation for Economic Co-operation and Development (OECD). (2004). SIDS, the SIDS plan and the SIDS dossier. In: *Manual for Investigation of HPV Chemicals.* OECD Secretariat. Paris: Organisation for Economic Co-operation and Development. 25 pp.

Owen, B.A. (1990). Literature-derived absorption coefficients for 39 chemicals via oral and inhalation routes of exposure. *Regulatory Toxicology and Pharmacology* 11: 237-252.

Ozawa, H., Tsukioka, T. (1987). Gas chromatographic determination of sodium monofluoroacetate in water by derivatization with dicyclohexyl-carbodiimide. *Analytical Chemistry* 59: 2914-2917.

Palmateer, S.D. (1989). Status of strychnine, compound 1080, and registered alternatives. In: *Ninth Great Plains Wildlife Damage Control Workshop Proceedings*. U.S. Department of Agriculture Forest Service General Technical Report RM-171, pp. 14-16.

Palmateer, S.D. (1990). Registration status of vertebrate pesticides with emphasis on 1080 and strychnine. In: Davis, L.R. Marsh, R.E., eds. *Proceedings 14th Vertebrate Pest Conference* University of California, Davis, pp. 113-115.

Parfitt, R.I., Eason, C.T., Morgan, A.J., Burke, C.M., Wright, G.R. (1994). The fate of sodium monofluoroacetate (1080) in soil and water. In: Seawright, A.A., Eason, C.T., eds. *Proceedings of the Science Workshop on 1080*. Royal Society of New Zealand Miscellaneous Series 28: 59-66.

Parkin, P.J., McGiven, A.R., Bailey, R.R. (1977). Chronic sodium monofluoroacetate (compound 1080) intoxication in a rabbiter. *The New Zealand Medical Journal* 85: 93-96.

Parliamentary Commissioner for the Environment (PCE). (1994). *Possum Management in New Zealand*. Office of the Parliamentary Commissioner for the Environment, Wellington. 196 pp.

Pattison, F.L.M., Peters, R.A. (1959). *Toxic Aliphatic Fluorine Compounds*. Amsterdam: Elsevier Publishing Company. 227 pp.

Paustenbach, D.J. (1989). Important recent advances in the practice of health risk assessment: Implications for the 1990s. *Regulatory Toxicology and Pharmacology* 10: 204-243.

Paustenbach, D.J. (1995). The practice of health risk assessment in the United States (1975-1995): How the U.S. and other countries can benefit from that experience. *Human and Ecological Risk Assessment* 1 (1): 29-79.

Paustenbach, D.J. (2000). The practice of exposure assessment: A state of the art review. *Journal of Toxicology and Environmental Health* Part B, 3:179-291.

Pease, W., Vanderberg, J., Hooper, K. (1991). Comparing alternative approaches to establishing regulatory levels for reproductive toxicants: DBCP as a case study. *Environmental Health Perspectives* 91: 141-155.

Pelfrene, A.F. (1991). Synthetic Organic Rodenticides. In: Hayes, W.J., Laws, E.R., eds. *Handbook of Pesticide Toxicology*, Volume 3.Academic Press, Inc. California. Pp. 1272-1277.

Peters, R.A. (1952). *Lethal Synthesis*. Proceedings of the Royal Society of London B, 139. pp. 143.

Peters, R.A. (1957). Mechanism of the toxicity of the active constituent of *Dichapetalum cymosum* and related compounds. *Advances in Enzymology and Related Subjects of Biochemistry* 18: 113-159.

Peters, R.A. (1963). In: *Biochemical Lesions and Lethal Synthesis*. P. III., ed. Pergamon Press. New York. pp. 88-115.

Peters, R.A. (1977). 1080 poisoning. *The New Zealand Medical Journal* 85: 295.

Peters, R.A., Shorthouse, M. (1971). Oral toxicity of fluoroacetate and fluorocitrate in rats. *Journal of Physiology* (London) 216: 40P–41P.

Peters, R.A., Shorthouse, M., Ward, P.F.V., McDowell, E.M. (1972). Observations upon the metabolism of fluorocitrate in rats. *Proceedings of the Royal Society of London*. Series B. 182: 1-8.

Peters, R.A., Wakelin, R.W. (1953). Fluoroacetate poisoning: Comparison of synthetic fluorocitric acid with the enzymically synthesised fluorotricarboxylic acid. *Nature* 171: 1111-1112.

Pesticides Act 1979. New Zealand.

Pesticides (Vertebrate Pest Control) Regulations 1983. New Zealand.

Pohl, H.R., Abadin, H.G. (1995). Utilising uncertainty factors in minimal risk levels derivation. *Regulatory Toxicology and Pharmacology* 22: 180-188.

Powlesland, R.G., Stringer, I.A.N., Hedderley, D.I. (2005). Effects of an aerial 1080 possum poison operation using carrot on invertebrates in artificial reuges at Whirinaki Forest Park, 1999-2002. *New Zealand Journal of Ecology* 29(2): 193-205.

Powlesland, R.G., Wills, D.E., August, A.C.L., August, C.K. (2003). Effects of a 1080 operation on kaka and kereru survival and nesting success. Whirinaki Forest Park. *New Zealand Journal of Ecology* 27(2): 125-137.

Privalova, L.I., Wilcock, K.E., Katsnelson, B.A., Keane, S.E., Cunningham, K. *et al.* (2001). Some considerations concerning multimedia-multipollutant risk assessment methodology: Use of epidemiologic data for non-cancer risk assessment in Russia. *Environmental Health Perspectives* 109 (1): 7-13.

Purchase, I.F.H. (1986). Unpredictability: An essay in toxicology. *Food and Chemical Toxicology* 42(4): 343-349.

Raffensperger, C., Tickner, J.A. (2001). Protecting public health and the environment: Implementing the precautionary principle. *Journal of Agricultural and Environmental Ethics* 14(3): 351-354.

Rall, D. (1979). Rall says "new toxicology" must be used to prevent human diseases. *Pesticide and Toxic Chemical News*. 25 April 1979. pp. 18.

Rammell, C.G. (1993). Persistence of compound 1080 in sheep muscle and liver. *Surveillance* 20(1): 20-21.

Rammel, C.G., Flemming, P.A. (1978). *Compound 1080: Properties and Use of Sodium Monofluoroacetate in New Zealand.* Animal Health Division, Ministry of Agriculture and Fisheries. Wellington. 112 pp.

Rammel, C.G., Flemming, P.A., O'Hara, P.J. (1977). 1080 poisoning. *The New Zealand Medical Journal* 85: 295-296. 112 pp.

Ramsay, J. (1977). 1080 poisoning. *The New Zealand Medical Journal* 85:295.

Rathore, A.K. (1985). Use of metoclopramide to prevent 1080-induced emesis in wild pigs. *Journal of Wildlife Management* 49: 55-56.

Reigart, J.R., Brueggeman, J.L., Keill, J.E. (1975). Sodium monofluoroacetate poisoning. *American Journal of Diseases of Children* 129(10): 1224-1226.

Renwick, A.G., Walker, R. (1993). An analysis of the risk of exceeding acceptable or tolerable daily intake. *Regulatory Toxicology and Pharmacology* 18: 463-480.

Resource Management Act 1991. New Zealand.

Ruppel, E. (1995). *An element of doubt. The* Atlantic Monthly 276 (6): 24-39.

Sand, S., Filiposson, A. F., Victorin, K. (2002). Evaluation of the benchmark dose method for dichotomous data: Model dependence and model selection. *Regulatory Toxicology and Pharmacology* 36(2): 184-197.

Savarie, P.J. (1984). Toxic characteristics of fluorocitrate, the toxic metabolite of compound 1080. In: Clark, D.O., ed. *Proceedings Eleventh Vertebrate Pest Conference*. University of California, Davis. pp. 132-137.

Schaefer, H., Machleidt, H. (1971). Conversion of fluoroacetic acid to amino acids in the mammal. *Biochemica et Biophysica Acta* 252: 83-91.

Scheuplein, R. (2000). Pesticides and infant risk: Is there a need for an additional safety margin? *Regulatory Toxicology and Pharmacology* 31: 267-278.

Scheuplein, R., Charnley, G., Dourson, M. (2002). Differential sensitivity of children and adults to chemical toxicity. *Regulatory Toxicology and Pharmacology* 35: 429-447.

Schultz, R., Coetzer, J.A., Kellerman, T.S., Naude, T.W. (1982). Observations on the clinical, cardiac, and histopathological effects of fluoroacetate in sheep, *Onderstepoort. Journal of Veterinary Research* 49: 237-245.

Scialli, A.R., Collie, C.F. (1997). Female reproductive toxicology. In: Massaro, E.J., ed. *Handbook of Human Toxicology*. Boca Raton FL: CRC Press, New York, pp. 981-1006.

Seawright, A. (1994). The environmental toxicology of 1080-key points revisited. In: Seawright, A.A., Eason, C.T., eds. *Proceedings of the Science Workshop on 1080.* Royal Society of New Zealand Miscellaneous Series 28: 166-168.

Shinoda, K., Mitsumori, K., Uneyama, C., Uehara, M. (2000). Induction and inhibition of testicular germ cell apoptosis by fluoroacetate in rats. *Archives in Toxicology* 74: 33-39.

Silbergeld, E.K. (1987). Five types of ambiguity: Scientific uncertainty in risk assessment. *Hazardous Waste Hazardous Materials* 4: 139-150.

Silbergeld, E.K. (1993). Risk assessment: The perspective and experience of the U.S. environmentalists. *Environmental Health Perspectives* 101: 100-104.

Smith, F.A., Gardner, D.E., Yuile, C.L., De Lopez, O., Hall, L.L. (1977). Defluorination of fluoroacetate in the rat. *Life Science* 20: 1131-1138.

Soiefer, A.I., Kostyniak, P.J. (1983). The enzymatic defluorination of fluoroacetate in mouse liver cytosol: The separation of defluorination activity from several glutathione S-transferases of mous liver. *Archives of Biochemistry and Biophysics* 225: 928-935.

Spielmann, H., Mayer-Wendecker, R., Spielmann, F. (1973). Influence of 2-deoxy D-glucose and sodium monofluroacetate on respiratory metabolism of rat embryos during organogenesis. *Teratology* 7: 127-134.

Stachel, B., Dougherty, R.C., Lahl, U., Schlosser, M., Zeschmar, B. (1989). Toxic environmental chemicals in human semen – analytical method and case studies. *Andrologia* 21: 282-291.

Stark, J.D., Banks, J.E., Vargas, R. (2004). How risky is risk assessment: The role that life history strategies play in susceptibility of species to stress. *Proceedings of the National Academy of Sciences of the United States of America* 101(3): 732-736.

Steensberg, J. (1989). Environmental health decision making, the policies of disease prevention. *Scandinavian Journal of Social Medicine* 42 (suppl.):121-295.

Sullivan, J.L., Smith, F.A., Garman, R.H. (1979). Effects of fluoroacetate on the testis of the rat. *Journal of Reproductive Fertility* 56: 201-207.

Sunshine, I. (1969). *Handbook of Analytical Toxicology*. The Chemical Rubber Company, Cleveland, Ohio, USA. p. 533.

Suren, A. (2006). Quantifying contamination of streams by 1080 baits, and their fate in water. *New Zealand Journal of Marine and Freshwater Research* 40: 159-167.

Suren, A., Lambert, D. (2004). *The Effects of 1080 on Invertebrate Communities and the Fish in West Coast Streams*. NIWA Client report: CHC2004-096. Animal Health Board. 44 pp.

Swartout, J. (1996). Subchronic-to-chronic uncertainty factor for the reference dose (Abstract F2.03). *Society for Risk Analysis Annual Meeting*. New Orleans.

Sykes, T.R., Quastel, J.H., Adam, M.J., Ruth, T.J., Nonjawa, A.A. (1987). The disposition and metabolism of fluorine-18 fluoroacetate in mice. *Biochemical Archives* 3(3): 317-24.

Taranaki Regional Council (TRC). (1993). Water quality monitoring of Stage 1 of the Department of Conservation/Taranaki Regional Council possum control operation on Mount Taranaki/Egmont, *TRC Technical Report 93-27*. Taranaki Regional Council, Stratford. 18 pp.

Tecle, B., Casida, J.E. (1989). Enzymatic defluorination and metabolism of fluoroacetate, fluoroacetamide, fluoroethanol, and (-)-erythro-fluorocitrate in rats and mice examined by 19F and 13C NMR. *Chemical Research in Toxicology* 2: 429-435.

Temple, W.A., Edwards, I.R. (1985). Toxic ducks 1080 residues in game birds. An exercise in applied toxicology. *Veterinary and Human Toxicology* 27: 20-21.

Thomas, J.A. (1981). Reproductive hazards and environmental chemicals: A review. *Toxic Substances Journal* 2: 318-348.

Thomas, M.D. (1994). Possum control in native forest using sodium monofluoroacetate (1080) in bait station. *Proceedings 47th NZ Plant Protection Conference*, pp. 107-111.

Timbrell, J. (2000) *Principles of Biochemical Toxicology*, Third Edition. Taylor and Francis Ltd, London. 349 pp.

Toxic Substances Act 1979. New Zealand.

Toxic Substances Regulations 1983. New Zealand.

Trabes J., Rason, N., Avrahmi, E (1983). *Journal in Clinical Toxicology* 20(1): 85-92.

Travis, C.C., Baes III, C.F., Barnthouse, L.W., Etnier, E.L., Holton, G.A., Murphy, B.D., Thompson. G.P., Suter III, G.W., Watson, A. (1983). Exposure assessment methodology and reference environments for synfuel risk analysis. *ESD Publication No. 2232*. Oak Ridge National laboratory, Oak Ridge, Tennessee. 104 pp.

Twigg, L.E. (1986). "The physiological, ecological and evolutionary significance of monofluoroacetic acid in relation to plant animal interaction in Australia". PhD. Thesis, Murdoch University, Australia. pp. 167-361.

Twigg, L.E. (1994). Occurrence of fluoroacetate in Australian plants and tolerance to 1080 in indigenous Australian animals. In: Seawright, A.A., Eason, C.T., eds. *Proceedings of the Science Workshop on 1080*. Royal Society of New Zealand Miscellaneous Series 28: 97-115.

Twigg, L.E., King, D.R. (1991). The impact of fluoroacetate-bearing vegetation on native Australian fauna: A review. *Oikos* 61: 412-430.

Twigg, L.E., King, D.R., Bowen, L.H., Wright, G.R., Eason, C.T. (1996). Fluoroacetate content of some species of the toxic Australian plant genus, *Gastrolobium* and its environmental persistence. *Natural Toxins* 4: 122-127.

Twigg, L.E., King, D.R., Bradley, A.J. (1988). The effect of sodium monofluoroacetate on plasma testosterone concentration in *Tiliqua rugosa* (Gray). *Comparative Biochemistry and Physiology* 91(2): 343-347.

Twigg, L.E., Mead, R.J., King, D.R. (1986). Metabolism of fluoroacetate in the skink (*Tiliqua rugosa*) and the rat (*Rattus norvegicus*). *Australian Journal of Biological Sciences* 39: 1-15.

U.S. Environmental Protection Agency (US EPA) (1979). *Proposed Rules – Teratogenic/Reproductive Health Effects*. U.S. Federal Register. 44: 44087.

U.S. Environmental Protection Agency (US EPA). (1989). *Risk Assessment Guidance for Superfund*, Volume 1, Human Health Evaluation Manual (Part A). EPA/540/1-89/002.

U.S. Environmental Protection Agency (US EPA). (1991). *Guidelines for Developmental Toxicity Risk Assessment.* U.S. Federal Register 56(234): 63798-63826.

U.S. Environmental Protection Agency (US EPA). (1992). *Guidelines for Exposure Assessment*: Notice. U.S. Federal Register 57(104): 22888-22938.

U.S. Environmental Protection Agency (US EPA). (1995). *The Use of the Benchmark Dose Approach in Health Risk Assessment.* Office of Research and Development, Washington, DC: EPA/630/R-94/007, February. 93 pp.

U.S. Environmental Protection Agency (US EPA). (1996). *Pesticides: Policy Issues Related to the Food Quality Protection Act.* U.S. Federal Register 64(130):37001-37009.

U.S. Environmental Protection Agency (US EPA). (1997). *Exposure Factors Handbook.* Volume 1, Washington Office of Research and Development, National Cancer for Environmental Assessment, U.S. Environmental Protection Agency. 1193 pp.

US. Environmental Protection Agency (US EPA). (2000). *Benchmark dose technical guidance document.* U.S. Environmental Protection Agency. Available on line http://www.epa.gov. Accessed on 15 June 2001.

U.S. Environmental Protection Agency (US EPA). (2001). *Benchmark Dose Software*, Version 1.3. Available on line http://www.epa.gov. Accessed on 15 June 2001.

U.S. Environmental Protection Agency (US EPA). (2002). *Child-Specific Exposure Factors Handbook.* National Center for Environmental Assessment, Washington, DC; EPA/600/P-00/002.Available from: National Information Service, Springfield, VA, PB2003-101678 and <hhtp:www.epa.gov/ncea>. Accessed on 1 December 2003.

US. Environmental Protection Agency (US EPA). (2003). *Benchmark Dose Tutorial.* U.S. Environmental Protection Agency. Available on line http://www.epa.gov. Accessed on 15 June 2001.

U.S. Food Quality and Protection Act 1996. U.S.A.

Van Leeuwen C.J. (1995). General introduction. In: Van Leeuwen, C.J., Hermens, J.L.M., eds. *Risk Assessment of Chemicals: An Introduction*, Kluwer Academic Publishers, Dordrecht, pp. 147-174.

Vickery, B., Vickery, M. L. (1975). The synthesis and defluorination of monofluoroacetate in some *Dichapetalum* species. *Phytochemistry* 14: 423-427.

Vickery, B., Vickery, M. L. Ashu, J. T. (1973). Analysis of plants for fluoroacetic acid. *Phytochemistry* 12: 145-147.

Walker, J.R.L. (1994). Degradation of sodium monofluoroacetate by soil microorganisms. In: Seawright, A.A., Eason, C.T., eds. *Proceedings of the Science Workshop on 1080.* Royal Society of New Zealand Miscellaneous Series 28: 50-53.

Walker, J.R.L., Bong, C.L. (1981). Metabolism of fluoroacetate by a soil *Pseudomonas* and *Fusarium solani*. *Soil Biology and Biochemistry* 13: 231-235.

Water Supply Regulations 1961. New Zealand.

Waxman, D.J., Chang, T.K.H. (2005). Hormonal regulation of liver cytochrome P450 enzymes. In: de Montellano, P.O., ed. *Cytochrome P450 Structure, Mechanisms and Biochemistry*, Third Edition. Plenum Publishers, New York. pp. 47-376.

Weaver, S. (2003). Policy implications of 1080 toxicology in New Zealand. *Journal of Rural and Remote Environmental Health* 2(2): 46-59.

Weil, C.S. (1972). Statistics vs. safety factors and scientific judgement in the evaluation of safety for man. *Toxicology and Applied Pharmacology* 21: 454-463.

Wellington Regional Council (WRC). (2000). "Effect of hand-baiting on water quality". Wairarapa Division Report No. 00/1. (unpublished). 23 pp.

Wheeler, S.H., Oliver, A.J. (1978). The effect of rainfall and moisture on the 1080 and pindone content of vacuum-impregnated oats used for control of rabbits, *Oryctolagus cuniculus*. *Australian Wildlife Research* 5: 143-149.

Whittem, J.H., Murray, L.R. (1963). The chemistry and pathology of georgina river poisoning. *Australian Veterinary Journal* 39: 168-173.

Wigle, D.T. (2003). *Child Health and the Environment*. Oxford University Press, Inc. New York. pp. 162-188.

Wilkinson, C.F. (1990). Reproductive toxicology of pesticides. In: Baker, S.R., Wilkinson, C.F., eds. *Advances in Modern Environmental Toxicology*. Scientific Press, Princeton, NJ, pp. 1-33.

Williamson, J.R., Jones, E.A., Azzone, G.F. (1964). Metabolite control in perfused rat heart during fluoroacetate poisoning. *Biochemical and Biophysical Research Communication* 17: 696-702.

Wilson, J.G. (1977). Embryotoxicity of drugs in man. In: Wilson, J.G., Fraser, F.C. eds. *Handbook of Teratology*. Volume 1, Plenum Press, New York, p. 309.

Wolfe, G.W. (1988). "Subchronic toxicity study in rats with sodium fluoroacetate". Hazleton Laboratories America, Inc. Contract Report HLA Study No. 2399-118 (unpublished). 91 pp.

Wong D.H., Kirkpatrick W.E., King D.R., Kinnear J.E. (1992a). Defluorination of sodium monofluoroacetate by microorganisms isolated from Western Australia soils. *Soil Biology and Biochemistry* 24(9): 833-838.

Wong, D.H., Kirkpatrick, W.E., King, D.R., Kinnear, J.E. (1992b). Environmental factors and microbial inoculum size and their effect on biodefluorination of sodium monofluoroacetate (1080). *Soil Biology and Biochemistry* 24: 839-843.

Wong, D.H., Kirkpatrick, W.E., Kinnear, J.E., King, D.R. (1991). Defluorination of sodium monofluoroacetate (1080) by microorganisms found in bait materials. *Wildlife Research* 18: 539-45.

World Health Organization (WHO). (1995). *Lead and Health.* Copenhagen, World Health Organization-Regional Office for Europe. 20 pp.

Wright, G.R.G. (1998). *Protocol for Environmental Water Sampling and Testing Associated with 1080 Pest Control Operations*. Landcare Research New Zealand Ltd. Lincoln. 7 pp.

Wright, G.R., Booth, L.H., Morris, G.A., Potts, M.D., Brown, L., Eason, C.T. (2002). Assessing potential environmental contamination from compound 1080 (sodium monofluoroacetate) in bait dust during possum control operations. *New Zealand Journal of Agricultural Research* 45: 57-65.

Yosie, T. (1987). How risk assessments are used in the Federal Government. *Environmental Science and Technology* 21: 526-531.

Zeckhauser, R., Viscussi, W.K. (1990). Risk with reason. *Science* 248: 559-564.

Appendix 1. Water analysis after major 1080 operations 1990-2002

Location	Date	Total no. of samples taken in operation area	No. with residues	Highest concentrations (µg/L or ppb)
Waipoua	1990	36	0	-
Rangitoto	1991	20	0	-
Blackstone Hill	1992	23	11	0.6
Mt Taranaki	1993	125	15	<0.3
Woodside	1993	55	0	-
Hunua Range	1994	136	7	0.7
Mt Taranaki	1994	63	0	-
Marlborough Sounds	1994	26	5	3.4
Wairarapa	1994	31	0	-
Hawke's Bay	1994	15	0	-
Ohakune	1994	6	1	0.2
Whangarei	1994	18	0	-
Karioi	1994	10	1	0.8
Manawatu	1994	21	0	-
Waimakariri	1995	4	1	0.2
Manawatu	1995	48	0	-
Hawke's Bay	1995	8	1	0.3
Ohakune Erua Forest	1995	3	0	-
Tongariro National Park	1995	8	0	-
Northland	1995	11	0	-
Tararua Ranges	1995	11	0	
Hawke's Bay	1995	9	0	-
Waimarino Forest	1995	4	0	-
Wairarapa	1996	7	0	-
Pirongia	1996	7	0	-
Raukumara Ranges	1996	37	1	0.2
Waikato	1996	4	0	-
Levin Buffer	1996	8	0	-
Erua State Forest	1996	3	1	3.5
Waitohu Stream	1996	4	0	-
Wairokau Stream	1997	4	0	-
Raukumara Ranges	1997	12	0	-
Ohakune	1997	10	0	-
Pareroa River, Timaru	1997	2	0	-
Rangataua Forest	1997	40	0	-

Appendix 1. Continued

Location	Date	Total no. of samples taken in operation area	No. with residues	Highest concentrations (µg/L or ppb)
Te Whaiau Spillway	1997	3	1	2.4
Raukumara Ranges	1997	9	1	0.5
East Cape	1997	12	0	-
Warawara Forest	1997	4	0	-
Mt Bruce/Mikimiki	1998	10	0	-
Mawheraiti, West Coast	1998	1	0	-
Kuharua	1998	1	0	-
Manawatu-Wanganui	1998	6	0	-
Toko	1998	3	2	9*
Wairarapa	1998	8	0	-
Manawatu-Wanganui	1998	8	0	-
West Taieri Stream	1998	4	0	-
Hook Bush, Timaru	1998	2	0	-
Haurangi Crown	1998	6	0	-
Northland	1998	9	0	-
Otorohanga, te Tahi	1998	3	0	-
Ahuroa/Maungatoroto	1998	2	0	-
Levin Buffer	1998	2	0	-
Lawrence/Waitahuna	1998	8	0	-
Northland	1998	5	0	-
Masterton	1998	6	0	-
Richmond	1998	9	0	-
Porangahau	1999	3	0	-
Northland	1999	7	0	-
Waipoua Forest	1999	1	0	-
Waipa River	1999	2	0	-
Holdsworth/Woodside	1999	3	0	-
Manawatu-Wanganui	1999	2	0	-
Hawke Hills	1999	2	0	-
Warawara Forest	1999	1	0	-
Waima	1999	2	0	-
Riwaka Forest	1999	2	0	-
Eastern Tararua R.	1999	7	0	-
Takaka	1999	6	0	-
Amuri Range	1999	1	0	-
Hawkins River	1999	1	0	-
Wakamarama	1999	15	0	-
Northland	1999	8	0	-
Wainuiomata	1999	26	0	-
Aorere	1999	2	0	-
Hauturu/Honikiwi	1999	2	0	-
Otorohanga	1999	1	0	-

Appendix 1. Continued

Location	Date	Total no. of samples taken in operation area	No. with residues	Highest concentrations (µg/L or ppb)
Wainuiomata	1999	25	0	-
Pembroke Wilderness	1999	6	0	-
Aorere	1999	6	0	-
Rotomanu	1999	2	0	-
Kaiiwi	1999	4	0	-
Inland Paparoa	1999	12	0	-
Te Kopia Scenic Res.	1999	10	2	4.0
Marlborough	1999	1	1	0.2
Tapu River/Te Mata Str.	1999	7	0	-
Te Kopia Scenic Res.	1999	1	0	-
Benhopai	1999	1	0	-
Eastern Tararua R.	1999	4	0	-
Hauhungaroa Range	1999	8	0	-
Hampden, Herbert	1999	14	0	-
Manawatu-Wanganui	1999	2	0	-
Waingawa	1999	1	0	-
Tapanui	1999	1	0	-
Murupara	1999	1	0	-
Manawatu-Wanganui	1999	1	0	-
Wairarapa	1999	20	0	-
Rotorua	2000	1	0	-
Northland	2000	9	0	-
Tapanui	2000	1	0	-
Manawatu-Wanganui	2000	2	0	-
Kaikoura	2000	7	0	-
Marlborough	2000	2	0	-
Banks Peninsula	2000	1	0	-
Gisborne	2000	3	0	-
Copland	2000	1	0	-
Richmond	2000	5	0	-
Greymouth	2000	2	0	-
Manawatu-Wanganui	2000	2	0	-
Aorere	2000	7	0	-
Takaka	2000	7	0	-
Richmond	2000	2	0	-
Richmond	2000	2	1	0.5
Manawatu-Wanganui	2000	6	0	-
Napier	2000	2	0	-
Taupo	2000	1	0	-
Omaka River	2000	2	0	-
Copland Valley	2000	1	0	-
Takaka	2000	1	0	-

Appendix 1. Continued

Location	Date	Total no. of samples taken in operation area	No. with residues	Highest concentrations (µg/L or ppb)
Whirinaki	2000	1	0	-
Ohara Stream	2000	1	0	-
Waitohu	2000	4	0	-
Waiotemarama	2001	1	0	-
Wanganui National P.	2001	1	0	-
Kapitea Creek, Westland	2001	2	0	-
Otira	2001	5	0	-
Waihopai Valley	2001	8	0	-
Mt. Thomas	2001	6	1	0.3
Wairarapa	2001	1	0	-
Taupo	2001	1	0	-
Northland	2001	5	0	-
Hokitika	2001	2	0	-
Wairarapa	2001	3	0	-
Taupo	2001	1	0	-
Hokitika	2001	2	0	-
Tennyson Inlet	2001	2	0	-
Aorere	2001	3	1	0.2
Buller	2001	9	0	-
Takaka	2001	3	0	-
Mangarakau	2001	2	0	-
South Motueka	2001	8	0	-
Kahurangi National P.	2001	2	0	-
Marlborough	2001	1	0	-
Mid-Motueka Valley	2001	2	0	-
Waihopai Dam	2001	2	0	-
Canaan, Golden Bay	2001	2	0	-
Upper Takaka	2001	7	0	-
Canaan, Upper Takaka	2001	11	0	-
Levin	2001	3	0	-
Waihopai Dam	2001	2	0	-
Mangatawhiri Stream	2001	1	0	-
Canaan	2001	4	0	-
Rangiora	2001	2	0	-
Takaka	2001	1	0	-
Pureora Forest	2001	4	0	-
Manawatu-Wanganui	2001	6	0	-
Masterton	2001	4	0	-
Gisborne	2001	4	0	-
Waingawa River	2001	2	0	-
Cobb Valley	2001	2	0	-
Waiohine, Waingawa	2001	7	0	-
Greymouth	2002	1	0	-

Appendix 1. Continued

Location	Date	Total no. of samples taken in operation area	No. with residues	Highest concentrations (µg/L or ppb)
Masterton	2002	4	0	-
Waikato River	2002	6	0	-
Wanganui	2002	1	0	-
Taupo	2002	1	0	-
Trilby Creek, West Coast	2002	1	0	-
Taupo	2002	1	0	-
West Coast	2002	8	0	
Whisky Gulley, Otago	2002	1	0	
Palmerston North	2002	1	0	
Taupo	2002	1	0	
Herbert/Hampden	2002	8	1	0.8
Waipori Falls, Otago	2002	2	0	
Motuihe Island	2002	5	0	
Pleasant Flat, West Coast	2002	1	0	
Mt Taranaki	2002	8	0	
Golden Bay	2002	8	0	
Mt Grey	2002	12	2	1.0
Hamilton	2002	1	0	
Nelson	2002	1	0	
Hamilton	2002	3	0	
Waiohine River	2002	2	0	
Golden Bay	2002	10	0	
Totals		**1465**	**57**	

Source: Eason (2002)
* Enquiries by Landcare Research's senior chemist identified that the sample had been collected by a worker with 1080 dust on his overalls and hands

Appendix 2. A Benchmark dose analysis for sodium monofluoroacetate (1080) using dichotomous toxicity data

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A benchmark dose analysis for sodium monofluoroacetate (1080) using dichotomous toxicity data

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Abstract

The use of a benchmark dose (BMD) as an alternative to a no-observed-adverse-effect-level (NOAEL) approach was investigated as a means to improve current risk assessment values of sodium monofluoroacetate (1080). The feasibility of implementing the two approaches was investigated for three critical toxicological end points, namely cardiomyopathy, testicular toxicity and teratogenic effects identified from the few available critical studies. The BMD provides better representation of the dose–response relationship, offering an advantage over the current NOAEL approach. The calculated BMDs and lower-bound confidence limits (BMDLs) for the three end points were estimated using the Weibull, probit and quantal linear models for each end point. All models passed the χ^2 test statistics ($p \geqslant 0.1$) for all three toxicity endpoints tested. A benchmark response (BMR) of 10% (extra risk) was chosen and the Akaike's information criterion (AIC) was used in selecting the appropriate model. The BMDL estimates derived were found to be generally slightly higher but comparable to the NOAEL for those same endpoints. The BMD_{10} and $BMDL_{10}$ for cardiomyopathy and testicular effects were 0.21 mg kg^{-1} bw and 0.10 mg kg^{-1} bw, respectively. These values are proposed for use in the eventual determination of the tolerable daily intake (TDI) for 1080.
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Keywords: Benchmark dose; NOAEL; 1080; Cardiomyopathy; Testicular; Teratogen; TDI

1. Introduction

It has been suggested by Crump (1984) that dose–response modelling, i.e., the benchmark dose (BMD) methodology rather than the traditional no-observed-adverse-effect-level (NOAEL) approach should be generally applied to systemic toxicity. Dose–response modelling is a commonly accepted method of estimating the response associated with a given exposure. However, not all human observations (if available) or animal experiments are amenable to BMD modelling (Crump, 1995), for instance, if there is a biologically significant increase in a rare malformation where it was found to be not statistically significant.

It is well-known that the NOAEL does not necessarily show that there is a zero risk dose below a threshold dose. Gaylor (1992) showed, for example, in a review of developmental toxicity studies, that the estimated risk of stillborn or resorbed or malformed fetuses ranged from 0% to 4.5% at the NOAEL. The true risk of exposure at the NOAEL can often vary from 0% to >20%, depending on the background variability of endpoints, spacing of doses, and numbers of animals used, or alternatively it could be manyfold lower than a true population threshold (Leisenring and Ryan, 1992; Gaylor, 1992; Renwick and Walker, 1993). This could particularly be the case if the effect modelled was an adaptive change and not necessarily adverse.

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Therefore, the NOAEL is not the same as the biological threshold and may underestimate or overestimate the true no-effect level (Renwick and Walker, 1993).

The BMD approach has been used in recent years as an alternative approach for calculating the tolerable daily intake (TDI) to avoid the shortcomings associated with the NOAEL (Crump, 1984). It has gained wide acceptance in carrying out health risk assessment and has been frequently used by various regulatory agencies, such as the US EPA and the WHO (Fowles et al., 1999). The BMD approach uses all of the experimental data to fit one or more dose–response curves. In using the NOAEL approach to calculate a TDI, the only data point used is the NOAEL (Gaylor et al., 1998). The BMD approach is not restricted to experimental NOAELs/LOAELs but also makes use of dose–response data and sample size. The TDI is similar in definition and intent to terms such as the reference dose (RfD) or reference concentration (IPCS, 1994) and uses the same uncertainty factors as are used in the derivation of the TDI/RfD.

The BMD is the dose (Barnes et al., 1995) calculated to be associated with an increase in the response (called the BMR) (Gaylor, 1992) for a given incidence (e.g., 5% or 10% incidence) of effect estimated from all toxicity data on that effect within the study (Crump, 1995). The BMD is assigned a lower confidence limit (BMDL) and is used as the point of departure in determining the TDI. The use of the BMDL has encouraged more statistically rigorous experiments to be conducted to obtain tighter confidence limits resulting in higher TDI values (Gaylor, 1996) and is therefore more accurate.

The BMR is a response level used to define a BMD. For quantal responses, the BMR is expressed in terms of a percent increase in risk of adverse outcome compared with background. The BMR is typically set at the lower end of the range of responses (e.g., 10% or 5% change) that can be detected experimentally. Currently, there is no scientific rationale for preferring a 5% or 10% effect level, and it appears that selection of one over the other would have minimal effect on the derived TDI in most cases (Barnes et al., 1995). For the purposes of this study, a BMR of 10% was used in calculating the BMD. This 10% value is consistent with the 10% BMR suggested by the US EPA (2003).

The purpose of this paper is to evaluate and use the BMD approach in the context of the adverse effects of 1080. 1080 is one of the most toxic vertebrate agents known and it has been proven to be effective in controlling possums (*Trichosurus vulpecula*). It has been used in New Zealand for several decades and its use continues to cause controversy to the general public. New Zealand is the only country in the world with a "possum problem". Uncontrolled possum populations are a direct threat to vulnerable areas of the conservation estate and the diversity of New Zealand's flora and fauna. In addition, possums are the major wildlife host of bovine tuberculosis which is New Zealand's main animal health problem. New Zealand is the largest user of 1080 in the world using approximately 80% of the world's production of manufactured 1080 (PCE, 1994). A clear understanding of possible risks to the environment was suggested by Parfitt et al. (1994) as being essential, since more than 3.2 tonnes of 1080 is applied annually. In other countries, 1080 is also being used, but in relatively small quantities.

In this study, the BMD approach, which involves fitting a mathematical model to toxicological dose–response data, is examined as an alternative to the use of a NOAEL. The BMD and BMDL estimates are calculated from pivotal studies available in published literature. In this analysis, three models are used and the fits of the models to each of the critical toxicity end points are determined. BMD estimates providing the best model fit are compared to corresponding NOAELs using statistically derived uncertainty factor. Conclusions with respect to the use of these models for BMD calculations for 1080 are provided.

2. Methods

A thorough literature review of relevant published articles was undertaken. The data collected were subsequently analysed to determine whether or not the studies were relevant for the purposes of health risk assessment. Only studies characterising a non-lethal effect in appropriate test species were considered for further analysis.

A comprehensive review of the relevant animal data revealed that the studies of Eason et al. (1999) and Eason and Turck (2002) provide the most appropriate studies for risk assessment and were chosen as the pivotal studies. Sprague–Dawley rats, about 6 weeks of age, were dosed with 1080-treated water at 0.025, 0.075 and 0.25 mg kg^{-1} by oral gavage for 90 days. Findings at necroscopy (date of terminal sacrifice not specified) included severe hypospermia of the epididymis and severe degeneration of the seminiferous tubules of the testes in male rats dosed with 0.25 mg kg^{-1} day^{-1}. It was confirmed that recovery from testicular damage did not occur even after 56 days without treatment. Increases in heart weight when compared with controls were reported. No effects were noted in the lower dose groups. Cardiomyopathy was only seen in 50% (10/20) of males dosed with 1080 at 0.25 mg kg^{-1} day^{-1} and 5% (1/20) female rat, suggesting a gender difference. The NOAEL for both the testicular and cardiomyopathy was 0.075 mg kg^{-1} day^{-1}. For the teratogenic effects, the critical study (Eason et al., 1999) confirmed that 1080 caused developmental defects in rats when pregnant females were exposed to 0.10, 0.33 and 0.75 mg kg^{-1} day^{-1} of 1080 diet by the oral route on a daily basis during the period of organogenesis (from days 6 through to 17 of gestation). The highest dose (0.75 mg kg^{-1} day^{-1}) showed irreversible limb abnormalities and the next highest dose (0.33 mg kg^{-1} day^{-1}) showed reversible rib defects. A NOAEL was reported at 0.10 mg kg^{-1} day^{-1}.

The toxicological end points for which the dose–response relationship was best characterised were the developmental (Eason et al., 1999), reproductive, and myocardial toxicities observed in the subchronic study in rats by Eason and Turck (2002). Whittem and Murray (1963) drew a similar conclusion that the heart was the most susceptible organ to pathologic lesions, while Sullivan et al. (1979) considered testis as the organ most vulnerable to the toxic effects of 1080.

Table 1 shows the critical effects, the NOAELs and the LOAELs, and experimental doses of 1080 in experimental animal tested for the critical-toxicity end points.

For the data investigated, three models were employed to provide a range of BMD estimates using the US EPA BMDS version 1.3 software (2001). The models were used to calculate the BMDLs for the quantal response variables at the 95% lower confidence limit and 10% level of extra risk. These models are summarised with their respective mathematical equation below as adopted from the US EPA (1995).

Table 1
Summary of critical quantal end points and effects arising from 1080 exposure in rats

Critical Endpoint	Parameter	Experimental dose	Critical Effect
Teratogenicity[a]	NOAEL	0.10 mg kg^{-1} bw day^{-1}	Malformations-irreversible forelimb malformations
	LOAEL	0.33 mg kg^{-1} bw day^{-1}	
Testicular toxicity [b]	NOAEL	0.075 mg kg^{-1} bw day^{-1}	Severe hypospermia in epididymis, severe degeneration of seminiferous tubules of the testes
	LOAEL	0.25 mg kg^{-1} bw day^{-1}	
Myocardial toxicity[b]	NOAEL	0.075 mg kg^{-1} bw day^{-1}	Cardiomyopathy
	LOAEL	0.25 mg kg^{-1} bw day^{-1}	

[a] Eason et al. (1999).
[b] Eason and Turck (2002).

Quantal linear $P(d) = c + (1 - c) \times \{1 - \exp[-q1 \times d]\}$

Weibull $P(d) = c + (1 - c) \times \{1 - \exp[-q1 \times d^k]\}$

Logprobit $P(d) = c + (1 - c) \times F(a + b \times \ln(d))$,

where $F(x)$ is the cumulative normal density function,

$F(x) = 1/2[1 + \mathrm{erf}(x/\mathrm{sqrt}(2))]$

US EPA (2003) recommended a minimum goodness of fit p value of $p = 0.1$ for model acceptance. The goodness of fit of the model was determined using the chi-square (χ^2) test. For the purposes of this investigation, a p value from the chi-squared test of <0.1 was set as the rejection level for the test hypothesis of adequate modelling. p values from chi-squared test for each model were obtained using the US EPA BMDS software. Models that met the default statistical criteria for adequacy and visually fit the data were retained in determining the BMD_{10}s and the $BMDL_{10}$s.

Akaike's information criterion (AIC) was considered for comparison among models and selection of the model for BMD and BMDL calculations. The AIC values were obtained using the US EPA BMDS software.

AIC can be calculated using the equation

$\mathrm{AIC} = -2 \log L + 2p$,

where L is the value of the likelihood function at the maximum-likelihood estimates (MLE) for the parameters, and p is the number of parameters estimated in the model (Sand et al., 2002). Although the AIC does not reach a conclusion about "statistical significance" and does not "reject" any model, it determines how well the data supports each model. Lower AIC values were preferred according to this procedure for estimating the BMD and the BMDL (Sand et al., 2002). The model with the smallest AIC value was selected among all plausible models and this criterion was used for final model selection.

The $BMDL_{10}$s calculated for each model were compared to one another and to the statistically defined NOAELs.

3. Results

3.1. Test of goodness-of-fit

All models used in the analyses met the χ^2 test criterion as shown in Table 2 and no model was rejected, except for the Weibull model of cardiomyopathy in female rats.

3.2. Model performance

The AIC values for the dose–response models used in the study are listed in Table 3. Analysing the overall model performance of various models, the three models gave comparable AIC values. If the BMDL estimates were within a factor of 3, they were considered indistinguishable, and the model with the lowest AIC was selected to provide the BMDL (US EPA, 2003). Since the BMD was chosen within or near the experimental dose range, it was relatively insensitive to the choice of the dose–response model, and an adequate fit to the most of the experimental data was achieved with all models (Gaylor et al., 1998).

Table 2
Goodness-of-fit tests for quantal models for various toxicity end points at 95% confidence limit with BMR of 10%

Toxicity end point	Probit	Quantal linear	Weibull
p value[c]			
Epididymis[b]	0.5211	0.5495	0.3213
Testicular[b]	1.0	0.4105	1.0
Cardiomyopathy[b]			
Male	1.0	0.4105	1.0
Female	0.5929	0.5971	[d]
Teratogenic effects[a]	0.9337	0.1297	0.9892

[a] Eason et al. (1999).
[b] Eason and Turck (2002).
[c] p value from χ^2 test at <0.1 is the rejection level.
[d] Rejected model (unable to run the data using the Weibull model).

Table 3
Model performance for quantal models for various toxicity end points

	Akaike's information criterion (AIC)[c]		
Toxicity end point	Probit	Quantal linear	Weibull
Epididymis[b]	51.5434	51.773	53.2315
Testicular[b]	31.7259	34.6013	31.7529
Cardiomyopathy[b]			
Male	31.7259	34.6013	31.7259
Female	21.4352	21.4528	[d]
Teratogenic effects[a]	48.125	53.3508	47.9442

[a] Eason et al. (1999).
[b] Eason and Turck (2002).
[c] AIC is the statistical measure of how well the model fit the data.
[d] Rejected model.

The parameters of the dose–response models were estimated by the maximum likelihood estimates. Details of the AICs are shown in Table 3.

3.3. Calculation of BMD_{10}s and $BMDL_{10}$s

As can be seen, the BMD_{10}s were typically only slightly higher than the $BMDL_{10}$s (Table 4). For the purposes of

Table 4
Modelling results with quantal endpoints at a 10% response rate (BMD) and its lower 95% confidence limit (BMDL)

Critical end point	BMD mg kg^{-1}			BMDL mg kg^{-1}		
	Weibull	Quantal linear	Probit	Weibull	Quantal linear	Probit
Forelimb malformations[a]	0.45	0.23	0.48	0.30	0.15	0.36
Testicular effects[b]	0.22	0.05	0.21	0.07	0.03	0.11
Epididymis[b]	0.07	0.04	0.09	0.03	0.03	0.06
Cardiomyopathy[b]						
Male	0.22	0.05	0.21	0.07	0.03	0.10
Female	[c]	1.83	0.89	[c]	0.20	0.21

[a] Eason et al. (1999).
[b] Eason and Turck (2002).
[c] Rejected model.

this study, the point of departure for BMD modelling for quantal end points is the BMDL associated with 10% BMR.

The BMD approach generates a slope term, which is a new parameter not available in the NOAEL approach. It has been recognised that the slope could provide significant information to the assessor. Most likely the threshold is more quickly approached with steep dose response curves than shallow slopes, all other items being equal.

For the purpose of this investigation, the slope was taken to be the slope term $q1$, where the x-axis is the dose and the y-axis corresponds to the number of animals responding adversely. A dose–response curve is fitted to the experimental data and the lower confidence limit on the dose corresponding to the BMR_{10} is obtained. This dose represents the estimate of the dose that produces a 10% increase in risk in the context of this paper. Thus, the $BMDL_{10}$ is the lower confidence limit of the dose that gives a 10% excess in abnormal responses above the spontaneous background level.

The NOAELs and LOAELs, and BMD_{10}s and $BMDL_{10}$s slopes for various critical quantal end points are shown in Table 5. The probit model was used in deriving the BMD_{10}s and the $BMDL_{10}$s for testicular, epididymis, male and female cardiomyopathy, and the Weibull model for teratogenicity based on AIC criteria. Fig. 1 demonstrates the dose–response curves for 1080 and the models chosen to fit the data at 95% confidence limit and BMR of 10% on various critical effects identified.

The BMD_{10}s and $BMDL_{10}$s calculated for each model were compared to one another and to the NOAELs (Table 5). The $BMDL_{10}$s for all quantal end points, using the best fit models, were about three times higher than the NOAELs for female cardiomyopathy and teratogenicty; and almost the same for the other end points. Given that the $BMDL_{10}$ estimates from the three models were within a factor of 3, except for epididymis which had the lowest $BMDL_{10}$ (Table 4), they were considered to show no appreciable model dependence and were considered to be indistinguishable in the context of the precision of the methods. The results were consistent with that of Gaylor et al. (1998).

For all critical end points a dose–response trend was observed. The probit model demonstrated steeper slopes for testicular and male cardiomyopathy while shallower slopes were observed for epididymis, female cardiomyopathy and teratogenicity compared with the other toxic effects.

The NOAELs established for critical end points were 0.075 mg kg^{-1} bw day^{-1} for testicular effects and cardiomyopathy and 0.1 mg kg^{-1} bw day^{-1} for teratogenicity (Table 5).

4. Discussion

Based on a comprehensive review of literature considered to be relevant to human health risk assessment, this study found that the critical effects arising from 1080 exposure were testicular/epididymis, myocardial toxicity

Table 5
NOAEL and LOAEL values and dose–response slopes with corresponding BMD_{10} and $BMDL_{10}$ values from various quantal end points

Toxicity end point	NOAEL mg kg^{-1}	LOAEL mg kg^{-1}	$q1$ Slope term	BMD_{10} mg kg^{-1}	$BMDL_{10}$ mg kg^{-1}	BMD Model (best fit)
Epididymis[b]	0.075	0.25	6.83	0.09	0.06	Probit
Testicular[b]	0.075	0.25	31.73	0.21	0.11	Probit
Cardiomyopathy [b]						
Male	0.075	0.25	31.73	0.21	0.10	Probit
Female	0.075	0.25	0.88	0.89	0.21	Probit
Teratogenicity[a]	0.10	0.33	1.42	0.45	0.30	Weibull

[a] Eason et al. (1999).
[b] Eason and Turck (2002).

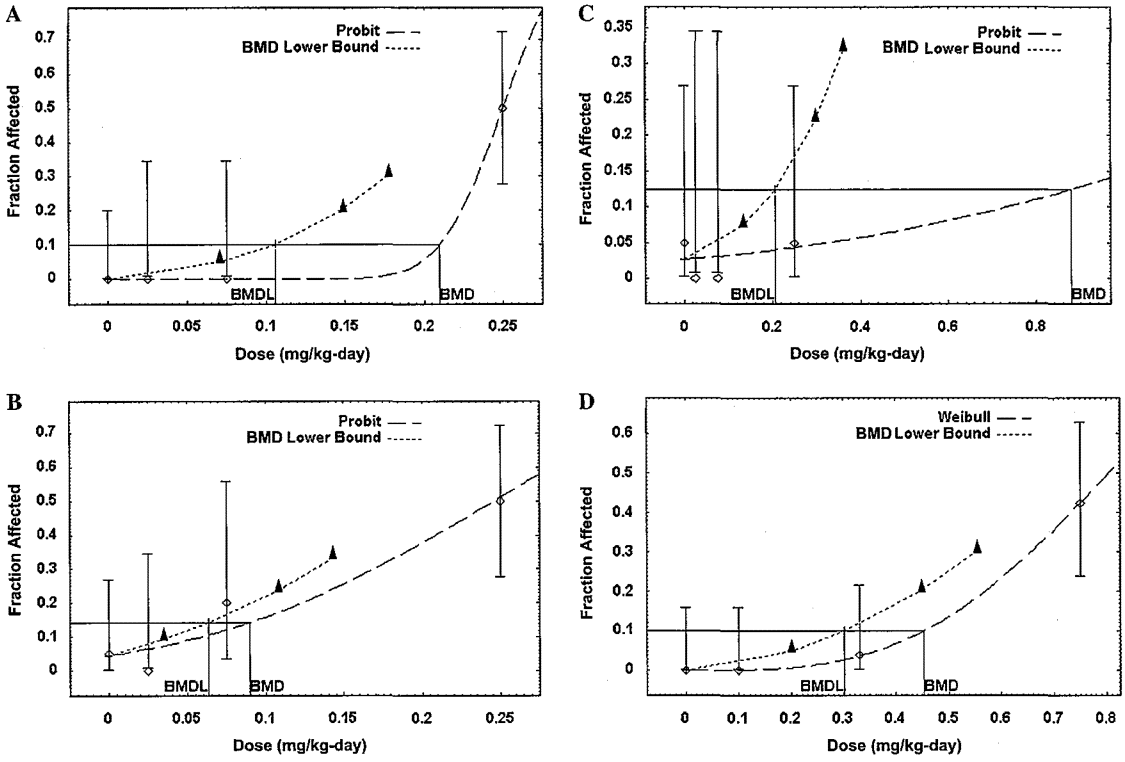

Fig. 1. Illustration of benchmark dose BMD) with corresponding models for 1080 critical data (A) Testicular and male cardiomoypathy (Probit model). (B) Epididymal effects (Probit model). (C) Female cardiomyopathy (Probit model). (D) Teratogenic effects (Weibull model).

and teratogenicity. The BMD approach utilised in the study demonstrated that the $BMDL_{10}$s for the quantal end points were generally slightly higher (but comparable) to the corresponding NOAELs for those same endpoints.

In the pivotal studies, test animals were exposed via the oral route and NOAELs were established for all the critical toxicity end points. All of the studies have at least one dose level above the NOAEL. In comparing the three quantal models (Table 2), all models passed the goodness of-fit-test although in most cases the Weibull and probit models generally provided a better fit to the data. A difference noted between the first two models and that of quantal linear was with the latter usually producing the more conservative $BMD_{10}/BMDL_{10}$, i.e., two to fourfold lower in all end points investigated (Table 4). The probit model provided the best fit to testicular and male cardiomyopathy data and was chosen in estimating the $BMDL_{10}$ for the determination of TDI. The quantal linear model was not chosen, although it provided the lowest $BMDL_{10}$, because it provided the worst fit among the models tested.

Model performance (Table 3) was analysed and the AIC values obtained for the three models were comparable. Gephart et al. (2001) suggested that the strength of the BMD methodology is that different models that properly fit the data should give similar BMD estimates for the same data set. The findings from this study generally concur with this notion, as the choice of dose response model had little effect on the estimated BMD_{10}. There was a little difference in BMD_{10}s results between models with a similar fit. Furthermore, the same authors claimed that if models were of equally good fit, then different models should give similar BMD estimates for the quantal data. Again, this notion was supported by this study (Table 4). In this sense, the results of this investigation support the argument made by Crump (1984) that model choice is not a critical factor for BMD estimation because model-based extrapolation to low doses is not required.

The BMD is dependent upon the slope of the dose–response. For effects that have the same NOAEL, the effect with the steeper dose–response will have a higher BMD (Gephart et al., 2001). Given that the data have the same NOAEL and different slopes, the BMD is likely smallest with shallower slope (M. Dourson, personal communication, 2005). This statement is particularly true in relation to epididymis exhibiting a shallower slope and a lower BMD_{10} compared with testicular and male cardiomyopathy with steeper slopes and higher BMD_{10}s (Table 5). However, the statement conflicts with the observation that the slopes of the dose–response curves for cardiomyopathy in females are smaller than that of cardiomyopathy in males and testicular effects, but the BMD_{10}s for cardiomyopathy in males and testicular effects are smaller than those for cardiomyopathy in females. The reason for this apparent discrepancy is that the relationship between the slopes and BMDs for different effects with similar NOAELs depends on the location of the BMR. If the BMR is below

the response at the LOAELs, then the effect with the steepest slope will likely have a higher BMD, while if the BMR is above the response at the LOAEL, the shallower slope will likely yield a higher BMD.

Fowles et al. (1999) indicated that less severe and frank effects tended to exhibit shallower and steeper probit slopes, respectively. This statement concurs with this investigation where testicular and male cardiomyopathy showed steeper slopes and shallower slopes for less critical effect, namely epididymal pathology. A major difference was also observed with respect to the susceptibility of males and females with the myocardial toxicity of 1080, males being more susceptible.

Gaylor et al. (1998) pointed out that when no clear dose response is obtained and/or the BMD is calculated to be above the highest experimental dose level, use of the NOAEL might be more appropriate for setting a TDI. The BMD_{10} for female cardiomyopathy was higher than the LOAEL, 0.89 mg kg^{-1} bw and 0.25 mg kg^{-1} bw, respectively so it may be more appropriate to use the NOAEL as a point of departure in this particular situation (Table 5). Fowles et al. (1999) and Gaylor (1996) suggested that the BMD should be below the observable LOAEL if it is to represent a point of departure for risk assessment. The $BMDL_{10}$ was 0.21 mg kg^{-1} bw which was lower than the LOAEL. The BMD_{10} for teratogenicity (0.45 mg kg^{-1} bw) was also higher than the LOAEL in the study (0.33 mg kg^{-1} bw). Although the BMD_{10} exceeds the LOAEL for female cardiomyopathy, the $BMDL_{10}$s are consistently below the LOAELs for the other toxic end points, and the $BMDL_{10}$ is recommended in deriving the TDI for health risk assessment. Also, Barnes et al. (1995) suggested that it was not realistic to assume that implementation of the BMD approach would end the use of the NOAEL approach because there will always be data sets that cannot be evaluated using the BMD approach. Hence, the NOAEL approach should be used where appropriate.

In summary, for quantal end points the $BMDL_{10}$s generated were generally slightly higher but comparable points of departure to the NOAEL approach. The BMD_{10} and $BMDL_{10}$ for male cardiomyopathy and testicular effects of 0.21 mg kg^{-1} bw and 0.10 mg kg^{-1} bw, respectively provide more meaningful and more statistically sound bases for establishing a TDI for the human health risk assessment for 1080.

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References

Barnes, D.G., Daston, G.P., Evans, J.S., Jarabek, A.M., Kavlock, R.J., Kimmel, C.A., Park, C., Spitzer, H.L., 1995. Benchmark dose workshop: criteria for use of a benchmark dose to estimate a reference dose. Regul. Toxicol. Pharm. 21, 296–306.

Crump, K.S., 1984. A new method for determining allowable daily intakes. Fund. Appl. Toxicol. 4, 854–871.

Crump, K.S., 1995. Calculation of benchmark doses from continuous data. Risk Anal. 15 (1), 79–89.

Eason, C.T., Wickstrom, M., Turck, P., Wright, G.R.G., 1999. A review of recent regulatory and environmental toxicology studies on 1080: results and implications. N.Z. J. Ecol. 23 (2), 129–137.

Eason, C.T., Turck, P., 2002. A 90-day toxicological evaluation of compound 1080 (sodium monofluoroacetate) in Sprague–Dawley Rats. Toxicol. Sci. 69, 439–447.

Fowles, J.R., Alexeef, G.V., Dodge, D., 1999. The use of benchmark dose methodology with acute inhalation lethality data. Regul. Toxicol. Pharm. 29, 262–278.

Gaylor, D.W., 1992. Incidence of developmental defects at the no observed adverse effect level (NOAEL). Regul. Toxicol. Pharm. 15, 151–160.

Gaylor, D., 1996. Quantalization of continuous data for benchmark dose estimation. Regul. Toxicol. Pharm. 24, 246–250.

Gaylor, D.W., Ryan, L., Krewski, D., Zhu, Y., 1998. Procedures for calculating benchmark doses for health risk assessment. Regul. Toxicol. Pharm. 28, 150–164.

Gephart, L.A., Salminen, W.F., Nicolich, M.J., Pelekis, M., 2001. Evaluation of subchronic toxicity data using benchmark dose approach. Regul. Toxicol. Pharm. 33 (1), 37–59.

International Programme on Chemical Safety (IPCS). (1994). Environmental Health Criteria 170: Assessing human health risks of chemicals: Derivation of guidance values for health-based exposure limits. Geneva, World Health Organization, International Programme on Chemical Safety.

Leisenring, W., Ryan, L., 1992. Statistical properties of the NOAEL. Regul. Toxicol. Pharm. 15, 161–171.

Parfitt, R.I., Eason, C.T., Morgan, A.J., Burke, C.M., Wright, G.R.G. 1994. The fate of sodium monofluoroacetate (1080) in soil and water. In: Seawright, A.A.; Eason, C.T. eds. Proceedings of the Science Workshop on 1080. Royal Society of New Zealand miscellaneous series 28, 59-66.

Parliamentary Commissioner for the Environment (PCE). 1994. Possum Management in New Zealand. Office of the Parliamentary Commissioner for the Environment, Wellington.

Renwick, A.G., Walker, R., 1993. An analysis of the risk of exceeding acceptable or tolerable daily intake. Regul. Toxicol. Pharm. 18, 463–480.

Sand, S., Filiposson, A.F., Victorin, K., 2002. Evaluation of the benchmark dose method for dichotomous data: model dependence and model selection. Regul. Toxicol. Pharm. 36 (2), 184–197.

Sullivan, J.L., Smith, F.A., Garman, R.H., 1979. Effects of fluoroacetate on the testis of the rat. J. Reprod. Fertil. 56, 201–207.

U.S. Environmental Protection Agency (US EPA). 1995. The use of the benchmark dose approach in health risk assessment. Office of Research and Development, Washington, DC: EPA/630/R-94/007, February.

US. Environmental Protection Agency (US EPA). 2001. Benchmark dose software. U.S. Environmental Protection Agency<http://www.epa.gov>.

US. Environmental Protection Agency (US EPA). 2003. Benchmark dose tutorial. U.S. Environmental Protection Agency. <http://www.epa.gov/ncea/bmds_training/methodology/model.htm>.

Whittem, J.H., Murray, L.R., 1963. The chemistry and pathology of georgina river poisoning. Australian Vet. J. 39, 168–173.

Appendix 3. The use of myocardial and testicular end points as a basis for estimating a proposed tolerable daily intake for sodium monofluoroacetate (1080)

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The use of myocardial and testicular end points as a basis for estimating a proposed tolerable daily intake for sodium monofluoroacetate (1080)

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Abstract

This paper presents the development of a tolerable daily intake (TDI) for sodium monofluoroacetate (1080) using the quantal myocardial and testicular toxicity end points derived from the traditional NOAEL and newer benchmark dose (BMD) methods. 1080 is a highly toxic vertebrate pesticide that has been proven to be effective in controlling possums and other pests. By convention, the TDIs are derived using the traditional no-observed-adverse-effect-level (NOAEL) and applying appropriate default uncertainty factors (UF). In addition to the default UF, a statistically derived UF was also employed in deriving the TDI. The TDIs derived from the NOAEL and BMD approach, 0.075 and 0.10 mg/kg bw/day, respectively, were compared. The resulting TDI estimates using the BMDL, a statistical lower confidence bound on the BMD, were generally consistently slightly higher than those derived using the NOAEL approach. Based on the best fit of modelled dose–response data, a TDI of 0.03 μg/kg bw/day is proposed for human health risk assessment of 1080.
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Keywords: Sodium monofluoroacetate (1080); Tolerable daily intake (TDI); Cardiomyopathy; Testicular effects; BMDL; NOAEL

1. Introduction

Compound 1080 (sodium monofluoroacetate) is one of the most toxic vertebrate agent known. Its principal use in New Zealand is to control possums (*Trichosurus vulpecula*), and to contain the spread of tuberculosis to livestock such as cattle and deer herds. However, despite its effectiveness, over several decades in New Zealand, its use continues to cause controversy amongst the general public reflecting the uncertainty associated with its use and potential for long-term effects on human health.

In one notable instance, the Mangapeka Educational Trust and 1080 Action Group in Golden Bay expressed concern about the teratogenic/reproductive effects of 1080. In addition, Takaka Area residents were angry when 1080 was mistakenly dropped in an area where they source their drinking water. Eason et al. (1993) suggested that the long-term use of 1080 needs to be further studied because of the continuing controversy concerning its use, fate in water, and effects on non-target species, especially livestock and invertebrates.

An extensive published database exists on the fate of 1080 in the environment and effects on non-target species. However, some of the toxicological and metabolic data generated between the 1950s and the 1970s are out of date and would not meet current registration standards. Of note, one of the major gaps in knowledge surrounding 1080 is its

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potential toxicity upon chronic low-dose exposure, and subsequent long-term effects on human health.

New Zealand uses approximately 80% of the world's production of manufactured 1080 (PCE, 1994) amounting to 3.2 tonnes of raw product in the period 1 July 2001 to 30 June 2002 (DoC and AHB, 2003).

The majority of public concerns about possum control operations relate to the possible contamination of drinking water supplies with 1080, resulting from aerially sown baits falling into streams. This route of contamination fuels an ongoing debate concerning the potential toxicological effects of the use of this chemical in the environment. Interest in the potential toxic effects of 1080 has resurfaced as a result of the latest findings from the animal toxicology studies commissioned by the DoC and the AHB, where 1080 was found to be teratogenic, a male reproductive toxin and a myocardial toxin in rats (Eason et al., 1999; Eason and Turck, 2002).

This paper evaluates available relevant toxicological data that may assist in human health risk assessment. Except for acute poisonings, no human data are known to date and the derivation of TDIs in this study is based on subchronic studies due to the absence of chronic studies. Pivotal studies with critical toxicological endpoints are selected from a comprehensive literature review. TDIs are derived using the traditional NOAEL approach and the BMD methodology and applying the conventional derivation of uncertainty factors (UF) and a statistically derived UF. The TDIs developed are compared and conclusions made with respect to the appropriateness of the TDI for human health risk assessment.

2. Methods

Relevant laboratory studies were analysed with respect to their adequacy for human health risk assessment. Studies on the possible adverse effects of 1080 from repeated exposures were limited, and the few chronic studies done have employed relatively high doses (e.g., sub-lethal doses), and/or unusual routes of administration, such as intraperitoneal injection and therefore may not be applicable to human exposures via ingestion, inhalation or dermal absorption. However, Chenoweth (1949) suggested that there was no striking difference between non-percutaneous routes of exposures on the resulting toxic effects of 1080, i.e., whether it was administered orally, subcutaneously, intramuscularly, intraperitoneally or intravenously, noting Chenoweth (1949) that this phenomenon was uncommon in the field of pharmacology. It is unknown whether this observation would apply to humans and therefore, studies of any route directly relevant to human exposures, were reviewed and assessed.

The TDI is similar in definition and intent to terms such as reference dose (RfD), reference concentration (RfC) and acceptable daily intake (IPCS, 1994). TDI is an estimate of the daily exposure to humans that is likely to be without appreciable risk of deleterious effects during a lifetime of continuous exposure. The derivation of a TDI involves identifying the critical effect(s), and selecting the pivotal study, the point of departure, and appropriate uncertainty factors (UFs).

Traditionally, the no-observed-adverse-effect-level (NOAEL) is the primary basis for the scientific evaluation of the risk posed to humans from systemic toxicity (Barnes and Dourson, 1988). The BMD approach has been proposed as an alternative approach for calculating TDIs to avoid the shortcomings associated with the NOAEL (Crump, 1984, 1995). A BMD is the dose (Barnes et al., 1995) calculated to be associated with an increase in the response, called the Benchmark Response (BMR) (Gaylor, 1992) (e.g., 5% or 10% incidence of the critical effects identified). The BMD is assigned a lower confidence limit (called the BMDL) when used to determine the TDI. The parameters used to estimate the benchmark doses are shown in Table 1.

3. Results

3.1. Identification of critical effect

3.1.1. Effects on testes

Reduction in plasma testosterone concentrations and degeneration of seminiferous tubules were observed in lizards exposed to repeated sublethal doses equivalent to 100 and 200 $mg\,kg^{-1}\,day^{-1}$ for 15 days (Twigg et al., 1988). Savarie (1984) and Eisler (1995) also observed that 1080 exposures resulted in testicular damage. Sullivan et al. (1979) considered that the testis was the organ most vulnerable to 1080 poisoning. Overt signs of toxicity were observed in rats after 7 days exposure to 1080. These effects included decreased testicular weight, morphological damage to the testes, degeneration of seminiferous tubules, and altered spermatogenesis.

Severe damage of the testes, characterised by massive disorganisation of the seminiferous tubules, nearly total loss of functional cells, absence of sperm, and damage to the Sertoli cells were reported by Smith et al. (1977) in rats exposed for a period of approximately four months to 26 ppm of 1080 in drinking water. Regressive modifications of the seminiferous tubules were observed by Mazzanti et al. (1965) in the testes of albino rats. Minks suffered severe impaired reproduction presumed to be due to oligo- or aspermia, or spermatopathy after dietary exposure to

Table 1
Summary of data used to calculate benchmark doses

Endpoint	Control	Doses (mg/kg bw/day)					
		0.025	0.075	0.10	0.25	0.33	0.75
Teratogenesis (irreversible forelimb malformations)[a]	0/26			0/26		1/26	11/26
Male fertility (degeneration of seminiferous tubules)[b]	0/20	0/10	0/10		10/20		
Epididymal hypospermia[b]	1/20	0/10	2/10		10/20		
Cardiomyopathy (males)[b]	0/20	0/10	0/10		10/20		
Cardiomyopathy (females)[b]	1/20	0/10	0/10		1/20		

[a] Eason et al. (1999).
[b] Eason and Turck (2002).

0.80 ppm of 1080 for two months (Hornshaw et al., 1986). Necrosis in spermatids, probably resulting from rapid and severe adenosine triphosphate (ATP) depletion, and apoptosis in spermatogonia from gradual and partial ATP depletion, was observed in Sprague–Dawley rats after a single oral dose of 1.0 mg kg^{-1} (Shinoda et al., 2000). Severe hypospermia of the epididymis and severe degeneration of the seminiferous tubules of the testes in male rats dosed with 0.25 mg kg^{-1} day by oral gavage for 90 days were reported by Eason and Turck (2002). It was confirmed that recovery from testicular damage did not occur even after 56 days without treatment.

3.1.2. Myocardial toxicity

Rammell (1993) and Eason et al. (1994) claimed that cumulative damage to the heart or other organs from repeated exposure to large sublethal doses of 1080 can occur in sheep (*Ovis aries*). Smaller doses of 1080 given at regular intervals produced cumulative effects (Annison et al., 1960) and resulted in myocardial damage in sheep, probably due to increased accumulation of citrate in the heart. The cumulative effect of 1080 has been noted in other species, such as the mouse and the rat. This has been attributed largely to slow renal clearance of fluoroacetate (Chenoweth, 1949). Sheep were affected differently from rats in that further doses following the initial administration of 1080 proved to be fatal. Rats were able to tolerate non-fatal dose of 1080 for the next 24–36 h following further administration of 1080. This finding appeared to suggest that larger animals are affected differently than smaller animals. However, there has been little reliable information on 1080's action and toxicity in the larger domestic animals (Annison et al., 1960) and therefore the observed differences could not be directly compared. Whether or not elimination mechanisms in larger animals, such as sheep, are relevant to humans has remained unknown.

Acute multifocal injury to the myocardium, after 1080 doses as low as 0.11 mg kg^{-1} day for 3–7 days, were observed in several research studies carried out in Australia (Eason et al., 1994). Whittem and Murray (1963) demonstrated mild but characteristic cardiac histopathology in sheep dosed with 0.055 mg kg^{-1} day of fluoroacetate by stomach tube, and typical cardiac histopathology at 0.11 mg kg^{-1} day. Similar acute myocardial lesions were found in the hearts of sheep and guinea pigs treated with potassium fluoroacetate. Whittem and Murray (1963) suggested that the most susceptible target organ is the myocardium as revealed by the pathologic lesions.

Eason and Turck (2002) noted increases in heart weight in both male and female Sprague–Dawley rats when compared with controls. The test animals were treated with 1080 in drinking water at doses of 0.025, 0.075, and 0.25 mg kg^{-1} day by the oral route for a period of 90 days. No effects were noted in the lower dose groups. Cardiomyopathy was seen in 50% (10/20) of males dosed with 1080 at 0.25 mg kg^{-1} day^{-1} and 5% (1/20) female rat, suggesting a gender difference. The NOAEL for rats was reported to be 0.075 mg kg^{-1} day^{-1} by the same authors.

3.1.3. Developmental toxicity (teratogenic effects)

De Meyer and De Plaen (1964) found that 1080 administered intraperitoneally on the 9th day of pregnancy in rats at a dose of 600 μg had caused eye anomalies, syndactylia, and evisceration. A more recent study by Eason et al. (1999) confirmed that 1080 caused teratogenic effects in rats. The highest dose (0.75 mg kg^{-1} day^{-1}) showed irreversible limb abnormalities and the next highest dose (0.33 mg kg^{-1} day^{-1}) showed reversible rib defects. A NOAEL was reported at 0.10 mg kg^{-1} day^{-1}.

Whittem and Murray (1963) concluded that the heart was the most susceptible organ to pathologic lesions while Sullivan et al. (1979) considered the testes as the organ most vulnerable to the toxic effects of 1080 poisoning. Eason et al. (1999) and Eason and Turck (2002) reported well characterised dose–response relationships for developmental (short-term exposure), reproductive, and myocardial toxicities after subchronic exposures. Testicular and myocardial effects are considered the most critical effects arising from 1080 exposures and represent the basis for the TDI.

3.2. Selection of pivotal study

A review of the few available critical studies revealed that the studies of Eason et al. (1999) and Eason and Turck (2002) provided the most appropriate studies for risk assessment as they were more recent, of good scientific quality, followed international OECD Guidelines, used recognised Good Laboratory Practice (GLP) and were able to establish NOAELs for critical effects in sensitive target organs. Therefore, these studies were chosen as the pivotal studies.

There were no available chronic exposure studies for any route of exposure in any species. Therefore, potential tolerable concentrations for exposures were calculated using subchronic studies with application of appropriate uncertainty factors.

3.3. Point of departure

The dose–response relationship provides a basis to infer a point of departure. Systemic (non-cancer) toxicity is usually assumed to have thresholds below which no effects occur (IPCS, 2000). For these toxicities, safety assessments are carried out with the establishment of TDIs seen as doses below these thresholds. The threshold concept led to the logical conclusion that exposure to substances at doses below the threshold was safe and therefore acceptable. From this concept, guidelines and standards to protect public health were developed.

The use of the BMDL has lead to improved experiments conducted to obtain tighter confidence limits, resulting in higher TDI values (Gaylor, 1996). In benchmark analysis, the BMDL is used as the principal criterion for regulatory

purposes. Therefore, the use of the BMDL as the point of departure was also explored in this study.

3.3.1. Estimation of BMDs and BMDLs

Foronda et al. (2006) investigated the use of a BMD as an alternative to a NOAEL approach to improve current risk assessment for 1080. The calculated BMD_{10}s and lower-bound confidence limits ($BMDL_{10}$s) at 95% lower confidence bound on dose for cardiomyopathy, testicular, and teratogenic effects were estimated using the Weibull, probit and quantal linear models based on their model performances for each end point. The Pearson X^2 test (U.S. EPA, 1995) was used to assess the fit of the models to the observed dose–response data. All models met the X^2 test except for Weibull model for the cardiomyopathy in female rats since this model could not use these data. Analysing the overall model performance of various models, the three quantal models gave comparable Akaike's information criterion (AIC) and the model with the lowest AIC was chosen to estimate the BMD. The probit model was used in deriving the BMD_{10}s and $BMDL_{10}$s for all the end points except for the teratogenic effects, while the Weibull model was chosen using the AIC criterion.

The BMD_{10}s and the $BMDL_{10}$s were estimated using the US EPA BMDS version 1.3 software (U.S. EPA, 2001) for the corresponding models chosen according to the AIC. $BMDL_{10}$s were calculated using the maximum likelihood method. The BMD_{10}s were typically only slightly higher than the $BMDL_{10}$s. A $BMDL_{10}$ at its lower 95% confidence limit of $0.10\,mg\,kg^{-1}\,bw^{-1}$ had been used to derive the TDI for 1080 (Foronda et al., 2006) and this value was adopted for the purposes of this study.

3.4. The use of uncertainty factors (UF)

An UF is a mathematical expression of uncertainty that is used to protect populations from hazards which cannot be assessed with high precision [International Programme on Chemical Safety (IPCS, 1992)]. Dourson et al. (1996) believed that the use of the UF approach to risk assessment was justified on the rationale that low dose risks remain largely unknown for both carcinogens and non-carcinogens. The application of an UF is also seen as a use of scientific judgment about low-dose exposures and risks.

3.4.1. Rationale of UFs applied in estimating the TDI

- A default factor of 10 (U_A) is used to take into account the interspecies variation. For example, the toxicokinetic and toxicodynamic differences between humans and rats (the test species used in the pivotal study) are not known as no relevant data exist for 1080 in humans, although based on lethal effects, rodents might be as sensitive, or perhaps more sensitive, than other mammals such as humans.
- An uncertainty factor of 10 (U_H) is used to account for intraspecies differences (i.e., human variability) in response to toxic chemicals. This UF was introduced to protect sensitive individuals within a population. Age, sex, genetic composition, nutritional status, and pre-existing diseases may all alter susceptibility to toxic chemicals. To be assigned a factor of less than 10, a chemical must have more than just an adequate, peer reviewed human database (Abernathy et al., 2003). Information on toxicokinetics and toxicodynamics variability in humans would also be useful for considering an uncertainty factor other than the default value of 10.
- An UF of 10 (U_S) was used to account for the use of data from a subchronic study as a surrogate for results from a chronic study. This UF appears to be warranted based on the evidence that prolonged exposure (21–126 days) to 1080 in the drinking water of laboratory rats caused depletion of spermatids, formation of spermatid and spermatocyte giant cells, and seminiferous tubule atrophy (Smith et al., 1977). Exposure to 1080 for two months severely impaired the reproduction of mink, which was presumed to be due to oligo- or aspermia (Hornshaw et al., 1986).

In addition, subchronic 90-day tests still have their limitations with regard to human health hazard assessment since exposure takes place only for a certain period [approximately 10% of the lifetime (Kroes, 1995)]. The length of this period may not necessarily be sufficiently long enough to reveal chronic effects, since the substance may produce different toxic responses when administered repeatedly over a long period of time, and the ageing process may alter tissue sensitivity, metabolism or physiological capability. Moreover, spontaneously occurring diseases may also influence the degree and nature of the effect of the substance.

3.4.2. Database uncertainty factor (U_D)

In relation to completeness of the overall database, the Beck et al. (2001) definition of a "complete database" was applied. Beck et al. (2001) suggested that when the database is limited, there is uncertainty as to whether the identified NOAEL might be significantly lower if other studies were performed, or whether a different NOAEL might have been identified if additional health endpoints had been evaluated. A complete database was defined by Beck et al. (2001) as having:

- two systemic toxicity mammalian studies in different species;
- one mammalian multigeneration reproductive study; and
- two mammalian developmental toxicity studies in different species.

(This is also consistent with the registration requirements of agrichemicals in the USA, Canada, Europe, and Japan).

If these five studies are available, and if clear thresholds can be identified from them, then there is a high degree of confidence that one has approximated an appropriate point of departure. Unfortunately, no mammalian multigeneration reproductive toxicity study on 1080 exists to date. Moreover, only one species has been tested (i.e., rats) with regard to teratogenicity whereas two species are normally required for toxicological evaluation. In this case, professional judgment is required to determine the appropriate value taking into account the scientific uncertainties of the studies and the overall database. A U_D of 3 is judged to be reasonable based on the availability of part of, but not the "complete database". The use of a 3-fold factor here, instead of a default value of 10, is also consistent with current practice (Dourson, 1994) in that the use of more than 3 areas of uncertainty with default values of 10 leads to overly conservative estimates of TDI (or RfDs). The common practice is to use only a 3-fold factor for the 4th area of uncertainty and an additional 3-fold factor for a 5th area of uncertainty. Alternatively, the uncertainty factors other than for interspecies and intraspecies variability can be viewed as all related to general database deficiencies and the overall factor for this area is between 1- and 100-fold (IPCS, 1994).

The U.S. Food Quality and Protection Act (FQPA) provides a new extra 10-fold safety factor to be added after the determination of the TDI to fully ensure that infants and children are protected (U.S. EPA, 1996). The additional safety factor under the FQPA is largely policy-based and not driven by scientific findings (Scheuplein et al., 2002). It has been recognised by both U.S. EPA and others (U.S. EPA, 2002; Fenner-Crisp, 2001; Dourson et al., 2002), that part of this safety factor overlaps with the database uncertainty factor discussed earlier, and that when the database factor is employed properly, no need exists for the toxicity component of the FQPA factor. Based on this rationale, no additional safety factor is proposed to be incorporated for children's increased susceptibility beyond that already incorporated to account for human variability.

Combined, the overall UFs and U_D that are proposed to be used in deriving the TDI for 1080 is 3000 (i.e., 10*10*10*3). The USEPA is currently using a cumulative maximum of 3000 UF in its risk assessment (Kodell and Gaylor, 1999; U.S. EPA, 2002).

The IPCS (1994) have recognised the imprecision of the cumulative default factors and in order to maintain credibility of the risk assessment process, IPCS has suggested that the total default UF should not exceed 10,000. If the risk assessment leads to a higher factor, then the resulting TDI would be so imprecise as to lack meaning.

3.4.3. Use of statistically derived UF

The objective of combining UFs is to provide a way to obtain an estimate of an upper percentile, say 95th, of the distribution of the response to the product TDI, $U_H \times U_A \times U_S \times U_D$, that will be sufficiently protective of the general population but not overly conservative (Kodell and Gaylor, 1999). Table 2 provides the estimated upper percentiles of distributions of the individual UFs compiled from information in Kodell and Gaylor (1999) with some unknown and/or unspecified rationale for the distribution function.

The formula for U_{HAS} gives a combined UF that is less conservative (but almost similar) than the conventional approach of simply multiplying together a set of UFs. Kodell and Gaylor (1999) stated that it is appropriate to use a larger percentile than the 95th percentile, but to still use a point estimate. Due to the limited information available, in particular the relevance of severe toxic end-points to humans, a more conservative approach appears to be warranted. Hence, the 99th percentile is proposed for the purposes of this study.

As can be seen in Table 2, the default maximum factor of 3000 recommended by the U.S. EPA for four factors approaches the estimated 99th percentile. There were three UFs ($U_{HAS} = 998$) in this study plus an extra factor of 3 to take into account the incompleteness of the database. Since Kodell and Gaylor (1999) did not include database uncertainty factors in their analysis, U_{HAS} will simply be multiplied by the U_D of 3, bringing the total UF to 2994.

3.5. Derivation of TDIs using the NOAEL approach and the BMD methodology

In general, TDIs are used to provide information on potential long-term toxic effects (Bender, 2002). Toxicity risk assessment currently relies on the estimation of TDIs based on the use of the NOAEL or BMDL divided by the

Table 2
Estimated upper percentiles of distributions of uncertainty factors

Uncertainty factor	95th Percentile Point Estimate	99th Percentile Point Estimate	Product of Default Factors
U_S	17	41	10
U_A	15	48	10
U_H	15	45	10
U_{HA}	46	228	100[a]
U_{HAS}	161	998[d]	1000[b]
U_{HASL}		4067	$1000 \times 3 = 3000$[c]

[a] Maximum conventional value for two uncertainty factors.
[b] Maximum conventional value for three uncertainty factors.
[c] Maximum conventional value for four uncertainty factors as suggested by the U.S. EPA.
[d] Maximum value for three uncertainty factors [with some unknown and/or unspecified rationale for the distribution function] (Kodell and Gaylor, 1999).

Table 3
Comparative TDIs from NOAEL and $BMDL_{10}$ values

Quantal toxicity endpoint	NOAEL ($mg\,kg^{-1}$ bw day^{-1})	NOAEL TDI ($\mu g\,kg^{-1}$ bw day^{-1})	$BMDL_{10}$ ($mg\,kg^{-1}$ bw day^{-1})	BMDL TDI ($\mu g\,kg^{-1}$ bw day^{-1})
UF		3000[a,b]		3000[a,b]
Epididymis	0.075	0.025	0.03	0.010
Testicular	0.075	0.025	0.11	0.037
Cardiomyopathy, male	0.075	0.025	0.10	0.033
Cardiomyopathy, female	0.075	0.025	0.21	0.070
Teratogenicity	0.10	0.033	0.30	0.10

[a] Maximum conventional value for four uncertainty factors as derived in Section 3.4.
[b] Maximum conventional value for uncertainty factors as suggested by the U.S. EPA.

UFs (Allen et al., 1994). However, the TDI value is not an absolute certainty as there is a low probability that adverse effects might occur and the absence of all risk to all people cannot be assured at this level (Barnes and Dourson, 1988). The existence of different TDIs need not imply that anyone of them is more "wrong" or "right" than the rest. It is more a reflection of the difference in scientific judgement of risk assessors (Barnes and Dourson, 1988).

The calculation of a TDI by applying a UF to a NOAEL will be referred to as a 'NOAEL approach' since the point of departure was the NOAEL for the critical adverse effects. The estimation of TDIs based on the use of the BMDL based on these same effects and divided by UFs will be called the 'BMD approach'.

For the purposes of this investigation, the assessments and calculations of TDI were done according to the WHO recommendations as described in the International Programme on Chemical Safety's "Environmental Health Criteria 104, Principles for the Toxicological Assessment of Pesticide Residues in Food" (IPCS, 1990). To derive the TDI, this can be represented mathematically using the following formula:

Tolerable Daily Intake (TDI) = NOAEL or BMDL/ (U_A*U_H*U_S*U_D*U_L),

where: U_A = interspecies extrapolation
U_H = intraspecies extrapolation
U_S = using subchronic data
U_D = using incomplete database
U_L = extrapolation from LOAEL to NOAEL (if needed), not used with BMDL

In this case, both the statistical and usual UFs have the same value, i.e., 3000. This figure was used in the final derivation of the TDI.

Thus, comparing the NOAEL and the $BMDL_{10}$ TDI derived values demonstrated that the TDIs from the BMD approach were generally slightly higher than the NOAEL approach and therefore less conservative values (Table 3).

Several BMDLs could be used to establish the TDI. The $BMDL_{10}$ of $0.10\,mg\,kg^{-1}$ bw day^{-1} for cardiomyopathy in male rats and testicular effects in estimating the risks from 1080 exposures was chosen because these were the most critical effects considered for 1080 by Sullivan et al. (1979), Eason et al. (1999), Eason and Turck (2002), and Whittem and Murray (1963). This value is considered a scientifically sound option and is therefore recommended for use in human health risk assessment (Foronda et al., 2006). This value may be considered as conservative (i.e., protective) and errs on the side of caution due to the incomplete information available, as already discussed.

4. Discussion

Non-cancer risk assessment is currently based on the assumption that a biologic threshold dose must be exceeded before exposure to chemical causes effects. Under this view, if a person is exposed to a dose below their threshold of response, no effect is experienced and thus no risk is involved. However, there is variability in the sensitivity of individuals to chemicals and thus in order to assess population risks the responses of sensitive individuals must be taken into account. Unfortunately, human epidemiologic data are very rare, and even when they are available, the data may be inadequate to determine with any precision the threshold for particularly sensitive individuals. Epidemiological studies are less often available and of reduced value because of the lack of quantitative information on the concentrations to which the people have been exposed or to what else the populations have been simultaneously exposed (Ministry of Health, 1995). Hence, the human threshold dose is typically extrapolated from animal data. Animal test data provide an estimate of the subthreshold dose, or NOAEL. Because true relationship between this animal threshold dose and the human threshold are unknown, uncertainty is inherent in the extrapolation. Interspecies UF is intended to adjust for two quite distinct concerns—(i) any genuine differences in susceptibility between laboratory animals and humans, and (ii) the limitations in the statistical power of laboratory bioassays involving relatively small number of animals (Baird et al., 1996).

The derivation of the TDI for 1080 was based on subchronic studies due to the absence of chronic studies. Higher UFs were utilised to take into account the uncertainties involved in the inter and intraspecies differences, the use of subchronic studies and the incompleteness of the overall database. In addition, critical information on the conditions of human exposure is lacking. Exposures to the general population are less well documented than occupational exposures due to limited availability of systems capable of measuring the exposures to specific risk agents

actually experienced by people (Covello and Merkhofer, 1993).

The statistically derived UF of 2994 (rounded to 3000) proposed in this study represents a viable alternative to the use of a product of default factors to establish the TDI. The UF provides a known level of confidence in health protection, without unnecessarily compounding the conservatism built into each individual factor. The same UF of 3000 was used for the BMD approach and the resulting TDIs for most end points were slightly higher than those calculated using the NOAEL approach. The BMD can provide a more consistent approach that avoids the occasional extreme behaviour of the NOAEL (Gaylor et al., 1998).

The NOAEL of $0.075\,mg\,kg^{-1}$ bw day^{-1} for testicular and cardiomyopathy from Eason and Turck (2002) might provide the most appropriate and relevant basis for 1080 TDI. A complementary study was also carried out with a NOAEL of $0.10\,mg\,kg^{-1}$ bw day^{-1} based on severe malformations as the toxic end point (Eason et al., 1999). As discussed earlier, teratogenic effects were also considered as a critical end point for the purposes of this study. However, the $BMDL_{10}$s generated by the probit model arising from the most critical end points, i.e., male cardiomyopathy and testicular effects of $0.10\,mg\,kg^{-1}$ bw day^{-1} were ultimately chosen to estimate the TDI, because the use of this model was able to capture more of the available data.

The TDI derived from the $BMDL_{10}$ was slightly higher than the TDI derived from the NOAEL value. TDI of $0.03\,\mu g\,kg^{-1}$ bw day^{-1} is proposed to be used for 1080 health risk assessment until additional studies are carried out since these studies may likely reduce the UF in deriving the TDI and thereby likely raise the value of the TDI. Two systemic toxicity mammalian studies in different species, one-multigeneration reproductive study, and two mammalian developmental toxicity studies in different species are the criteria used to define a "complete database". There is a lack of toxicology studies relating to chronic 1080 exposure, and this hinders the determination of an appropriate TDI and results in higher UFs. The UFs can be reduced if additional studies are carried out to generate a "complete database" providing a better understanding of the interspecies and intraspecies variability of 1080.

The TDI may be considered conservative, as the general population may not be exposed to 1080 throughout their entire life, whereas this methodology has been widely used to develop TDIs based on the assumption that the general population may be exposed to the chemical in question for lifetime.

An attempt to estimate population threshold for humans is fraught with uncertainty because of poorly studied toxicokinetics and toxicodynamics between the test species and humans, and because of heterogeneity in these processes among human populations. In addition, the paucity of information about the toxicokinetics of 1080 in humans indicates the need to carefully limit and monitor occupational and environmental exposures to achieve a better understanding and management of human toxicity (Temple and Edwards, 1985).

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References

Abernathy, C.H., Donohue, J.M., Cicmanec, J., Poirier, K.A. Reference doses (RfDs): Factors in the selection of human intraspecies uncertainty factor (Ufh) when using human data. Undated report from the 2003 Society of Toxicology meeting, USA.

Allen, B.C., Kavlock, R.J., Kimmel, C.A., Faustman, E.M., 1994. Dose–response assessments for developmental toxicity: II. Comparison of generic benchmark dose estimates with NOAELs. Fundam. Appl. Toxicol. 23, 487–495.

Annison, E.F., Hill, K.J., Lindsay, D.B., Peters, R.A., 1960. Fluoroacetate poisoning in sheep. J. Comp. Pathol. 70, 145–155.

Baird, S.J.S., Cohen, J.T., Graham, J.D., Shlyakhter, A.I., Evans, J.S., 1996. Non-cancer risk assessment: a probabilistic alternative to current practice. Hum. Ecol. Risk Assess. 2, 79–102.

Barnes, D.G., Daston, G.P., Evans, J.S., Jarabek, A.M., Kavlock, R.J., Kimmel, C.A., Park, C., Spitzer, H.L., 1995. Benchmark dose workshop: criteria for use of a benchmark dose to estimate a reference dose. Regul. Toxicol. Pharmacol. 21, 296–306.

Barnes, D.G., Dourson, M., 1988. Reference dose (RfD): description and use in health risk assessments. Regul. Toxicol. Pharmacol. 8, 471–486.

Beck, B.D., Blayton, T.M., Calabrese, E.J., Baldwin, L., Rudel, R., 2001. The use of toxicology in the regulatory process. In: Hayes, A.W. (Ed.), Principles and methods of toxicology, fourth ed. Taylor and Francis, Philadelphia, pp. 23–75.

Bender, J., 2002. The use of noncancer endpoints as a basis for establishing a reference concentration for formaldehyde. Regul. Toxicol. Pharmacol. 35, 23–31.

Chenoweth, M.B., 1949. Monofluroacetic acid and related compounds. Pharmacol. Rev. 1, 383–424.

Covello, V.T., Merkhofer, M.W., 1993. Risk Assessment Methods Approaches for Assessing Health and Environmental Risks. Plenum, New York.

Crump, K.S., 1984. A new method for determining allowable daily intakes. Fundam. Appl. Toxicol. 4, 854–871.

Crump, K.S., 1995. Calculation of benchmark doses from continuous data. Risk Anal. 15 (1), 79–89.

De Meyer, R., De Plaen, J., 1964. An approach to the biochemical study of teratogenic substances in isolated rat embryos. Life Sciences 3, 709–713.

Department of Conservation and Animal Health Board (DoC and AHB), 2003. The use of 1080 to control possums and other pests: a resource document. Department of Conservation and Animal Health Board, Wellington.

Dourson, M.L., 1994. Methods for establishing oral reference doses (RfDs). In: Mertz, W., Abernathy, C.O., Olin, S.S. (Eds.), Risk Assessment of Essential Elements. ILSI Press, Washington, DC, pp. 51–61.

Dourson, M.L., Charnley, G., Scheuplein, R., 2002. Differential sensitivity of children and adults to chemical toxicity: II. Risk and regulation. Regul. Toxicol. Pharmacol. 35, 448–467.

Dourson, M.L., Felter, S.P., Robinson, D., 1996. Evolution of science-based uncertainty factors in noncancer risk assessment. Regul. Toxicol. Pharmacol. 24, 108–120.

Eason, C.T., Frampton, C.M., Henderson, R., Thomas, M.D., Morgan, D.R., 1993. Sodium monofluorocetate and alternative toxins for possum control. N.Z. J. Zool. 20, 329–334.

Eason, C.T., Gooneratne, R., Rammell, C.G., 1994. A review of the toxicokinetics and toxicodynamics of sodium monofluoroacetate in

animals. In: Seawright, A.A., Eason, C.T. (Eds.), Proceedings of the Science Workshop on 1080. Royal Society of New Zealand Miscellaneous Series 28, pp. 82–89.

Eason, C.T., Turck, P., 2002. A 90-day toxicological evaluation of compound 1080 (sodium monofluoroacetate) in Sprague–Dawley rats. Toxicol. Sci. 69, 439–447.

Eason, C.T., Wickstrom, M., Turck, P., Wright, G.R.G., 1999. A review of recent regulatory and environmental toxicology studies on 1080: results and implications. N.Z. J. Ecol. 23 (2), 129–137.

Eisler, R., 1995. Sodium monofluoroacetate (1080) hazards to fish, wildlife, and invertebrates: a synoptic review. US Department of the Interior Biological report 27, 47 p.

Fenner-Crisp, P., 2001. The FQPA 10× safety factor—How much is science? How much is sociology? Hum. Ecol. Risk Assess. 7 (1), 107–116.

Foronda, N., Fowles, J., Smith, N., Taylor, M., Temple, W., 2006. A benchmark dose analysis for sodium monofluoroacetate (1080) using dichotomous toxicity data. Regul. Toxicol. Pharmacol., 47 (1), 84–89.

Gaylor, D.W., 1992. Incidence of developmental defects at the no observed adverse effect level (NOAEL). Regul. Toxicol. Pharmacol. 15, 151–160.

Gaylor, D., 1996. Quantalization of continuous data for benchmark dose estimation. Regul. Toxicol. Pharmacol. 24, 246–250.

Gaylor, D.W., Ryan, L., Krewski, D., Zhu, Y., 1998. Procedures for calculating benchmark doses for health risk assessment. Regul. Toxicol. Pharmacol. 28, 150–164.

Hornshaw, T.C., Ringer, R.K., Aulerich, R.J., 1986. Toxicity of sodium monofluoroacetate (Compound 1080) to mink and European ferrets. Environ. Toxicol. Chem. 5, 213–233.

International Programme on Chemical Safety (IPCS), 1990. Environmental health criteria 104: Principles for the Toxicological Assessment of Pesticide Residues in Food. Geneva, World Health Organization, International Programme on Chemical Safety.

International Programme on Chemical Safety (IPCS), 1992. Chemical Safety. Fundamentals of Applied Toxicology. Geneva, World Health Organization, International Programme on Chemical Safety.

International Programme on Chemical Safety (IPCS), 1994. Environmental health criteria 170: Assessing human health risks of chemicals: Derivation of Guidance Values for Health-based Exposure Limits. Geneva, World Health Organization, International Programme on Chemical Safety.

International Programme on Chemical Safety (IPCS), 2000. Environmental Health Criteria 214: Human Exposure Assessment. Geneva, World Health Organization, International Programme on Chemical Safety.

Kodell, R.L., Gaylor, D.W., 1999. Combining uncertainty factors in deriving human exposure levels of noncarcinogenic toxicants. Ann. NY Acad. Sci. 895, 188–195.

Kroes, R., 1995. Toxicity testing and human health. In: Van Leeuwen, C.J., Hermens, J.L.M. (Eds.), Risk Assessment of Chemicals: An Introduction. Kluwer Academic Publishers, Dordrecht, pp. 147–174.

Mazzanti, L., Lopez, M., Berte, M.G., 1965. Atrophy of the testis produced by sodium monofluoroacetate in albino rats. Experientia 21, 446–447.

Ministry of Health, 1995. Drinking Water Standards for New Zealand. Ministry of Health, Wellington.

Parliamentary Commissioner for the Environment (PCE), 1994. Possum Management in New Zealand. Office of the Parliamentary Commissioner for the Environment, Wellington.

Rammell, C.G., 1993. Persistence of compound 1080 in sheep muscle and liver. Surveillance 20 (1), 20–21.

Savarie, P.J., 1984. Toxic characteristics of fluorocitrate, the toxic metabolite of compound 1080. In: Clark, D.O. (Ed.), Proceedings Eleventh Vertebrate Pest Conference. University of California, Davis, pp. 132–137.

Scheuplein, R., Charnley, G., Dourson, M., 2002. Differential sensitivity of children and adults to chemical toxicity. Regul. Toxicol. Pharmacol. 35, 429–447.

Shinoda, K., Mitsumori, K., Uneyama, C., Uehara, M., 2000. Induction and inhibition of testicular germ cell apoptosis by fluoroacetate in rats. Arch. Toxicol. 74, 33–39.

Smith, F.A., Gardner, D.E., Yuile, C.L., De Lopez, O., Hall, L.L., 1977. Defluorination of fluoroacetate in the rat. Life Sci. 20, 1131–1138.

Sullivan, J.L., Smith, F.A., Garman, R.H., 1979. Effects of fluoroacetate on the testis of the rat. J. Reprod. Fertil. 56, 201–207.

Temple, W.A., Edwards, I.R., 1985. Toxic ducks 1080 residues in game birds. An exercise in applied toxicology. Vet. Hum. Toxicol. 27, 20–21.

Twigg, L.E., King, D.R., Bradley, A.J., 1988. The effect of sodium monofluoroacetate on plasma testosterone concentration in *Tiliqua rugosa* (Gray). Comp. Biochem. Physiol. 91 (2), 343–347.

U.S. Environmental Protection Agency (U.S. EPA), 1995. The use of the benchmark dose approach in health risk assessment. Office of Research and Development, Washington, DC: EPA/630/R-94/007, February.

U.S. Environmental Protection Agency (U.S. EPA), 1996. Pesticides: policy issues related to the Food Quality Protection Act. Fed Reg 64(130), pp. 37001–37009.

U.S. Envirnomental Protection Agency (U.S. EPA), 2001. Benchmark dose software, Version 1.3. Available from: <http://www.epa.gov>.

U.S. Environmental Protection Agency (U.S. EPA), 2002. Child-specific exposure factors handbook. National Center for Environmental Assessment, Washington, DC; EPA/600/P-00/002. Available from: National Information service, Springfield, VA, PB2003-101678 and <http:www.epa.gov/ncea/>.

Whittem, J.H., Murray, L.R., 1963. The chemistry and pathology of georgina river poisoning. Aust. Vet. J. 39, 168–173.

Appendix 4. Application for a Permission for the Use of Vertebrate Toxic Agent(s)

Application for a Permit For the Use of Vertebrate Toxic Agent(s)

Hazardous Substances and New Organisms Act 1996 (HSNO)

This application is to be used when applying for a Permit to use any HSNO approved vertebrate toxic agent (VTA) for which a permission is required under section 95A of the HSNO Act. This includes the VTAs listed in Schedules 1 of the Hazardous Substances (Vertebrate Toxic Agents) Transfer Notice 2004 and the Hazardous Substances (Sodium Fluoroacetate) Transfer Notice 2005.

A Permit is issued by a person acting under powers delegated by the Environmental Risk Management Authority ("the delegated person").

Attachments

The application form contains a series of attachments requesting information necessary for issuing permit. Complete all the attachments that apply to this operation. If an attachment is not relevant, return the attachment as part of the completed application form and write "not applicable" across it.

Return this application to the contact person below.

LOCAL PUBLIC HEALTH CONTACT

Application for Permit to use a Vertebrate Toxic Agent

(Pursuant to section 95A of the Hazardous Substances and New Organisms Act 1996)

Name of applicant and/or organisation on whose behalf vertebrate toxic agent is to be applied.

Explanatory Note: A Permit may be issued to the applicant or to a person holding a controlled substance license. If the permit is granted to a controlled substance licensee give his/her name and provide a copy of the controlled substance licence. If the operation is "contracted out", the agency conducting the operation must complete the application form, including Attachment E.

Contact details: (address, postal address, telephone, cell phone, facsimile, e-mail):

Start Date:	Finish Date:

Give reasons if a permit is required to continue an operation over an extended period (e.g., 12 months).

Vertebrate toxic agent, e.g. potassium cyanide	Strength, e.g., 800g/kg	Form, e.g., pellets	Application rate (for aerial operations)	Purpose, e.g., for possum control

Application frequency/Number of applications: If more than one VTA or different forms of the same VTA are to be used, specify which product the information below refers to, and use p.3 for other VTAs.

Specify all strategies for the VTA to be used: If more than one VTA is involved, use the boxes on p.3.

Strategies to be used:	***(Tick applicable box)*** **Yes**	**No**		**Yes**	**No**
Aerial	❑	❑	Bait stations	❑	❑
Broadcast	❑	❑	*State heights of bait stations:*		
Turf spits	❑	❑	*Types of bait stations:*		
Traps	❑	❑			
Other control methods *(Describe briefly below)*	❑	❑			

Operation Name / Locality:

Operation Size (ha):

If the applicant has carried out an earlier operation in this area, report:
Date of Operation: _____ Application Identification Code: _____--

Name (print):	Signature:	Date:	Application identification code: (Office use only)

VTA Information (Cont)

Vertebrate Toxic Agent to be Used: _____

Application frequency/Number of applications:

Specify all strategies for the VTA

Strategies to be used:	*(Tick applicable box)* Yes	No		Yes	No
Aerial	❑	❑	Bait stations	❑	❑
Broadcast	❑	❑	*State heights of bait stations:*		
Turf spits	❑	❑	*Types of bait stations:*		
Traps	❑	❑			
Other control methods *(Describe briefly below)*	❑	❑			

Vertebrate Toxic Agent to be Used: _____

Application frequency/Number of applications:

Specify all strategies for the VTA

Strategies to be used:	*(Tick applicable box)* Yes	No		Yes	No
Aerial	❑	❑	Bait stations	❑	❑
Broadcast	❑	❑	*State heights of bait stations:*		
Turf spits	❑	❑	*Types of bait stations:*		
Traps	❑	❑			
Other control methods *(Describe briefly below)*	❑	❑			

Add new entries if more than four VTAs are involved in the operation.

ATTACHMENTS – A TO P

Complete the attachments that apply to this application. Tick the "yes/no" boxes below. If an attachment is not relevant, write "not applicable" across it. **Return all attachments.**

Note that different VTAs may require varying levels of detail to be provided with the attachment. Similarly aerial and ground operations will have different information requirements.

Page No.	Attachment Reference A to P		Applicable *Tick applicable box*		Office use only
	General		*YES*	*NO*	
5	**A**	Operational Maps	❑	❑	❑
6	**B**	Risk Assessment	❑	❑	❑
7	**C**	Community Consultation	❑	❑	❑
8	**D**	Consultation with Maori	❑	❑	❑
9	**E**	Operation Delivered by Subcontractor	❑	❑	❑
10	**F**	Transport, Storage and Disposal of VTAs	❑	❑	❑
	Excluded Areas: Mark clearly on map(s)				
11	**G**	Drinking Water Supply Catchments and Intakes (Public and Private Commercial)	❑	❑	❑
13	**H**	Dwellings, Adjacent Landowners/Occupiers	❑	❑	❑
14	**I**	Areas That Are Easily Accessible	❑	❑	❑
15	**J**	Tramping Huts and Shelters	❑	❑	❑
16	**K**	Walking Tracks and Roads	❑	❑	❑
17	**L**	Other Excluded Areas	❑	❑	❑
	Risk Communication				
18	**M**	Schools and Early Childhood Centres	❑	❑	❑
19	**N**	Notifications	❑	❑	❑
20	**O**	Warning Notices and Information Boards	❑	❑	❑
	Special Requirements				
21	**P**	Aerial Operations using VTAs	❑	❑	❑

Applicant

Ensure you return all attachments with this application. If an attachment is not relevant, write "not applicable" across it.

Office use

Additional information (may be) included with some attachments.

ATTACHMENT A: OPERATIONAL MAPS

The use of the maps is to provide sufficient specific information for this operation.

- Provide a description of the operational area. Include here the name of the area/reserve, and the name(s) of the landowner(s), clearly noting public and private land ownership.

- Operational maps should provide an adequate level of detail INCLUDING LOT NUMBERS WHERE APPROPRIATE. A number of map options are available e.g., topographical (e.g., NZS 260 series), GIS (geographic information systems), aerial photos, etc.

- Include: - area ground control _____ha
  - area aerial control _____ha
  - territorial local authority

- If using more than one VTA, show on the map where each VTA will be stored and where it will be applied.

- Identify where the helicopter loading zones will be and bait processing sites for carrot 1080 operations. If there is more than one loading zone or processing site, ensure all are clearly identified. (With carrot operations, one or more processing sites exist and also perhaps one or more loading zones). This information may also be recorded in Attachment F.

- **Attach operational map(s):** More than one map may be needed to include all the information. Use maps of different scales if necessary.

  Identify the following on your map(s) by using a colour code, a number code or similar:

	Refer to attachment
- Drinking Water Catchments and Intakes (Public and Private Commercial Water Supplies)	(G and P)
- Dwellings, Adjacent Landowners/Occupiers	(H)
- Areas Easily Accessible to Public	(I)
- Tramping Huts and Shelters	(J)
- Walking Tracks and Roads	(K)
- Other Excluded Areas	(L)
- Schools and Early Childhood Centres	(H and M)
- Warning Notices and Information Boards	(O)

(Letters in brackets refer to corresponding attachments)

Attach: Operational maps

❑ **(For official use)**

ATTACHMENT B: RISK ASSESSMENT

Do people take drinking water from water supplies originating in the operational area?

Think about drinking water in parks, island and camping sites even when there is no permanent or local population.

Yes ❑ Refer Attachments C, D and G

No ❑ If no, on what is this assessment based?

Do members of the public live within or adjoining the operational boundary?

Yes ❑ Refer Attachments H

No ❑ If no, on what is this assessment based?

Do the public have access to the area?

Think about areas reached by walking tracks, roads and boating access, which can be used by the public.

Yes ❑ Refer Attachments C, D, I, J, K, L and O

No ❑ If no, on what is this assessment based?

Are there any schools or early childhood centres within or near the operational boundary?

Yes ❑ Refer Attachment M

No ❑ If no, on what is this assessment based?

Is the operational area used for outdoor pursuits, groups/clubs such as hunters, campers, trampers, mountain bikers, scouts, schools, etc?

Yes ❑ Refer Attachments C, D, I, J, K, N and O

No ❑ If no, on what is this assessment based?

Is the operational area close to a village, town, other residential area, educational centre, marae or camping ground? If yes, describe.

Yes ❑ No ❑

Refer Attachments C and D

ATTACHMENT C: COMMUNITY CONSULATION

Do you expect any public concern about this operation? Yes ❑ No ❑

If yes, describe the nature of the concern:

What is the source of your information?

If no, on what is this assessment based?

Consultation with community groups

What community groups did you consult with in relation to this application?

Name the individuals/groups consulted:

Detail what, if any, concerns these individuals/groups identified.

How are you planning to avoid, mitigate or remedy any adverse effects identified by these individuals/groups?

Attach any evidence of the consultation (correspondence, minutes of meetings, record of phone calls, etc).

If you have not consulted any community groups about this application, ask the resource consent planner at your local council to help identify the appropriate groups to contact.

ATTACHMENT D: CONSULTATION WITH MAORI

When consulting with Maori, you need to take into account Section 6(d) of the HSNO Act: "The relationship of Maori and their culture and traditions with their ancestral lands, water, sites, waahi tapu, valued flora and fauna, and other taonga".

What Maori groups (iwi/hapu/whanau) did you consult with in relation to this application?

Name the individuals/groups consulted:

Identify what, if any, concerns these individuals/groups identified:

How are you planning to avoid, mitigate or remedy any adverse effects identified by these individuals/groups?

Attach any evidence of the consultation (correspondence, minutes of meetings, record of phone calls, etc):

If you have not consulted the Maori community about this application, ask the resource consent planner at your local council to help identify the appropriate groups to contact.

ATTACHMENT E: OPERATION DELIVERED BY SUBCONTRACTOR

Name of subcontractor:	Controlled Substance Licence Number: Date of Issue:

List the work experience the subcontractor has with the VTAs to be used:

Contact details of the subcontractor (address, postal address, telephone, cell phone, facsimile, e-mail):

Name of principal agency: _____

Signature: _____

Chain of responsibility – Complete as applicable to this operation.

It is now common practice for pesticide operations to be subcontracted to other agencies. All agencies involved have responsibilities to ensure the safe use of VTAs. Any subcontracting arrangements must be documented.

Example

Agency / Authority	Area of Responsibility
Principal Agency (AHB, DoC)	*e.g. Control of Bovine TB. Conservation etc*
Contractor (Local Authority)	*e.g. Contracted by AHB Possum Control*
Subcontractor (Name of approved operator)	*e.g. Field operations*

	Agency / Authority	**Area of Responsibility**
Principal Agency:		
Contractor:		
Subcontractor:		

Attach: Documentation showing subcontracting arrangements

❑ **(For official use)**

ATTACHMENT F: TRANSPORT, STORAGE and DISPOSAL OF VTAs

Give the name and address of VTA suppliers:

Name:

Address:

Estimate the quantity of VTAs required for the operation for which this permit is sought.

Where will the VTAs be stored prior to the operation:

Describe storage security *(locked secure compound, electronic surveillance etc)*:

How will the VTAs be transported to the operation site (land, sea or air):

Note that you must comply with the requirements of the Land Transport Rule: Dangerous Goods 1999 and any air/sea regulatory requirements that apply.

Where and how will any unused VTAs be stored or disposed of:

Where and how will empty containers be disposed of:

Record any resource consents held for the disposal of toxic waste from the operation:

Attach: Copy of Resource Consent for disposal (if this applies)

❑ (For official use)

ATTACHMENT G: DRINKING WATER SUPPLY CATCHMENTS (Public and Private Commercial Water Supplies)

The intent of this section is to minimise the risk of people drinking water contaminated with VTAs.

A **drinking water catchment** is an area from which water is likely to be taken for use as drinking water for human consumption. This includes surface water and ground water catchments. There may be public and private commercial water supplies such as camping grounds, hotels and pack packers to identify as well as domestic supplies to individual properties.

A drinking water catchment is defined as "Any area from which rainfall flows into a body of water, that is proximate enough to an abstraction point which supplies water for human consumption, that it can be said that the water is drawn from that area". Public water supply means "All water supplies that are not to self-supplied buildings". [Note: These two definitions apply **only** to their use for the purposes of issuing permissions for VTAs under the HSNO Act and its regulations, including the Hazardous Substances (Vertebrate Toxic Agents) Transfer Notice 2004 and the Hazardous Substances (Sodium Fluoroacetate) Transfer Notice 2005.]

Locations of intakes of drinking water for VTA aerial operations

Provide topographical NZMS Grid below. References for water supply intakes you have marked on your attached operational map (Attachment A). All locations shall be obtained using at least a GPS unit set up for use in New Zealand and using the following Map Datum:-New Zealand Geodetic Datum 1949. All GPS locations recorded in the field shall be plotted out on a NZS 260 series map prior to submission, and plotted points assessed against field knowledge gained from site visits to ensure correctness.

Intake ___(insert your map code)
Name of Supply:_____
NZSM Grid Ref. of intake: E_ _ _ _ _ _ _ N_ _ _ _ _ _ _
Type of Supply:_____

Intake ___
Name of Supply:_____
NZSM Grid Ref. of intake: E_ _ _ _ _ _ _ N_ _ _ _ _ _ _
Type of Supply:_____

Intake ___
Name of Supply:_____
NZSM Grid Ref. of intake: E_ _ _ _ _ _ _ N_ _ _ _ _ _ _
Type of Supply_____

Add new entries if there are more than three drinking water intakes.

List or mark on the topographical map (Attachment A) all public and private drinking water supplies, including catchments, reservoirs etc.

Has the applicant physically inspected all water supply intake locations with the landowner/supply operator to ensure that location of the supply as detailed in this application form is correct?
Yes ☐ ***No*** ☐

Has the applicant sought written permission from the authorities (e.g., TLAs) that operate public drinking water supplies?
Yes ☐ ***No*** ☐

Send a copy of the completed application form, accompanying location maps and attachments to the authorities which have drinking water catchments and/or intake structures within the operational area.

A copy of each written permission given by the authority that operates a public drinking water supply must be forwarded to the Public Health Unit having jurisdiction over the operational area.

Attachment G (Cont.)

For aerial and broadcast operations: Dairy Farms
Are there any dairy farms within 3 km of the operational area?

Yes ❑ **No ❑**

Attach copies of relevant hydrogeogical and hydrological reports and letters from consumers where needed.

Attach: Hydrology and hydrogeological reports

❑ (For official use)

ATTACHMENT H: DWELLINGS, ADJACENT LANDOWNERS/OCCUPIERS

Specify (or identify on a map) all dwellings within or adjacent to the boundary of the operational area.
Note: This requirement may be covered by Attachment A (Operational Maps).

In areas where there are more than 30 adjacent residential properties/landowners involved, the identification of the properties on a map may be sufficient.

How will you tell the occupiers, adjacent residents and landowners about this operation?

How will you ensure that VTA baits are not applied near occupied dwellings?

Has the occupier, adjacent residents and landowners list attached or described on the operational map (Attachment A) been checked and updated by the applicant?

Attach:

1. **Mark location of residents names/addresses, adjacent residents names/addresses on operational map (Attachment A) (all applications)**
2. **List names/addresses of residents and landowners/ adjacent residents and landowners (optional if more than 30)**
3. **Supply copy of the information to residents**

☐ (For official use)

ATTACHMENT I: AREAS THAT ARE EASILY ACCESSIBLE

The intent of this attachment is to identify the potential for exposure of young children and others who cannot read or who do not understand the dangers of poisoned baits.

Note: In some circumstances it may be possible and necessary to close any high use area.

Give the sources of your information:

List areas used by the public, including lay-bys for motorists (or identify on operational map: Attachment A):

List private land which has a high public use (or identify on operational map: Attachment A):

Estimate the number of people visiting the operational area. In particular, is it a high use area or will the number of people using it during the operation, increase for specific events or according to the season. Circle the appropriate response.

HIGH	*MEDIUM*	*LOW*
(more than 50 people per day)	(fewer than 50 people per day)	(fewer than 10 people per day)

List any areas to be closed to the public:

Are there likely to be people who are at risk of poisoning who may visit the operational area e.g., children or venturesome tourists?

List high use areas which will receive mid-week baiting strategy (or identify on operational map):

Attach

1. **List public areas, or mark on operational map (Attachment A)**
2. **List of any areas closed to the public during the operation**

☐ **(For official use)**

ATTACHMENT J: TRAMPING HUTS, BIVVIES/SHELTERS, TENT CAMPING SITES, PICNIC AREAS, PUBLIC ROAD LAY-BYS and WATERCRAFT LANDING POINTS

The intent of this section is to cover those places where the public may be gathered temporarily.

Are there any tramping huts, bivvies/shelters, tent camping sites, picnic areas, public road lay-bys and watercraft landing points within the operational area?

Yes ❑ No ❑

If yes, list tramping huts, bivvies/shelters (or identify clearly on operational map: Attachment A):

Give the source(s) of your information:

Describe the baiting plan in areas near huts, shelters etc:

Name of the person who provided the information: _____

Signature: _____

ATTACHMENT K: WALKING TRACKS and ROADS

Where it is necessary to carry out baiting on walking tracks and roads that are likely to receive high use, consideration should be given to closing the operational area to the public until it is deemed to be safe.

Obtain the following information from a knowledgeable third party (e.g., the landowner) and have this party sign off the information as being up to date and correct.

List all public walking tracks and their level of use:

Use the criteria below to assess the level of use of the track.

HIGH	*MEDIUM*	*LOW*
(more than 50 people per day)	(fewer than 50 people per day)	(fewer than10 people per day)

List all public roads and walking tracks within the area (or identify on operational map: Attachment A):

Give the source(s) of your information:

Name of the person who provided the information: _____

Signature: _____

Attach: List of public walking tracks and roads, or mark on operational map (Attachment A)

❑ (For official use)

ATTACHMENT L: OTHER EXCLUDED AREAS

The intent of this attachment is to identify any other place not listed in this application where the use of VTAs may directly or indirectly harm human health e.g., where the toxin could enter the food chain by contaminating animals, fish or food crops.

List any other excluded areas not recorded elsewhere in the application (or identify on operational map; Attachment A):

Describe the control methods for this area:

ATTACHMENT M: PRIMARY SCHOOLS, SECONDARY SCHOOLS, KINDERGARTENS and OTHER EARLY CHILDHOOD CENTRES (ECCs)

(ECCs are facilities attended by pre-school children)

The intent of this attachment is to help to protect young children (and others who are unable to understand notices) from the risk of contact with VTAs. For example, young children walking or cycling to school may visit friends, explore or take short cuts through operational areas (therefore their parents/caregivers need to receive warnings of the whereabouts of VTAs in the area).

Explanatory Note - "Appropriate Distance"

This applies to the size of a circle around an operational area in which schools and early childhood centres may be found. Urban schools are likely to have pupils coming from shorter distances than those in rural areas, which have children coming from further afield. For example, a 2 km-radius circle area around an operational area may be suitable in an urban setting, but a 10 km radius may be more suitable in a rural area. The appropriate distance should be identified after consultation with school staff and with the delegated person.

List all schools and early childhood centres located within 150 metres of the operational area:

List all schools and early childhood centres located within an "appropriate distance" of the operational area:

Provide a copy of the information that will be supplied to these schools and early childhood centres:

Attach: Copy of lists and information as requested above

☐ (For official use)

ATTACHMENT N: NOTIFICATIONS

Notification is required to ensure that the general public is aware of any poisoning operation scheduled to take place.

Hunting permits for the general area of operation are required to carry a warning to hunters that poisoning is planned for certain localities. The appropriate authorities (DoC, Regional Local Authorities or Unitary Local Authorities, or Forest Managers) must be notified in advance of the operation to ensure that this happens.

Attach a copy of the information to be provided to groups and agencies. A record or list of names/addresses of contacts is to be maintained by the applicant. This record is to be kept by the applicant for 12 months from the date of issue of the Permit and shall be made available to the delegated person on request.
Local health/medical services/police:
Veterinary clinics:
Hunting/kennel clubs/game packing houses, out door pursuits/clubs:
Any other known groups that are likely to have access to the area:
Attach: Copy of information to groups and agencies **☐ (For official use)**

ATTACHMENT O: WARNING NOTICES, INFORMATION BOARDS, PUBLIC INFORMATION CENTRES, KIOSKS etc

The intent of this attachment is to ensure that a clear warning is given to people of the presence and danger of the VTA. Where foreign tourists frequently visit an area, it may be useful to provide signage in the appropriate language. As a minimum, warning notices must be erected at every place where people normally obtain access to the treatment area, including beaches and other landing points from waterways.

***Explanatory Note**: The term "regular" should be interpreted to suit local conditions. Where vandalism is to be expected, notices will need to be checked daily. If vandalism is not expected in the operational area, longer periods may be allowed to elapse between inspections.*

List locations of warning notices and information boards (or identify on operational map: Attachment A):

Attach: Copy of notices and information boards

❑ **(For official use)**

ATTACHMENT P: AERIAL OPERATIONS USING VTAs

Explanatory Note: *The log is a summary report of operations. The log may include summaries of several operations providing they occur within the same approval period.*

It is acknowledged it is not always physically possible to inspect all boundaries. If this is the case, discuss with the delegated person.

List drinking water supply reservoirs or storage facilities and waterways (and identify on operational map; Attachment A):

List areas to be inspected (and identify on operational map; Attachment A):

Appendix 5. Permission for use of Vertebrate Toxic Agent(s)

PERMIT FOR USE OF VERTEBRATE TOXIC AGENT(S)

Pursuant to section 95A of the Hazardous Substances and New Organisms Act 1996

To (name of applicant): _____

Of (postal and physical address of applicant: _____

Application Identification Code: _____

Purpose of Application* _____

Application Location/Area* _____

Start date: _____ Finish date: _____

I ..... a person acting under powers delegated by the Environmental Risk Management Authority (the Authority), GRANT PERMISSION for the use of the following vertebrate toxic agent(s):

.....
.....
.....

This permit is subject to the CONDITIONS set out in SCHEDULE 1 attached hereto.

Signed: _____

Name: _____

Title: _____

Date: _____

Contact Person: _____

Appeals: Section 125 (1A) of the Hazardous Substances and New Organisms Act 1996 (HSNO Act): A person may appeal to the District Court against a decision of the Authority, under section 95A about the terms and conditions of a permission held by the person.

Notice of appeal: Section 127 of the HSNO Act: Before or immediately after the filing and service of a notice of appeal, the appellant shall serve a copy of the notice on the Authority, and every other party to the proceedings, and any other person who made a submission to the Authority.

SCHEDULE 1 – PERMIT CONDITIONS

Application Identification Code:

Application Location/Area:

In addition to requirements specified under the Hazardous Substances and New Organisms (HSNO) Act and its regulations, including the Hazardous Substances (Vertebrate Toxic Agents) Transfer Notice 2004 and the Hazardous Substances (Sodium Fluoroacetate) Transfer Notice 2005, the following conditions shall apply:[10]

1 (insert conditions here in numbered paragraphs)
2 condition
3 condition
4 condition
5 condition
6 condition
7 condition
8 etc

(Note to officer: check there is a page number on each page, and initial each page of conditions at the bottom)

[10] The requirements under HSNO are minimum requirements, which must be met. A person acting under a delegation from the Authority may impose additional (stricter) conditions.

MODEL CONDITIONS that may be imposed by a person acting under delegation of the Authority when granting permission/s FOR USE OF VERTEBRATE TOXIC AGENT(S)

Under the Hazardous Substances and New Organisms Act 1996

The requirements under HSNO are minimum requirements, which must be met. A person acting under a delegation from the Authority may impose additional (stricter) conditions.

The following are model conditions for a vertebrate toxic agent (VTA) operation, which may be set from time to time to meet local conditions within the operational area and surrounds. The conditions of a permit may be selected from these model conditions, depending on the delegated person's assessment of the local circumstances. The model conditions may also be modified or new conditions imposed at the discretion of the delegated person. All conditions should be listed under Schedule 1 (Permit Conditions) of the permit.

Model conditions are in standard type; comments in italics indicate where additional information is to be inserted.

For all operations using vertebrate toxic agents

1 (*Insert contact name person from page 1)* of *(insert name of PHU issuing the permit*) is to be notified by telephone and/or in all instances confirmed in writing before the vertebrate toxic agent(s) phase of the operation begins.

2 All incidents and complaints relating to the operation that may impact on public health shall be documented and notified to (*contact name person from page 1)* of *(insert name of PHU issuing the permit*).

3 If any circumstances relating to the application or the operation change, the person issuing this permit (*insert contact name person from page 1*) shall be informed immediately and they retain the right to modify or withdraw the permission.

4 Hand-laid bait or paste shall not be laid near specified walking tracks, formed public roads, or any areas used by the public (lay-bys, parks, etc) where the bait or paste is within sight of or easily accessible to the public from those areas.

(*If PHUs wish to stipulate a particular distance, they can still do so*).

5 The applicant must specify the maximum and minimum time period during which the majority of the bait may be toxic, after application. The applicant must advise in writing the Public Health Unit issuing this permit (*insert contact name person from page 1*) when baits have ceased to be toxic.

6 Any vehicle used to transport vertebrate toxic agent(s) or its wastes shall be kept locked when the vehicle is left unattended for any period of time.

7 Prior to commencing the operation, the applicant shall notify persons who take drinking-water downstream from the operational zone (i.e., water supplies with catchments and intakes inside the operational area or on adjoining properties) of the operation and its duration.

8 Residents and landowners adjacent to the operational area shall be identified by the applicant and shall be provided with information on safety and precautions with respect to the vertebrate toxic agent(s) being used.

9 All reasonable steps shall be taken to prevent contamination with the vertebrate toxic agent(s) of all areas within 150 metres (or within a distance mutually agreed in writing with occupiers) of the dwellings (including stock and drinking water supply) identified.

10 All places where the public may stay, camp, play, exercise or assemble (including any approved camping ground, tramping huts, bivvies/shelters, tent camping sites, picnic areas, public road lay-bys and watercraft landing points) shall be identified and must be excluded from the operation by way of a (*specify distance*) metre buffer zone around each place in which no vertebrate toxic agent shall be laid.

11 No vertebrate toxic agent(s) shall be applied to land that receives high public use (whether it is public or privately owned) during school holidays or public holidays, unless that area is closed to the public.

"High public use" means that there are more than 50 people visiting the operational area per day.

12 Land that receives high public use (whether it is public or privately owned) shall be made safe from vertebrate toxic agent(s) before the beginning of school or public holiday periods, unless the area is closed to the public.

13 For areas that receive high public use, a mid-week vertebrate toxic agent baiting strategy shall be used, unless limited use is expected due to seasonal or climatic conditions, or due to closure of the area.

14 The applicant shall notify local health services of the poisoning operation and provide appropriate safety information. Local health services include: GPs and other primary health services, ambulance services, Police, hospitals and emergency clinics (e.g., Emergency Departments at local hospitals), and veterinary clinics in the operational area.

15 The public shall be given notice, e.g., by advertisements in the local newspaper, (*specify time*) prior to the proposed application of a vertebrate toxic agent.[11]

16 Warning signs shall be checked at regular intervals, and must be repaired/replaced within 24 hours of discovery or notification of damage or theft. Where warning signs are located some distance from the operational zone these signs shall include a map showing the operational zone and the location of the sign(s).

17 The warning signs must include an international symbol for toxic substances (e.g., skull and crossbones) and a statement advising that children should not be allowed to wander (e.g., WATCH CHILDREN at all times).

18 No vertebrate toxic agent is to be applied where it is accessible by grazing stock.

19 The applicant must provide a copy of this permit and its conditions to the Person in Charge of the operation.

For aerial operations using vertebrate toxic agents

20 Vertebrate toxic agent(s) shall not be aerially applied within (*specify distance*) metres of any approved camping ground, formed public road currently in use, lay-bys, picnic areas, tramping huts, bivvies/shelters, tent camping sites, watercraft landing points, streams, rivers, lakes, ponds and reservoirs specified by the delegated person.

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[11] This condition does not to be specified if the operation is only using 1080 bait for aerial application, as the Hazardous Substances (Sodium Fluoroacetate) Transfer Notice 2005 already imposes such a requirement.

21 The bait must be hand laid if it is to be applied closer than the distance specified in condition 20 with respect to those areas specified in that condition.

22 All toxic baits must be cleared from the walking tracks and roads listed within 48 hours from the time the vertebrate toxic agent was applied, unless the tracks or roads are closed to the public.

23 High use tracks must be checked and cleared of baits within 24 hours from the time the vertebrate toxic agent was applied, unless the high use tracks are closed to the public.

24 If any such walking track or road listed is closed to the public, it must be scrutinised for baits and cleared before re-opening.

25 Following initial clearance, walking tracks and roads are to be regularly inspected for toxic baits that may have fallen from the tree canopy. For high use tracks, this will be on a daily basis.

26 An operator's log *(report)* must be compiled of activities associated with the aerial application and a copy of this log is to be forwarded to the Public Health Unit issuing this permit (*insert contact name person from page 1*) within four weeks of the date of the vertebrate toxic agent being laid.

As a minimum, the log shall include:

(a) time, date and place of the application
(b) amount of vertebrate toxic agent applied and its formulation
(c) list of supervising operators
(d) names of subcontractors with services provided
(e) name, address and rating number of pilot(s)
(f) any incidents that occurred and problems that arose during the operation, including the investigation undertaken and where necessary the remedial actions taken
(g) any involuntary transgressions of the conditions in this approval, including an explanation of each transgression and the remedial actions taken
(h) copy of GPS printouts of toxic flight lines
(i) a completed copy of the Aerial Operation Form.

27 Differential Global Positioning System (DGPS) shall be used at all times for aircraft carrying bait-sowing equipment.

28 After aerial application of a vertebrate toxic agent, any areas that are required to be inspected shall be inspected. This may include any boundaries which adjoin the land of a different tenure, or, any nearby areas in which aerial application of the vertebrate toxic agent is not permitted (*specify all areas that are to be inspected*).

For operations (aerial and hand-laid) where 1080 is laid in a drinking water catchment

29 Water testing is required for all public water supplies *(specify named supply/location)*. Water samples must be collected within *(person issuing permit to specify time)* hours after a 1080 poison operation.

30 Water testing is required for all private water supplies *(specify named supply/location)*. Water samples must be collected within *(person issuing permit to specify time)* hours after a 1080 poison operation.

If you impose a condition for water testing under conditions 29 and/or 30, the applicant must seek advice from the local regional council hydrologist/water quality scientist when designing the water monitoring programme, including the sampling periods.

31 An alternative drinking water supply shall be provided and water testing shall be carried out to show that the supply contains less than 2 parts-per-billion (ppb) 1080 before the reopening of the water supply ,except when one or more of the following applies:

(a) Where test results gathered from previous operations, covering the same catchment or groundwater supply and at the same or greater application dose, show that the 2 ppb level was not exceeded in any test.
(b) Where drinking-water comes from a secure bore supply *(hydrogeological report).*
(c) Where the water from the water catchment in the treatment area is sufficiently diluted by other water sources *(hydrological report).*
(d) Where there is sufficient distance between the 1080 treatment area and the draw-off point for the water supply from that water catchment *(in most cases 3 km).*
(e) Where another source of water is available (such as a separate catchment, roof tank or reservoir) that is not subject to possible 1080 contamination, and the consumer is advised in writing to use that alternative supply.
(f) Where baits are not laid in any place where they can fall or be washed into water sources or drinking-water supplies.
(g) Where the 1080 is applied using bait stations.
(h) Where consumers state in writing that they do not want an alternative drinking-water supply and that the operator has advised them in writing of the risks.

If any of exceptions (a) to (h) apply, the applicant must have provided the relevant documentation as part of their application for a permit.

Appendix 6. Model Permit Conditions for the use of sodium monofluoroacetate (1080) issued by the Medical Officer of Health

Additional conditions which may be imposed at the Medical Officer of Health's (MOH) discretion to meet local needs.

The following are model conditions which may be set from time to time to meet different local needs and may be selected from, or added to, depending on the MOH's assessment of local circumstances.

1. For All Operations

1.1 The agency conducting the operation shall notify the Medical Officer of Health if there is any alteration to the intended date of the application.

1.2 All schools, play centres and child care centres specified by the Medical Officer of Health within an appropriate area shall be provided with information on safety precautions (e.g., 1080 information kit) by the agency conducting the operation.

Generally the "appropriate area" will be 10 km, however, this may vary from one locality to another. Therefore, the "appropriate area" should be established by the local Medical Officer of Health following appropriate consultation.

1.3 Notification of the poisoning operation and appropriate safety information is to be provided by the agency conducting the operation to GPs, ambulance services, Police, hospitals and emergency clinics (e.g., Accident & Emergency Departments), and veterinary clinics in the operational area of the operation.

This requirement is a precautionary measure so that these agencies/bodies can make themselves aware of what should be done in the event of an emergency relating to 1080.

1.4 Loss of the toxic material and other incidents that may pose a hazard to the public must be notified to Medical Officer of Health as soon as possible but at least within 24 hours.

1.5 All complaints relating to possible impacts on public health (e.g., contamination of public water supplies) during a 1080 operation should be documented and notified to the Medical Officer of Health who will maintain a record.

1.6 Notices that are stolen or obscured should be repaired/replaced by the agency conducting the operation within 24 hours of notification of loss.

1.7 No baits are to be present during school and public holidays in areas to which the public have ready access.

Although the Ministry of Health understands that there is a legal requirement for signs to be displayed showing 1080 has been applied, its main concern is young children who cannot read so don't understand the danger of poisoned baits.

This condition depends upon the discretion of the Medical Officer of Health after discussion with the applicator and interested parties. *Consideration should be given to ensuring that toxic bait laying operations do not occur when a large number of children are likely to be using the area. Some schools are moving to a four-term year, and in areas where a three-term year also occurs, application of this condition would preclude control work from a significant portion of the control season. It should be noted that areas where control work is occurring will be closed to the public.*

1.8 Hunting permits for the general area of operation shall carry a warning to hunters that 1080 poisoning is planned for certain localities.

2. For Aerial Operations

2.1 An inspection is to be made of boundaries which adjoin land of a different tenure after an aerial application of baits and of areas in which aerial application of bait is not permitted, i.e., roads, major waterways. If bait is in the wrong area, arrangements should be made to clear the area of stock or toxic bait.

It is noted that it is not always physically possible to inspect all boundaries.

2.2 All walking tracks and formed public roads specified by the Medical Officer of Health must be cleared of toxic baits within 48 hours of the completion of the operation.

2.3 The contractor applying the bait must keep a log for one year of activities associated with the aerial application, i.e., time, date, place, weather, flight paths,

wind direction and amount dropped. The log must be made available to the Medical Officer of Health, on request.

a) No aerial application of 1080 is to be made within 20 metres of any camping ground (as defined in the Camping Ground Regulations 1985), formed public road currently in use, picnic areas, lake, pond, water supply intake or stream/river specified by the Medical Officer of Health.

Applications near streams and rivers should be discussed with the Medical Officer of Health before the permit is issued.

Consideration should be given to provide the residents with an alternative drinking-water source if 1080 has been allowed to be applied in any drinking water catchment.

The provisional Maximum Acceptable Value (MAV) for 1080 in the New Zealand Drinking-Water Standards 2005 is 3.5mg/L (3.5 ppb).

b) Bait applied within 60 metres of the areas in (a) must be applied by helicopter either with a competent observer in the aircraft, or by an aircraft fitted with and using a recording Differential Global Positioning System (DGPS).

A DGPS is a satellite and computer-based aircraft navigation system which can accurately record bait application in aerial poisoning operations. It enables auditing of flight paths and the area targeted and improves the targeting of bait coverage. However, the use of DGPS cannot be imposed in all cases because of the limited number of DGPS available in the country.

c) The bait must be hand laid if it is to be applied closer than 20 metres to the areas specified in (a).

2.4 No aircraft carrying 1080 for aerial application is to fly in transit over a water supply (dams, reservoirs, or public water supply intakes) and flight paths must not cross a waterway within 100 metres upstream of an intake.

2.5 Where 1080 baits have been laid in a public water supply catchment, the Medical Officer of Health requires the agency applying the bait to monitor the water

quality during the operation and for a specified period thereafter. This shall include chemical analyses of public water supplies.

2.6 All aircraft and loading equipment must be thoroughly decontaminated before the aircraft or equipment leaves the operational area following the Animal Health Board operational protocol.

3. For Ground Operations (including 1080 paste):

Please note that the Medical Officer of Health's approval is only required for ground applications within 'restricted areas' under regulation 12 of the VPC Regulations (now repealed).

3.1 Hand-laid 1080 bait or paste shall not be laid within five metres of specified walking tracks and formed public roads.

3.2 The Medical Officer of Health may require public notice by advertisements for hand laying of 1080.

3.3 Rural/domestic water supply streams and publicly visible sites shall be inspected and all carcasses collected where feasible from places where public health could be at risk.

Appendix 7. Preliminary information collected by the Public Health Units (PHU)

The purpose of this study was to obtain an overview of how 1080 was being used in each local PHU[12]. The findings from this study were intended to help address some of the questions raised regarding the perceived risk from the use of 1080.

Methodology

On 15 August 2002, the author (NF) requested each PHU to provide information on the way 1080 is being used in their area. The following questions were e-mailed to eleven PHUs throughout New Zealand.

Question 1	Is 1080 ever used in your area?
Question 2	Approximately, how many 1080 operations occur annually in your area?
Question 3	In your permit conditions, has 1080 been permitted to be applied in any catchment area from which water is drawn from human consumption?
Question 4	What precautions do you usually require to minimise the possibility of water contamination?
Question 5	Have you received any complaints relating to 1080 operations?
Question 6	If yes, briefly summarise each.

PHUs replied directly to the author (NF) and responses were summarised for analyses (Table 1). A code was assigned to each PHU to ensure the anonymity of the respondents. The information provided by each PHU was summarised and analysed by this author (NF). Key findings were presented under the 'Results and Discussion' section.

[12] Designated officer in each PHU means a Medical Officer of Health, a Health Protection Officer or other officer designated by the Director-General of Health. The primary responsibility of a designated officer is to fulfill his or her statutory duties and responsibilities.

Results and Discussion

A summary of the survey is shown in Table 1 and key findings are listed below:

- In all areas covered by each PHU, 1080 was permitted to be used in catchment areas from which water was drawn for human consumption.
- 1080 has been or is being used in all areas covered by each PHU.
- 1080 operations varied from each region with 1080 being used more frequently in some areas than others.
- All PHUs received a number of complaints relating to 1080 operations except in one area (PHU 1) where none was received despite having a number of publicly notified 1080 pest control operations. PHU 5 commented that no complaints were received but they received "protests" prior to or during the operation. Protests and complaints may have been used interchangeably in this context, such as in PHU 8 where 1080 activists are present in their area.
- Accidental dropping of 1080 baits in non-target areas cannot be ruled out as demonstrated in this survey.
- There was a general lack of knowledge on legislative requirements and the risks involved when handling 1080 inappropriately.
- Non-compliance appeared to be a major issue and the agency conducting the operation should ensure that contractors were familiar and complied, with such requirements.
- The results of the survey suggested that in water catchment areas where 1080 was permitted to be applied, one of the conditions imposed was consultation with affected homeowners and that alternative drinking water supplies should be provided to affected people until such time that the drinking water met the Ministry of Health's recommendation that the levels of 1080 did not exceed 2 ppb.

Complaints of public health significance were:

- Possible contamination of drinking water catchments after 1080 aerial application; 1080 baits have fallen outside the operational zone;
- Lack of notification that a 1080 operation is occurring at a certain date;
- 1080 baits found in water supply catchment; too late for (or the lack of) consultation prior to 1080 poisoning operation;
- No signage used in walking tracks and baits found in a creek and picnic ground accessible by the public;

- Bait stations were visible and too close to a public road; 1080 baits were not removed from walking tracks; theft of 1080.

It appears from the information provided by PHUs that there were legitimate reasons for the public to be concerned about the use of 1080. It has been acknowledged that there were contraventions made in some DoC 1080 operations (PHU 2; P. Reid pers. comm. 2005), i.e., 1080 baits were laid in exclusion zones. Also PCE (1998) reported that there has been an increasing trend for control agencies to contract out their possum control operations which has created implications for monitoring the performance of their operators.

Preliminary information from PHU

In relation to conditions imposed by the PHU, response from the PHUs suggested that standard conditions[13] were applied (Appendix 5). Some PHUs, such as PHU 2 and 4, have included additional controls to complement the standard conditions, i.e.,

- warning signs were translated into foreign languages;
- high use walking tracks were closed until staff could safely walk through these areas;
- water intake was disconnected from other intake/s; and
- provision of alternative drinking water.

Because dogs are very susceptible to the toxic effects of 1080, most of the complaints received were about dog deaths. Dog owners have been warned to keep their dogs away during 1080 operations using leaflets, such as that produced by the NPCA, "1080 Is Not Kid's Stuff" (undated), has been distributed.

There was the possibility of accidental ingestion occurring, especially in the case of young children. A young child found some 1080 baits in an urupa (Maori cemetery) (PHU 3). The parents apparently found the child with a broken 1080 pellet and some green material in her mouth. The child was rushed to the hospital where following examination she was found to be well with no evidence of having actually consumed any bait material. Investigation showed that the urupa was indeed baited during an aerial 1080 operation. The area was identified by the operator of the local iwi during public consultations planning phase.

PHU 8 reported that trampers, who were unaware that a 1080 operation was to be carried out, entered an operational zone. They were showered with 1080 baits the following day. There was a legal requirement under the Pesticides (VPC) Regulations (now repealed) to erect warning notices

[13] Conditions specified in the Medical Officer of Health permit form.

at every place where people normally obtain access to the baited area including the intended date on which it is to be applied.

There was also an incident where a farmer's property was dropped with 1080 baits without the farmer's knowledge (PHU 3). Another complaint received by PHU 3 concerned forestry crew being showered with baits during aerial operation. Apparently, the company employing the crew did not pass on vital information concerning the commencement of the baiting operation.

As can be seen, only PHU 1 has suggested that they did not receive any complaints although the number of 1080 operations was comparable with other PHUs receiving complaints. On average, it appears that PHU 10 granted the highest number of 1080 operations while PHU 9 granted fewer permits but the Minister's office has received a number of complaints/concerns from this region (S. Gilbert pers. comm. 2004). In PHU 6, concerns were addressed by sending relevant 1080 information to the public and stating that they could be contacted if they wish to discuss the information.

There were local iwi oppositions received in relation to the possible contamination of water (PHU 7). Water is taonga (treasure) to Maori and the application of 1080 may likely to be of concern to local iwi and hapu. The PHU had dealt with this issue by requesting that the water be tested to ensure that the drinking water met the Ministry of Health's recommendation that the levels of 1080 did not exceed 2 ppb.

PHU 8 stated that if 1080 is allowed to be dropped in drinking water catchment areas, the water treatment facility supplied by two catchments was to be closed down. Strict controls were also required in relation to private water supplies, including:

- The regional council involved was required to ensure that the water tank supply was replenished as needed. Bottled water was supplied if reserve tank was not available.
- Operators were asked to inform all those affected to fill reserve tanks before the operation and disconnect water intake/s before 1080 aerial operation.
- Users of drinking water will only be advised to collect water from the affected area/s when the Medical Officer of Health has been satisfied that the drinking water complies with the Ministry of Health's recommendation, as confirmed by water laboratory analysis.

In PHU 2, operators appeared to understand how high levels of concern should be addressed as they themselves suggested special precautions to be included in the permit conditions to alleviate the concerns from the community. In addition, if there were conditions that the PHU considered appropriate for inclusion these were discussed in the first instance with the operators to determine

whether or not these were achievable and/or practical, before such conditions were added as part of the permit conditions. The PHU still received complaints over the use of 1080 in spite of earlier comment that they communicate well with the operators. In addition, major oversights concerning 1080 operations have seen a complete rethink by DoC about their contracting of sensitive tasks in the area.

PHU 3 has claimed that 1080 baits were found in a popular walking track following 1080 aerial application. In this particular situation, the operator apparently believed that 48 hours were allowed to check the track following bait application in accordance with the standard approval conditions. Theft was also mentioned as one of the complaints received by PHU 3. Investigation revealed that the 25 kg bag of 1080 pellets stolen was part of a consignment of bait material ordered 12 months previously by DoC. The consignment had apparently been stored at a contractor's warehouse and the theft has been detected at the time. 1080 was classified as "Deadly Poison" under the Toxic Substances Regulations. Although, people who are engaged in 1080 commercial activities can legally use 1080, it is legally required that this product should be strictly kept out of reach of unauthorised individuals and must be stored under lock and key and not ordinarily stored in a warehouse accessible to the public.

Unforeseen circumstances could occur in aerial operations. PHU 8 claimed that in a DoC 1080 operation, 2-3 baits were thought to have fallen from a bait bucket while flying over an area outside the operational zone. A child picked up a bait but the child's mother was able to intercept the bait before the child was able to do anything with the bait. Unfortunately, the child's dog ate the bait and subsequently died. The child could have been poisoned had the mother not seen her child pick up the bait. This incident clearly illustrates that accidental dropping of 1080 in public areas outside the operational zone has indeed occurred. In the model permit conditions (Ministry of Health 1995b), the use of DGPS cannot be imposed in all cases because of its limited availability in New Zealand. Only four firms have DGPS available which is considered to be inadequate to cater for all the aerial operations by both the DoC and AHB (PCE 1994). This information appears to be out of date as the number of DGPSs has increased since these documents were published (M Kennedy pers. comm. 2007)

Unsubstantiated claims were also reported, includings:

- A father reported that his son had picked up a bait and a dog died after eating some baits in the same incident and that this track was outside the operational zone. There was a suspicion that the baits in question were deliberately placed after having been stolen from an earlier operation and the Police have investigated this incident.

- There were also claims that baits were dropped outside the operational zone, although some incidents may have related to windfall baits being deposited on paths some days after the aerial operation. DGPS records indicated no breaches of the operational zone occurred during aerial bait operations.

Summary and Conclusion

The information provided by the PHUs suggests that there were genuine reasons for the general public to be concerned from 1080 usage as demonstrated on a number of occasions, for instance, 1080 baits have fallen outside the operational zone, lack of notification that a 1080 operation is occurring at a certain date, 1080 baits found in water supply catchment, baits stations were found in areas where the public have ready access, and baits not removed from walking tracks. 1080 hazards in places where people expect to be safe, e.g., public places, are hazards that will be perceived by the public in a context wider than that of scientific risk assessment.

Table 1. Preliminary information on the way 1080 is used involving Public Health Units

PHU	Q1	Q2	Q3	Q5
1	Yes	Approx 6	Yes	No
2	Yes	25 average	Yes	Yes
3	Yes	10 aerial 14 ground	Yes	Yes
4	Yes	2-3	Yes, but only private supplies	Yes
5	Yes	Average 4	Yes	No (PHU 1)
6	Yes	8 aerial; 5 ground	Yes	Yes
7	Yes	15 average	Yes	Yes
8	Yes	2-3 aerial 2-3 hand-laid	Yes	Yes,
9	Yes	30-35 average	Yes	Yes
10	Yes	78 average	Yes	Yes
11	Yes	40 average	Yes	Yes

Data were collected in 2002
PHU (number.) – code assigned to each PHU to keep anonymity of respondent

Q1 – Is 1080 ever used in your area?
Q2 – Approximately, how many 1080 operations occur annually in your area?
Q3 – In your permit conditions, has 1080 been permitted to be applied in any catchment area from which water is drawn from human consumption?
Q4 – What precautions do you usually require to minimise the possibility of water contamination?
Q5 – Have you received any complaints relating to 1080 operations?
Q6 – If yes, briefly summarise each.

Table 1. Continued

PHU	Q4	Q6
1	Conditions imposed were based on the Ministry of Health's model permit conditions for 1080 and Medical Officer of Health's permit conditions	None
2	Standard conditions[14] plus: Exclusion of school holidays/long weekends/duck shooting season for areas where people pressure will be higher, particularly when people from outside the area may be visiting. Requirements for warning signs to be translated to foreign language where appropriate. Inclusion of a request for operators to have a very low threshold for notification of incidents in areas where there are sensitive for any reason. Closure of high use walking tracks until staff can safely walk through these areas.	Few complaints. None that have been substantiated. Complaints about the death of dog and sending abusive letters to the PHU.
3	Conditions listed in Section H of the Medical Officers of Health conditions.	Off target application of 1080 which is purported to have killed a dog. Secondary poisoning resulting to dog's death. Green material purported to be 1080 bait found on public road following a 1080 operation. Analysis of material found no 1080 present. Aerial application of 1080 to a popular walking track. Discovery by Police of an unopened 25kg bag 1080 pellets while exercising a search warrant in a house. The finding of 1080 baits on a urupa by a young child. Forestry crew showered with baits during aerial operation.
4	Water tests include potable water extraction points. Asked applicants to communicate within all water users.	Signs not removed after an operation. A forestry worker complained that he was being poisoned three years after the application took place. Secondary poisoning of dogs.
5	Exclusion of the immediate intake zone and upstream 200m; if practical the intake was disconnected; contingency emergency plans for aerial applications; liaison with water supplier; audit of bait placement for ground operations.	No complaints are received but "protests" prior to or during operations. Operators are required to record complaints sometimes these are audited.

[14] Conditions specified in the MOH permits

6	Section H of the Medical Officer of Health's model conditions applied. Alternative water supplies.	Call mainly from adjacent landowners or deerstalkers that were concerned about upcoming operations.
7	Standard conditions are imposed. Waterways used for water supply to be inspected after the operation any wayward baits were removed. Water supply monitoring to be carried out.	Dog poisoning. 1080 paste (confirmed) found by children in a detergent bottle. Complaint re 1080 application that did not have approval. Complainant concerned that they (including neighbour) were not informed re upcoming 1080 operation. Operator did not follow own guidelines or read the approval. 1080 poisoned possum carcasses disposed in offal fits and may affect groundwater. Possible 1080 contamination of spring/stream/river supplying water. Iwi opposition to 1080 operation re water contamination.
8	Attachment H of the Application for Permission imposes strict conditions on the applicant to protect the quality of drinking water. Any accident is to be immediately reported to the MOH to enable remedial action. Water supplies are switched off if necessary.	1080 activists group is by far the largest group of complaints received. A child picked up a bait outside the operational zone. Trampers entered the aerial zone the night before the operation before signs were erected on the morning of the operation. They were unaware that they had entered a "closed area" and baits falling from the helicopter struck them. A number of dog deaths complaints followed the RC's operation. Claims that baits were dropped outside operational zone.
9	Standard conditions apply Homeowners are consulted and alternative water supplies are instituted upon request by affected people and this remains until the water is tested as free from 1080. Signed permission forms from affected persons are sought before permission is granted.	Community opposed to 1080, especially aerially applied. Concerns include possible water and environmental contamination, human and animal health risks, community stress. 1080 baits found in water supply catchment. 1080 baits found in water supply catchment and intake. No consultation until 2 days prior to the aerial application of 1080. Baits ended up in a creek and picnic ground accessible by the public. The picnic area was however closed by the Council for the operation, but anti 1080 groups went into area and found the baits in the creek bed. Baits were found on walking racks along with dead possums, and an absence of signage.

10	Standard conditions apply	Deer hunters not wanting 1080 to be aerially dropped as they kill whitetail deer. A farmer concerned about an aerial operation and that the baits should not be dropped to his property. Objections raised relating to air and waterways being polluted by 1080 during public meetings regarding possum control by the local iwi. Complaints from the public that bait stations were visible and too close to a public road. Complaint received from the local DOC staff regarding bait being laid too close to a public walking track. Local residents were concerned about the hand laying of 1080 within the vicinity of their town's water supply. A complaint made by deerstalkers about dead animals in a water catchment area and also comments about carrot bait in a water supply zone.
11	Condition 1-4 sect H of the application form for all baiting operations; Condition 5 for aerial application where water supply is from surface or gallery source. Depending on the catchment type, a minimum distance from the water edge. .	1080 baits not being removed from some areas of walking tracks in DOC Forest Park prior to tracks being reopened to the public. Inadequate cleanup of farm airfield loading site (fall of snow covered some bait residues which were then discovered a few days later after snow melt). Opposition to an aerial 1080 operation on to a water catchment area. A number of complaints relate to dogs deaths. Often notices were removed or defaced.

Appendix 8a. Postal survey on work characteristics of 1080 workers

Less is known about the patterns of exposure of children and other individuals living in households with 1080 workers. No study has been carried out to address whether these individuals may have been potentially exposed through this route of exposure.

This survey aimed to determine the likely exposure of members of the public that may arise from associating with people directly involved in handling 1080. This involved personal behaviours, and their interaction with people living in the same household. Although occupational exposures were excluded from this study, their inclusion in this part of the survey was to identify working habits that may affect the exposure of people living in the same household. Because there is considerable scientific interest in the manner in which workers were exposed to 1080, these findings may potentially be important in informing policy and programmes that are aimed to train workers in 1080 safety.

Selected studies reviewed

The "take-home" exposure pathway was shown to be a significant contributor to residential contamination in the homes of agricultural workers (Hood 2002). Since there are no studies that are available relating to 1080 "take-home" exposure, "take-home" exposure pathways arising from the use of pesticides relevant to this study were reviewed. In addition, studies which may not be due to "take-home" exposures (studies were not described as "take-home') but were due to contamination of their homes because of their proximity to the treated area were also included in the review for information and interest.

Curl *et al.* (2002) reported that "take-home" exposure among families of farm workers in Washington State found that azinphos-methyl was the most commonly detected pesticide in both house dust and vehicle dust. Azinphos-methyl was found in 85% of the household dust samples and 87% of the vehicle dust samples above the limit of detection which showed a significant correlation between pesticide concentrations in house dust and vehicle dust. Furthermore, urine sample analysis showed that one of the metabolites of azinphos-methyl was present in the urine of 88% of the children and 92% of the adults. This evidence supported the likelihood that the pesticide was transported from the clothing or skin of workers into the vehicles and eventually into their homes. In another study, Zahm and Ward (1998) investigated "take-home" exposures of parents occupationally exposed to pesticides and childhood cancer. Although the research was limited by non-specific pesticide exposure information, small numbers of exposed subjects, potential for recall bias, and a small number of studies for most cancers, the magnitude of the risks was often greater than adults, indicating greater susceptibility of children to the carcinogenic

effects of pesticides. Of concern were leukaemia, neuroblastoma, Wilm's tumour, soft tissue sarcoma, Ewings sarcoma, non-Hodgkin's lymphoma, and cancers of the brain, colorectum, and testes.

Lu *et al.* (2000) found that concentrations of azinphos-methyl and phosmet in the house dust of agricultural workers were elevated above concentrations of these pesticides in the house dust of non-agricultural workers. This occurred regardless of proximity to the farmland. Residues of agricultural pesticides were detected on the work boots, vehicle steering wheels, and children's hands of many of the agricultural families, but not of the reference families. Moreover, children whose parents reported garden use of insecticides had higher levels of organophosphate pesticide metabolite than did children whose parents did not use garden insecticides. Workers who were involved in mixing, loading, or applying pesticide formulations had detectable levels of pesticide residues in their house or vehicle dust, compared to those who did not perform these job tasks (Coronado *et al.* 2004). It was found that workers who thinned crops appeared to have greater levels of pesticide residues in their homes and vehicles than workers who did not thin crops. This probably contributed to the levels of pesticides to which children in the households were exposed. It would appear that pesticides brought home on workers' bodies, clothing and shoes accumulated in the home environment, thus potentially exposing children and other family members. The presence of a "take-home" pathway of pesticide exposure was also demonstrated in Oregon by McCauley *et al.* (2001) who showed a direct correlation between the number of agricultural workers living in a household and the concentration of azinphosmethyl found in dust collection from the home. It was estimated by the authors that the median levels would increase by approximately 40% for each additional person living in the house.

Data from a preliminary study conducted by Hernandez-Valero (2001) showed that children of migrant farm workers who were exposed to pesticides *in utero* or through breast-feeding were at high risk of developing associated health problems. Garry *et al.* (2002a) compared the frequencies of birth defects among live-born male and female children according to paternal fungicide use. More male children were born to families whose male partner did not apply fungicides than those who applied these products. Regarding birth defects, more male children were born with birth defects than female children. Comparing birth defect frequencies during the first year of life showed a 1.5 fold or more increase in the frequency of most birth defects compared with an earlier cohort study conducted by the same authors. Spouses of pesticide applicators who used herbicides, insecticides, and fungicides had more miscarriages than any other pesticide application group (Garry *et al.* 2002b). The age at menarche between rural and urban women was also investigated in the same study. Authors suggested that the reproductive life span (menarche to natural menopause) among women who live on farms or rurally (36.5 yr) was somewhat shorter than for women currently living in an urban setting (38.9 yr). This 2.4-yr difference in reproductive life-

span was significantly different. It appears that women who live on farms or in rural areas where pesticides may be used are at greater risk than women living in urban areas. In the same study, significant reductions in male births in relatively small populations were observed. The 25% reduction in male births in the children of applicators that apply herbicides, insecticides, and fungicides was significant, but subject to question on biological grounds. Paternal exposure and use of dithiocarbamate pesticides and combinations of other pesticides led to significant increases in the spontaneous abortion rate among farm women (Savitz *et al.* 1997).

The population of greatest potential risk of exposure to pesticides found in carpet dust are infants and toddlers (ages 0.5 -5 years) who may ingest dust through mouthing of hands, toys and other objects (Whitmore *et al.* 1994). It was concluded in this study that dust ingestion could constitute a substantial proportion of a child's exposure to pesticides in some homes. The data also suggested that a child may be exposed to a greater number of pesticides in the home by ingestion of house dust than by inhalation. Dermal absorption of pesticides from house dust may also be a potential route of exposure for small children. Loewenherz *et al.* (1997) suggested that 44% of children of pesticide applicators were found to have detectable levels of organophosphate residues.

Simcox *et al.* (1995) studied 59 families involved in farming, families residing on farms, and non-agricultural families in the Yakima Valley, and levels of four organophosphate pesticides were compared. Chlorpyrifos was detected in 95% of the homes. House dust concentrations were consistently higher for agricultural families than for non-agricultural families. Pesticide applicators tended to have higher house dust concentrations compared to nonapplicators. There was a 3-fold difference in median chlorpyrifos house dust concentration between farm workers who did not directly handle pesticides and reference families of nonfarm workers who lived in agricultural communities.

Methodology

A statistician (G. Purdie) was consulted concerning the survey instrument, the sample size, and whether the answers (e.g, coding) results were statistically analysable. The outcome of this consultation is summarised below:

Sample size

The names and addresses of individuals who were accredited members of the NPCA were provided to the researcher (NF) through the assistance of that organisation. The NPCA also provided a letter endorsing the survey and seeking for the support of their members (Appendix 8a). The NPCA members included workers who were directly or indirectly involved with 1080. Since the intent of

this survey was only to include workers directly involved in handling 1080, a request was made to the NPCA for a list of 1080 workers. However, the NPCA was unable to identify who were actually handling 1080 and/or contractors carrying out 1080 work. In addition, the NPCA also raised privacy issues regarding the willingness of the contractors providing names of 1080 users. Therefore, the survey questionnaire was sent to all the NPCA accredited members (total = 531).

Survey instrument

A simple postal questionnaire (Appendix 8b) consisting of 15 questions relating to whether or not the respondent is using 1080, job tasks, protective practices and demographic characteristics was developed to gauge the public's exposure to 1080 workers and their families and close contacts. A copy of the questionnaire was sent to the NPCA for any comments/suggestions. The NPCA found the questionnaire acceptable.

Ethical approval (Departmental level) was obtained from the University of Otago Ethics Committee before the survey was conducted. As a requirement of the Ethics approval the completed questionnaires were to be stored at the University of Otago for a period of five years.

Mailing labels of study participants were printed and these were numbered to match numbers on the questionnaires. In this way, responders and non-responders could be tracked down. The questionnaire was sent with a covering letter, endorsement from NPCA, and an addressed stamped envelope. The covering letter highlighted that the results from the survey were strictly confidential and anonymity of replies was ensured in that respondent names would not be recorded for the purposes of data analysis.

Follow-up

The researcher made two telephone calls to two non-respondents, five weeks after the questionnaires were sent out, reminding them to submit their questionnaires prior to the follow-up survey. The follow-up call provided an opportunity to determine that the survey questionnaire was not returned because the participants were not directly handling 1080. It may have been possible that other participants may have also thought the same way, even though the questionnaire requested participants to return the questionnaire and that they should tick the 'NO' box on the questionnaire if they were not handling 1080.

Due to the low response rate (35%) follow-up letters were sent to non-respondents, six weeks after the first mail out. Follow-up letters highlighted an instruction to tick the 'NO' box if they were not handling 1080 and return the questionnaire to the researcher.

Bias

Bias was minimised by sending questionnaires to all NPCA members (see Sample size) as members would represent those who are directly and indirectly handling 1080. The samples would be sufficient to represent the behaviour of 1080 handlers' population. The questionnaires were coded (see Appendix 8b) and encoding was developed with the statistician (G. Purdie) and the validity of the codes was tested by verifying whether or not the codes were statistically analysable. This was done by taking few samples and entering the codes on the data entry programme (see Data entry). The interviewers were trained how to enter the codes on the data entry programme.

Response rate

The follow-up survey increased the response rate to 74% (excluding participants with wrong addresses, total N=474) and a 66% response rate based on the total number of participants (total N=531). The total number of respondents related to those who were directly handling 1080 or not. Among the total number of respondents, 127 respondents were identified as directly handling 1080.

Eligibility criteria

All respondents who were directly handling 1080 were eligible for inclusion in this study. Therefore, only the responses from 127 workers directly handling 1080 were included in the final data analysis.

Data entry

A data entry programme was developed using Microsoft Access 2000. The programme was developed with the assistance of a statistician (G. Purdie) to ensure that the correct coding was entered into each question.

Contractors were trained to enter the data on the data entry programme. During the data entry process, it was found out that there was no field created for "other" for protective clothing. Interviewers provided the data as "write ins", and these were later entered on by the author (NF) to the database prior to statistical analysis.

Validation of data

It was intended to validate data by generating 30 random numbers using Microsoft Excel. However, the survey questionnaires which should have been kept in a secure location in the Department, as a requirement of the Ethics approval, could not be located. It was assumed,

therefore, that the data entered were accurate representation of the data from the survey questionnaires.

Statistical method

Ideally, a power test should be done a priori, in order to determine the sample size. A post-hoc power analysis could have been done to determine the test's power to detect differences of magnitudes that were scientifically meaningful, at the alpha rate employed. However, the sample size had already been constrained by practical issues related to recruiting subjects, i.e., the sample size could not be increased whether or not a power test was carried out, hence a power analysis post-hoc was not performed.

Results from this survey were analysed statistically using the Statistical Analysis System (SAS). The Chi-square test (exact) was the method employed to determine the statistical significance of the data because this test is often used to analyse categorical data (Downie 1983; Harraway 1992).

Data analysis

Ethnicity was categorized as European, Maori/Pacific and Asian/Others, consistent with how the data in the telephone survey (Appendix 9c) were handled. Age groups were formed (as for groupings in the telephone survey) with the added category of "less than 18 years" as there were fourteen respondents in this category.

The sample was small producing even smaller subgroups. However, statistical tests to determine significance of the differences were conducted by forming new variables. Groups were combined in order to perform statistical tests with small subgroups. On their own, some subgroups could not have any analysis done on them. But since the relative proportions of the subgroups pre and post combination are intact, this should not be an issue.

These were:

- A new q11 variable called 'nq11', was formed to have two categories: "Living with others" and "Not living with others";

- Similarly, a new q12 variable referred to as 'nq12' was formed with categories: "Living with children" and "Not living with children";

- Questions 4 and 7 were combined to form a variable with categories: "Brings home contaminated equipment" and "Does not bring home contaminated equipment";

- Questions 8 and 9 were combined to form a variable with categories: "Contaminated vehicle" and "Not contaminated";

- A new q3 variable was formed with categories: "Wears protective clothing" and "Does not wear". A respondent who wears any of the choices listed under question 3 was classified under the first category.

- Similarly for question 5: "Careful with contaminated personal equipment" and "Not careful" (if yes to any of choices 3, 5, 7);

- Same for question 6: "Takes precaution" and "Does not take precaution" (Yes to choice 5).

- Significance tests were performed on each of nq3, nq4_7, nq6, nq8_9 vs. each of nq11, nq12, nq14, and nq15.

- There was no analysis of gender as there were only 6 female respondents.

Results and Discussion

A number of studies have demonstrated that pesticides brought home on worker's bodies, clothing and shoes accumulate in the home environment, thus potentially exposing children and other family members. This statement could potentially apply to 1080 and the likely exposures of people living with them would depend on their working behaviour. A study conducted, for instance by Lu *et al.* (2000), Simcox *et al.* (1995), and Curl *et al.* (2002) suggested that the "take-home" pathway has been a significant contributor to residential contamination in homes of agricultural workers.

Table 2

Description of protective clothing applied by 1080 workers

Protective clothing	Percentage*
Disposable overalls	32
Non-disposable overalls	65
Disposal gloves	60
Non-disposal gloves	41
Mask	57
Boots	82

N=125

* same respondents listed >1 protective clothing

The respondents were asked what types of protective clothing they used when handling 1080 or 1080 baits. The 1080 workers applied one or more of the protective clothing listed in Table 2. Other protective clothing employed but not listed on the Table (frequency =1 or 2) included earmuffs and hardhats/helmets, eye protection, face shield, goggles, raincoat and legging, and wet weather gear.

Table 3

Demographic characteristics of 1080 workers and their work practice of using protective clothing

Characteristic	Uses protective clothing (%)	Does not use protective clothing (%)	Chi-Square
	N = 115		P = 0.49
Living with others	76	10	
Not living with others	13	1	
	N = 113		P = 0.90
Living with children	47	6	
Not living with children	42	5	
Ethnicity	N = 112		P = 0.36
Maori/Pacific Islander	12	0	
NZ European	68	10	
Asian/Others	9	1	
Age (years)	N = 125		P = 0.70
Less than 18	10	1	
18 to 24	3	0	
25 to 34	24	4	
35 to 44	19	2	
45 to 54	24	4	
55 and up	9	0	

There were no associations observed between "uses protective clothing" and "does not use protective clothing" and "living with others" or "not living with others", "living with children" or "not living with children", age and ethnicity (Table 3). No significant associations implied that whether or not there were other people or children living with the respondents did not affect their behaviour regarding use of any protective clothing (they may or may not use protective clothing).

Table 4

Percentage of 1080 workers with respect to bringing home contaminated materials

Work Practice	Percentage
Bring home contaminated materials	24
Does not take home	76

N = 125

Table 4 illustrates the number of 1080 workers who took or did not take home-contaminated materials with them. As can be seen, only a small proportion of 1080 workers took home-contaminated materials, suggesting good work practice.

Table 5

Demographic characteristics of 1080 workers and their work practice of bringing home contaminated materials

Characteristic	Bring home (%)	Does not bring home (%)	Chi-Square
	N = 115		P = 0.75
Living with others	19	3	
Not living with others	67	11	
	N = 113		P = 0.81
Living with children	11	11	
Not living with children	42	36	
Ethnicity	N = 112		P = 0.80
Maori/Pacific Islander	4	9	
NZ European	17	61	
Asian/Others	1	8	
Age (years)	N = 125		P = 0.12
Less than 18	4	7	
18 to 24	1	2	
25 to 34	5	23	
35 to 44	3	18	
45 to 54	6	22	
55 and up	5	4	

There were no associations observed between "bringing home" and "does not bring home contaminated materials" and "living with others" or not "living with others", "living with children" or "not living with children", age, and ethnicity (Table 5).

Table 6

Behaviour of 1080 workers with their personal equipment that have been contaminated with 1080

Work Habits	Percentage*
Leave at work	43
Wash / clean boots	59
Wash separately	61
Wash with other clothes	8
Dry clean	8
Mixed with clean material	3

N =115
* same respondents listed >1 work habits

Respondents demonstrated various working habits with respect to what they did with their contaminated personal equipment (Table 6). There were 61% respondents who washed their clothes separately, followed closely by wash/clean boots before re-entering the work vehicle (59%), and 43% for those who left their items at work to be cleaned. A small percentage appeared to be not taking precautionary measures, for example, those who washed work clothes with other clothes (8%) and mixed them with clean materials (3%).

Other working habits (Frequency = 1) mentioned were:

- protective clothing carried in special container/separately
- rinse and clean all gear on job
- boots changed before entering vehicle/ change footwear
- contaminated clothes on rear of ute in locked box
- disposable gear or contaminated clothing destroyed by company or hazchem unit or goes to landfill
- don't leave contaminated site until it has been fully decontaminated
- lunch is packed separately

Table 7

Demographic characteristics of 1080 workers and their work practice of being careful with contaminated personal equipment

Characteristic	Careful (%)	Not careful (%)	Chi-Square
	N = 115		P = 0.98
Living with others	81	5	
Not living with others	13	1	
	N = 113		P = 0.79
Living with children	48	4	
Not living with children	45	3	
Ethnicity	N = 112		P = 0.88
Maori/Pacific Islander	12	0.5	
NZ European	74	4	
Asian/Others	9	0.5	
Age (Years)	N = 125		P = 0.70
Less than 18	10	1	
18 to 24	3	0	
25 to 34	26	2	
35 to 44	20	3	
45 to 54	26	1	
55 and up	8	0	

Significance tests were performed between "careful with contaminated personal equipment" and the "not so careful" respondents vs. the various demographic characteristics used in the survey. No significant associations were noted in all cases as demonstrated in Table 7.

Table 8

Precautionary measures of 1080 workers to minimise the possibility of contaminations

Precautions	Percentage*
Wash hands	96
Wash face	67
Wash arms	61
Take a shower	34
Wash boots	55
Remove work clothes	61

N = 115
* same respondents listed >1 precautions

When asked what precautionary measures were applied to minimise the possibility of contamination of other materials, all of the respondents appeared to perform one or more of the precautionary measures listed in Table 8. Only one respondent answered that no washing was being undertaken. Other precautionary measures not listed in Table 8, accounting for one response each, include "change boots before leaving", "burn", and "packaged and stored in plastic".

Table 9

Demographic characteristics of 1080 workers and precautions employed to minimise the possibility of contamination of other materials

Characteristic	Take precautions (%)	Does not take precautions (%)	Chi-Square
	N = 115		P = 0.01*
Living with others	86	0	
Not living with others	13	1	
	N = 113		P = 0.29
Living with children	53	0	
Not living with children	46	1	
Ethnicity	N = 112		See Note
Maori/Pacific Islander	13	-	
NZ European	77	-	
Asian/Others	10	-	
Age (Years)	N = 125		P < 0.0001**
Less than 18	4	6	
18 to 24	3	-	
25 to 34	28	-	
35 to 44	21	-	
45 to 54	28	-	
55 and up	9	-	

** Significant at 1% level

* Significant at 5% level

Note: No statistics computed for the ethnicity data as the row or column sum is zero.

It was found from this survey that those who "live with others" appeared to be "more careful" (86%) than if they lived by themselves (13%) (Table 9). However, when the question was focussed primarily on children, the answers of the respondents changed dramatically. It was observed that there was an almost equal proportion of them "being careful" whether they "live with children" (53%) or have "no children living with them" (46%) (Table 9). It appears that children were not treated in a special way as with others living in the same household. This finding was inconsistent with the question relating to "living with others" as respondents were careful irrespective of whether or not children are living with them. The 25-34 (28%), 35-44 (21%), and 45-54 (28%) age

groups were found to be more the "careful" group compared with the other age groupings (Table 9). Age appeared to have a significant effect on the working habits of the respondents.

Children should not be treated as "little adults" (Olin and Sonawane 2003) as they are likely to be more vulnerable to the toxic effects of 1080 because they breathe more air and consume more food and water in proportion to their body weight, 1080 workers should be more vigilant with respect to their decontamination practices. One respondent (not directly handling 1080) commented that "little effort is made to prevent contamination and workers just get on with bagging and throwing up".

With respect to ethnicity, New Zealand Europeans accounted for 77% of the "careful" group. However, the New Zealand Europeans comprised 77% of the respondents and so this may not necessarily imply that the New Zealand Europeans tend to be more "careful" than the other ethnicities. The high percentage may reflect the predominance of New Zealand Europeans in the 1080 workforce.

A strong association ($P<0.0001$) was observed between "taking" or "not taking precautions" and age while an association at 5% level of significance ($P=0.01$) was observed with "living or not living with others". No association was noted between "taking" and "not taking precautions" and with "living or not living with children" (Table 9).

Table 10

Responses of 1080 workers with respect to "vehicle contamination"

Vehicle Contamination	Percentage
Contaminated vehicle	50
Not contaminated vehicle	50

N = 125

In Table 10 there was an equal split between respondents who answered that their service vehicle was being used for personal purposes or that their private vehicle was used to go to work and may have been contaminated with 1080 (50%) and those who "do not contaminate" (50%). It would appear that a large proportion of 1080 workers could be potentially contaminating clean personal belongings and also other people or passengers when the contaminated vehicle is being used for personal purposes. This finding concurs with Curl *et al.* (2002) and Coronado *et al.* (2004) where

the vehicle used for travel to and from work was a vector of chemical transmission, and that the residues found in the vehicle were markers of contamination from worker clothing or skin. Applying these findings to those of the 1080 survey suggests that measures should be taken to minimise vehicle contamination from exposed workers.

Table 11

Demographic analysis of 1080 workers and their attitude towards vehicle contamination

Characteristic	Contaminated (%)	Not contaminated (%)	Chi-Square
	N = 115		P = 0.46
Living with others	45	41	
Not living with others	9	5	
	N = 113		P = 0.07
Living with children	24	28	
Not living with children	30	18	
Ethnicity	N = 112		P = 0.03*
Maori/Pacific Islander	10	2	
NZ European	40	38	
Asian/Others	4	6	
Age (Years)	N = 125		P = 0.87
Less than 18	2	9	
18 to 24	1	1	
25 to 34	13	16	
35 to 44	11	10	
45 to 54	17	12	
55 and up	6	2	

* Significant at 5% level

Whether or not children are living with respondents appeared to not change the worker's behaviour in relation to "vehicle contamination". Similarly, this finding appeared to apply with respect to age, although the 45-54 age group comprised the highest proportion involved with "vehicle contamination" (17%) while for those who "did not contaminate" the 25-34 age group were most frequent (16%). It should be noted that the overall pattern between the 25-34, 35-44, and the 45-54 age groups was the same for these age groups (Table 11).

At the 5% level of significance (P=0.03), an association was detected between "contaminated" or "not contaminated vehicle" and ethnicity. However, no such associations were observed between "contaminated" or "not contaminated vehicle" and "whether or not living with others", "whether or not living with children", and age (Table 11).

When respondents were asked what precautions they applied to minimise the possibility of contaminating other passengers or users of their vehicles, 47% answered that they did not transport contaminated materials, 4% answered that they did not take precautions, 44% pack separately contaminated materials, and other precautions accounted for 5 %.

Table 12

Protective practices of 1080 workers and relationship with their work activities

Activities	Baiting only (%)	Factory and baiting (%)	Chi-Square
	N = 129		P = 0.18
Does not use protective clothing	8	-	
Use protective clothing	79	13	
	N = 119		P = 0.19
Bring home contaminated clothing	23	1	
Does not bring home contaminated clothing	63	13	
	N = 119		P = 0.54
Careful	83	14	
Not careful	23	1	
	N = 119		P = 0.86
Does not take precaution	4	1	
Take precautions	82	13	
	N = 119		P = 0.23
Contaminated vehicle	42	9	
Not contaminated vehicle	44	5	

There were no associations observed between 1080 activities (baiting or factory and baiting) and "whether or not respondents use protective clothing", and "whether or not they bring home contaminated materials", and "whether or not they are careful", and "whether or not they take precaution", and "whether or not their vehicle is contaminated" (Table 12).

The mode of 1080 activities the responders were engaged with did not appear to have affected their working habits. Of respondents who were involved in baiting operations, 79% used protective clothing, 63% did not take home-contaminated materials, 83% were careful, and 82% took precautions. With respect to "vehicle contamination", 42% have answered that they "contaminate their vehicle" while 44% did not appear to contaminate their vehicle (Table 12). Although it appears that a majority of the respondents have exercised some form of precautionary measures, a moderate proportion of the respondents may not be applying precautionary measures thus increasing or potentially putting the health of people living with them at risk.

The PCE report (1994) noted that the possum control industry spent insufficient time and resources developing quality control standards and this attitude has resulted with the public distrust of poisons.

Some comments from those who were not using 1080 are summarised below:

- Most of the work in their area is contracted out now which has created implications for monitoring the performance of their operations (this was also mentioned in the PCE 1998).
- Odd 1080 pellets were seen on the ground.
- Interested in doing work on the effects of land, micro fauna, micro flora, etc.
- Do not work directly with 1080 but on occasion come close to those that do and have noticed that little effort is made to prevent contamination. "Workers just get on with bagging and throwing up".

Summary and Conclusion

This study found several interesting results that would warrant further investigation. Risk perception studies could, in principle, provide information which, together with other kinds of information, such as complaints raised by the general public, would constitute a useful background against which policy can be formed.

1080 workers may be routinely exposed to 1080 as part of their occupation. Many of these workers perform job tasks that have high risk for direct exposure to 1080, such as mixing, loading, or applying 1080 formulations. Under the Health Safety in Employment Act employers are required to ensure that their employees wear personal protective equipment and training be provided to these workers. The workers need to be well informed about risks and appropriate actions that need to be taken.

Respondents appeared to use precautionary measures while engaged in 1080 activities. A minority of respondents had poor working habits which may result in contamination of the people living with them, in particular children. Of great concern was the behaviour of 1080 workers with respect to the use of their vehicles, where half of the respondents appeared to be not taking precautions to prevent their vehicle from being contaminated and may be potentially exposing the people who are in contact with the vehicle to the risk of contamination.

Of particular interest are children and how they may be at greater risk of being exposed to 1080. Cleaning activities at home play a major role in reducing children's exposure. Since, the home environment is not subject to degradative environmental processes such as sun, rain, and soil microbial activity (Simcox *et al.* 1995), the biodegradation of 1080 could occur at a slower pace, on the assumption that the house has been contaminated, than in outdoor soil. Children may be uniquely susceptible to this exposure because they spend greater amounts of time on carpets and floors (where 1080 may accumulate), and they engage in hand to mouth behaviour (increasing their likelihood of ingesting 1080 contaminated materials) (Mills and Zahm 2001).

The findings also suggested that the working behaviours of 1080 workers were not altered according to whether or not they lived with others, including children. Since other studies of pesticides (e.g., Curl *et al.* 2002; Lu *et al* 2000,) have demonstrated "take-home" exposures, 1080 workers also need to be more vigilant with respect to their working behaviour to not only to keep themselves safe but also the people around them.

Studies commissioned by DoC and AHB showed 1080 levels in the urine of 1080 workers, for instance by O'Connor *et al.* (2000, 2001) where there were some samples showing levels above the BEI set by the Department of Labour (Workplace Services). Since biological monitoring was outside the scope of this study, urine samples of those people living with 1080 workers were not determined. However, evidence has suggested that 1080 workers were indeed exposed to 1080 while carrying out 1080 activities. The possibility that 1080 workers may be contaminating people living with them and thus potentially putting them at risk cannot be ruled out. Adequate precautionary measures must be employed at all times when workers are involved with 1080 activities.

Appendix 8b. Endorsement letter from NPCA

NPCA NATIONAL POSSUM CONTROL AGENCIES

Level 5, Agriculture House, 12 Johnston St, PO Box 11 461, WELLINGTON 6034
Telephone +64 4 499 7559 Facsimile +64 4 473 1603;
Email npca@xtra.co.nz Web www.npca.org.nz

Survey into Pesticide Related Issues

A survey being carried out by the University of Otago on issues related to the use of pesticides is commended for your support.

Details on the aims and process to be used are contained in the enclosed letter.

Research into public attitudes on pesticide use should improve our understanding on the safe use of toxins and assist associated public awareness programmes with the challenge of maintaining a supportive climate for pesticide use.

For these reasons we are happy to endorse this survey and your co-operation will be appreciated.

If you have any queries then please direct them to Natalia Foronda, Environmental Health Team, Ministry of Health, Wellington. Refer to the enclosure for contact details.

Yours sincerely,

Maurice Kennedy
National Co-ordinator - NPCA

Appendix 8c. 1080 workers postal survey questionnaire

QUESTIONNAIRE

Q.1 Are you using or working with1080?

❑ Yes	❑ No
↓ Go to Q.2	Please return the questionnaire

Q.2 Which of the following activities are you involved? (PLEASE TICK ALL THAT APPLY.)

- ❑ Factory exposure:
  - ❑ Mixing & handling 1080 concentrate solution
  - ❑ Manufacturing of 1080 cereal baits
- ❑ Baiting operations using 1080
  - ❑ Aerial, carrot
    - ❑ Preparation of 1080 baits, i.e. spraying of diced carrots
    - ❑ Loading & handling 1080 carrot baits
  - ❑ Aerial, cereal
    - ❑ Loading & handling 1080 baits
  - ❑ Ground application
    - ❑ Application of 1080 baits, e.g. bait stations
    - ❑ Loading & handling 1080 baits

Q.3 What types of protective clothing do you use when handling 1080 or 1080 baits? (PLEASE TICK ALL THAT APPLY.)

❑ Disposable overalls	❑ Non-disposable overalls
❑ Disposable gloves	❑ Non-disposable gloves
❑ Mask	❑ Boots
❑ Other (specify):_____	

Q.4 Do you bring home contaminated clothes/overalls, shoes/boots, and other personal equipment from your place of work? (PLEASE TICK ONE BOX.)

❑ Yes ❑ No

Q.5 What do you do with your contaminated personal equipment? (PLEASE TICK ALL THAT APPLY._

- ❑ Leave at work to be cleaned
- ❑ Wash/clean boots before re-entering the work vehicle
- ❑ Place with uncontaminated materials such as clean clothes
- ❑ Wash work clothes separately
- ❑ Wash with other clothes
- ❑ Dry clean
- ❑ Pack together with lunch bag
- ❑ Other

Q.6 What precautions do you apply to minimise the possibility of contamination of other materials? (PLEASE TICK ALL THAT APPLY.)

- ❑ Wash hands
- ❑ Wash face
- ❑ Wash arms
- ❑ Take a shower
- ❑ No washing undertaken
- ❑ Wash boots thoroughly before leaving place of work
- ❑ Remove work clothes before leaving work
- ❑ Other

Q.7 Do you take home-contaminated equipment other than personal items from your place of work? (PLEASE TICK ONE BOX.)

❑ All the time ❑ Some of the time ❑ Never

Q.8 Do you use your service vehicle (if any) for personal purposes other than 1080 related activities? (PLEASE TICK ONE BOX.)

❑ All the time ❑ Some of the time ❑ Never

Q.9 Does your private vehicle used to go to work get contaminated with 1080? e.g. loading contaminated equipment and/or personal belongings? (PLEASE TICK ONE BOX.)

- ❑ All the time
- ❑ Some of the time
- ❑ Never
- ❑ Use public transport instead

Q.10 What precautions do you apply to minimise possibility of contaminating other passengers or users of your vehicle? (PLEASE TICK ONE BOX.)

- ❑ Pack separately contaminated materials
- ❑ No precautions
- ❑ Not applicable (don't transport contaminated materials home)
- ❑ Other

Q.11 How many people are living with you? PLEASE SPECIFY _____

Q.12 How many children are living with you? PLEASE SPECIFY _____

Q.13 Your Gender

❑ Male ❑ Female

Q.14 Your Age (Please specify) _____years

Q.15 Your Ethnicity. (PLEASE TICK ONE OR MORE IF APPROPRIATE).

- ❑ European
- ❑ Maori
- ❑ Pacific People
- ❑ Asian
- ❑ Other (Specify)_____

Thank you. Please return your survey using the envelope provided.

Appendix 9a. Telephone survey on public perception of risk from the use of pesticides and 1080

Disclaimer: This telephone survey was conducted by contractors. This survey was excluded from the main text of the thesis because of some issues raised with respect to the 100% reported response rate in the regions surveyed by the contractors in comparison with about 50% or more response rates generally achieved in such surveys, and found in the survey conducted by the author (NF). Apparently, there has been a miscommunication between the contractors and NF and the number of non-respondents were not recorded. The analyses were based on the data provided, and the author does not make any warranty for the accuracy of the data. This Appendix is attached for readers' information and interest, and the data have been used for comparison purposes only because of reservations around the response rate.

Public perception of risk from the use of pesticides and 1080

In June 1990, the Department of Health (now the Ministry of Health) commissioned a study describing the public attitudes to the use of chemicals (Department of Health 1990). A sample of 800 respondents was randomly selected from the 18 regional telephone directories (White Pages). The survey was conducted by telephone. The survey findings indicated a significant level of public concern over the risk from pesticides. There was little support for an absolute ban on these products and there appeared to be a considerable support for more regulatory control.

The 1990 report recommended conducting a similar survey in 1995 to check if public attitudes have changed (Department of Health 1990). However, no follow-up study was carried out which may likely be due to changes in the health sector. Therefore, this study has included a follow-up telephone survey with respect to risk perception from the current use of pesticides with emphasis on 1080.

Selected studies reviewed

An attempt was made to carry out a literature search on the risk perception of pesticides, with emphasis on 1080. Only the most relevant research studies were reviewed for the purposes of this study. Other subjects, such as electromagnetic field were also included, for example, for interest.

People respond to hazards that they perceive (Slovic *et al.* 1981). Environmental threats, such as for instance drinking water contamination, air pollution, hazardous waste disposal, can have a tremendous impact on the public. Classic examples were the Love Canal[15] and the Three Mile Island[16], which created intense community concern, e.g., potential health (Schwartz *et al.* 1985)

[15] Love Canal was a landfill for chemical waste disposal and subsequently converted to residential properties.
[16] Accident happened when a nuclear reactor suffered a partial core meltdown.

and the confidence of the public with respect to the ability of the government in protecting its constituents (Bruhn 1992). In New Zealand, 1080 aerial application has been challenged by the community because it involved high environmental risks, particularly contamination of drinking water and impacts on non-target animals (Morgan 1998).

Attitudes to "pest seriousness" tend to vary according to the age and sex of the person concerned. In general, older respondents were more concerned about pests than were younger people. Nearly 65% of the respondents thought that not enough was being done to control possums, with a higher proportion of older people and males perceiving this (Sheppard and Urquhart 1991). For possums control, 70% of the rural people supported the use of trapping while the urban population accounted for 54%. Males appear to support the use of cyanide more than women, accounting for 58% and 33%, respectively. Over 50% of males found the use of 1080 for possum control "very suitable" or "suitable" while only 38% of the females supported its use. There were 56% females who considered the use of 1080 "very unsuitable" or "unsuitable" vs 39% of the male respondents.

In a telephone survey conducted by Fitzgerald *et al.* (2000), respondents were asked to rate their acceptability to manual (shooting and trapping), poisoning (aerial and ground baiting), and biological methods for killing possums. Females were found to be less accepting of all the technologies mentioned than males. The most acceptable methods for killing possums were shooting (82%) and trapping (67%). The poisoning method included ground application of 1080 poisoned bait, aerial application of 1080 poisoned bait, other poisons, and a hypothetical poison that kills only possums. Of these, a poison that kills only possums was considered the most acceptable, and was rated the most acceptable of all the technologies used in the study. Aerial application of 1080 and use of other poisons were the least acceptable of all the control methods listed. An apparent growing concern over the use of poisons, especially the use of 1080 was confirmed by the public focus group included in the study. Aerial use of 1080 was seen as of greater risk by respondents as opposed to biological controls, with males rating the risks lower than females. Participants, especially the females did not trust experts, despite reassurances about the safety of 1080.

A study carried out by Horn and Kilvington (2002) suggested that Maori opposed to 1080 use were of the view that the risk to human health and the environment was "worse" when 1080 was dropped aerially because they felt that this was a less uncontrollable operation that when bait stations are used. Dog owners were concerned about their animals because of the proven 1080 toxicity to dogs. The same authors also mentioned that respondents considered 1080 as a problem because it was most commonly used in large-scale aerial operations.

Several characteristics of individuals, such as gender, race, and sociopolitical attitudes, were related to differing levels of risks. Flynn *et al.* (1994) found that perceptions of risk were higher for women for every hazard studied which included a diverse set of technologies (e.g., nuclear power, commercial air travel), lifestyle risks (e.g., cigarette smoking, drinking alcohol), and environmental conditions (e.g., ozone depletion, radon). The concern about technological and environmental health risks shown by people of colour (e.g., Hispanic, Asian, Black, American Indian) was also clearly documented in the same study. The percentage of high-risk responses was greater among people of colour on every item. This study showed that "non-white" males and females were much more similar in their perceptions of risk than were white males and females. Finucane *et al.* (2000) studied the perceptions on a wide variety of environmental and health hazards, including blood transfusions, motor vehicles, nuclear power plants, and vaccines. The study showed gender differences in risk perception on every item, more females had high-risk responses than males. Racial differences were also reported, the percentage of high-risk responses was greater for "non-whites" (e.g., African-Americans, Hispanic, Asia, American Indian) on every item. White males differed from others in their ratings of perceived risks to individuals and the public, a finding that has come to be known as the "white-male effect". In New Zealand context, "non-whites" will include Maori, Asians, Pacific Islander, Africans, etc.

Concern about contamination of a public drinking water supply was highest among the younger respondents, among women, and among those whose children were under 18 (Hamilton 1985). Similarly, toxic waste problems were particularly alarming to women with young children (Hamilton 1985). Howe (1990) investigated the relationship between regional differences and public health concern about chemicals. The results showed that women were "more concerned" than men about exposures, pollution, and related health effects regardless of region. Sex was modestly but significantly correlated to overall attitudes on pesticide use, with women being more "anti-pesticide" than males (Dunlap and Beus 1992).

In a study of the perception of risks of prescription drugs, Slovic *et al.* (1989) has failed to find gender differences but detected some age-related influence. An American study (Anon 1978) which reviewed the attitudes of Americans towards predator control suggested that people opposed to predator control were most likely to be urban; aged 18-29 years; white females; students or those with a college education; single; and bird watchers, backpackers or anti-hunting advocates. Conversely, people in favour of control tended to be rural, to be associated with the livestock or fur trapping industries, and to have less than eighth grade education.

A research study by Dunlap and Beus (1992) found that responses to three general items (i.e., safety of pesticides for the human food supply; safety of pesticides for the environment; and possible pesticide contamination of groundwater), indicated a "moderately high level of public

concern" over the safety of pesticides for the food supply, a "higher level of concern" over the safety for their environment, and a "very high level of concern" over pesticide contamination of water supplies, even when pesticides "are used according to approved directions." Results from the same study, concluded that sex, age, and education were found to be modestly but significantly correlated to overall pesticide attitudes. Women, younger adults, and the well-educated were more anti-pesticide than their counterparts. When the safety of pesticides was examined, women were significantly more likely to be more concerned about safety than men and younger adults were slightly more concerned about safety. For the perceived necessity of pesticide use, education was found to be significantly related, with the more educated being more likely to see pesticide use as necessary (Dunlap and Bues 1992). Younger respondents, the well-educated, and those in higher income levels were found to be more likely than their counterparts to express "distrust" in the food industry in protecting consumers from pesticides (Dunlap and Bues 1992). McStay and Dunlap (1983) suggested that women were more likely to express their concern than men for environmental quality through everyday decisions regarding personal behaviour, whereas men are a bit more likely to express their concern by attempting to influence the decisions and behaviours of others.

Risk perceptions relating to "hazardous waste site" showed that concern was "extremely high" before clean up was carried out and "moderately high" after cleanup (Bord and O'Connor 1992). Respondents or someone close to them were asked about their own level of concern arising from exposure to toxic chemicals. Over 80% expressed "high concern" for adult and childhood cancers, birth defects, and leukemia. Over 70% expressed "high concern" for liver, kidney, and bladder problems, lung problems (not cancer), miscarriages, skin problems, and other serious childhood diseases. As supported by previous studies mentioned, e.g., McStay and Dunlap (1983), females tend to make higher health risk estimates than males. The pattern for education was found interesting as it was suggested that concern was not significantly linked with education. It may be possible that education improves people's risk estimates, but may not lower their levels of concern.

Most often, expert and lay views of environmental health risks were found to be inconsistent. Judgements of lay people of risk were related more to other hazard characteristics, for instance, catastrophic potential or threat to future generations (Slovic 1987). Slovic *et al.* (1981) suggested differences in risk judgements between lay people and experts, and reported many similarities between the lay people's groups while the views expressed by the experts differed markedly from them. For example, the experts viewed electric power, surgery, swimming and X-rays as "more risky" than did the other groups and they judged nuclear power, police work and mountain climbing to be much "less risky". Lay people sometimes lack certain information about hazards. However, their basic conceptualisation of risk was much richer than that of the experts and

reflected legitimate concerns that were typically omitted from expert risk assessments (Slovic 1987).

The extent and nature of the risks posed by pesticides have been clarified by several risk perception studies which compared the perceived risks of pesticides to those of range of technologies and activities (Dunlap and Beus 1992). For example, results of a survey of three Northern California communities survey showed that 63 percent of respondents were "very concerned" over "pesticide residue in food," and ranked fourth in a list of ten potential hazards (Pilisuk *et al.* 1987). The findings of Slovic (1987) generally concur with these results, which demonstrated that the risks posed by pesticides were ranked "relatively high" (generally in the top third) among a wide range of 30 potential risks by both citizen groups and experts. "Unknown risks" and "dread risk" (i.e., nuclear power and nuclear war) were consistently found to produce high ratings of overall riskiness. The public tended to view pesticides as constituting a relatively major risk. This was not surprising as pesticides were viewed as a threat that was not well understood; that has delayed, long-term, and potentially fatal consequences; and therefore "dreaded" (Dunlap and Bues 1992).

In the UK, issues that were associated with "popular concerns" and "outrage" were landfill sites, chemicals, food additives, dental amalgam and so on, and not smoking, obesity, poor diet, speeding and lack of exercise (Wessely 2005). This demonstrates that voluntary risks were far more acceptable than involuntary ones. Risks under an individual's direct control were less threatening. Hazards considered to be voluntary tend to be judged as controllable, and hazards whose adverse effects were delayed tended to be seen as posing risks that were not well known (Slovic 1987).

Potter and Bessin (2000) carried out a telephone survey to ascertain people's attitudes and understanding about termites and their control. Ninety three percent of respondents expressed "concern" about the application of termiticides inside their home while 75 percent indicated they were "very concerned". In their 1994 survey, there were only 36 percent who said that they would be "very concerned" about using pesticides in their home. This was an increase of 39 percent compared with the 2000 study. Women were found to be "more apprehensive" than men, where 85% of female respondents expressed a "high level of concern" about termites vs 68% of males. Fischer *et al.* (1991) explored what risks laypeople were concerned about. Women mentioned "environmental risks" much more than men, whereas men were more likely to mention "safety and health risks". Women were, however, more likely to mention "environmental risks", (e.g., conventional pollution, exotic pollution), and respondents were more likely to mention "mundane risks" to "health, safety, and personal and social well-being".

More women were concerned about risks than were men in all the items describing "technological risks" used in a study conducted by Pilisuk *et al.* (1987). Contaminated drinking water ranked first

(79%) in the "very concerned" group. In contrast to the gender differences, age of respondents was not significantly associated with expression of concern on any item. While males and people with higher levels of income and education were "less concerned" than lower status females, concerns were, however, expressed by major percentages among every category of respondents. Those who expressed "nonconcern" on one or more of the items tended to be males, with more years of education, less religious, and with higher incomes. Thirty five percent of the respondents felt that people living in the affected communities had little or no influence on risk decision outcomes, while a majority (65%) responded in the "great influence" category.

There was a wide perception that the quality of the environment was deteriorating and this deterioration was seen as posing a direct threat to the health and well-being of humans (Dunlap 1991). Three significant correlations were found among the 25 hazards (e.g., water pollution, storms, pesticides and herbicides) listed in the Environmental Appraisal Inventory (EAI) and demographic variables (Schmidt and Gifford 1989). Females "perceived slightly" more threat to the environment from the hazards listed in the EAI than males. Males perceived "higher levels of controls" than females, and "perceived control" increased with age. Water pollution was ranked 4th as a "threat to the individual" and 5th as a "threat to the environment". Close ranks were seen in pesticides and herbicides, 7th as a "threat to the individual" and 5-6 as a "threat to the environment". Although the "perceived threats" were high, respondents "perceived water pollution, pesticides and herbicides" as more controllable than the other hazards being 4th and 11th in rank, respectively.

The public concerns among three New York regions with respect to sociodemographic characteristics (i.e., gender, age, education, race, urbanisation, and home ownership) and "perceived proximity" to potential exposure sources were explored by Howe (1990). Regional differences were observed and most concerns were noted in the Long Island residents, followed by western New York. In all three regions, "concern about exposure" was significantly higher for women, among persons with 9 to 11 years of education. Exposure concerns were highest among respondents who believed that they "lived either close or very close to a toxic dump site or to an area of high pesticide use".

The difference between the opinion of French and Belgian public with respect to risk was investigated by Carle *et al.* (2004). The data for the two populations were rather similar with respect to perception of "nuclear risk" as compared to perception of "chemical risks". French people considered the "chemical risk" to be more important than the "risk of nuclear power stations", which could probably be due to the chemical plant disaster that occurred in Toulouse[17] in 2001. This difference was much smaller in Belgium. When asked whether the truth has been told

[17] Explosion of a warehouse that stored ammonium nitrate.

to them, most of the people thought they have not been told the truth about risks. In France, the number of people that assumed that they were not informed correctly about the fallout of Chernobyl [18]was remarkably high.

Whitford (1993) suggested that farmers were inclined to positive attitudes about pesticides because they were familiar with the risks and benefits of preventing crop destruction from pests that can be observed easily and immediately. While the non-agricultural population was more inclined to focus negatively on the "potential risks of pesticides" because they have no control over other pesticide applications, don't understand or were doubtful of the value of pesticides in the agricultural system, and were concerned about unknown or delayed health problems.

The association between social equity and risk was investigated by Zimmerman (1993). The question of whether or not "hazardous waste sites" were disproportionately located in communities that may have fewer financial and political resources to alleviate such conditions showed that for more than 600 communities housing over 800 hazardous waste disposal sites on the National Priority List (NPL) sites, Black populations were approximately 50% higher than the equivalent proportions in the nation as a whole. When the weighted average percentage of Blacks, Hispanics and persons below the poverty level were compared, taking into account concentrations of minorities in large communities, communities with NPL sites had a larger proportion of Blacks than was typical of the nation (18.7% vs 12.1% or about 50% or more). A similar pattern was found for Hispanics, while no pronounced difference appeared for percentages of the populations below the poverty level.

A small survey (N = 43) was conducted by Hammitt (1990) relating to risk perceptions and consumer choice between organically (without pesticides) and conventionally grown produce. Consumers perceived residual pesticides and other synthetic chemicals as creating a "significant health risk". Respondents who purchase organic produce were willing to pay a substantial premium to avoid pesticide residues. They also said they were fearful of a broad range of ill effects due to pesticide residues, growth stimulants, and fertiliser. The adverse effects arising from these substances were believed to be cumulative and delayed.

Maderhaner and Guttmann (1978) reported the hazard perceived by the respondents in relation to the distance of seven types of public facilities, i.e., nuclear reactor, oil refinery, airport, gas works, prison, district heating facility, and mental hospital. The study suggested that frequent contact with a nuclear reactor "reduces the perceived hazard". The study group living 1.4 km from the reactor has perceived to be "riskier" than the nearer group (0.5 km) and the control.

[18] Explosion of Chernobyl nuclear power plant.

Cultural and environmental features may affect the element of perceived risks. Australia and New Zealand may perceive risks differently from people of other nationalities because of the differences in real risks (Rohrmann 1994). Australia and New Zealand have unique climates and environments and also unique lifestyles, which may heighten or attenuate real risks and be reflected in risk perceptions. For instance, Rohrmann (1994) found that, compared with Germans, Australians and New Zealanders gave lower risk ratings for "conventional" technologies such as airports (which were more likely to seem essential to Australians given their relative isolation from other countries) and coal power plants (also essential because of Australia's less advanced industrialisation). However, Australians and New Zealanders gave higher risk ratings than Germans to environmental pollution and large-scale technology such as nuclear power. Given that no nuclear power plants existed in Australia and New Zealand, perceptions of nuclear power may be reflecting fears of the unknown and of catastrophic consequences.

The risk perception before and after reading the brochure on electromagnetic fields (EMF) was also investigated by MacGregor *et al.* (1994). The findings suggested that the naive beliefs about the potential of EMF exposure to cause harm were highly influenced by specific content elements of the brochure. Concerns were relatively low for most sources of exposure to fields prior to reading the brochure. Respondents expressed the following concerns after the brochure: "higher perceived risks" from sources of EMF exposure; "greater dread", particularly regarding power line risks; "greater perceived control" over these risks; "less perceived" equity; and "greater concerns" regarding health effects of EMF.

Methodology

A statistician (G. Purdie) has been consulted concerning the survey instrument, selection criteria and the sample size and advised the following:

Sample size

There were a total of 500 participants to this survey. Aside from the number of people surveyed, the response rate is important. A method giving a higher response rate with a smaller number of respondents might be better than one with a lower response rate with a higher number of respondents (G. Purdie pers. comm. 2004). The gain in accuracy between 200 responders (confidence limits for a proportion was not more than +/- 7.1%) and 300 responders (confidence limits for a proportion was not more than +/- 5.8%) was not great. Therefore, based on the assumption that the survey would have at least a 50% response rate, telephone survey of about 500 would be adequate to obtain approximately 250 respondents. The aim was to have reasonable number of respondents that would be statistically analysable, within budget and would not compromise the results of the survey. It is worth noting that the survey was carried out at a time

when marketing companies were making use of telephone promotions and surveys, which may have lessened people's willingness to participate, as experienced in the Wellington region. Another major consideration that was taken into account in determining the number of participants was the budget allotted for the survey.

Selection criteria

The total number of participants to be called in each region was calculated by roughly counting the number of people in each directory (business addresses excluded) and proportionately calculating how many people would be called in each area to provide a total of 500 participants. The numbers of people called for each region were:

Northland = 15
Auckland = 144
Waikato, King Country, Thames Valley = 44
Bay of Plenty = 36
Gisborne = 6
Hawkes Bay = 20
Taranaki = 15
Wanganui = 7
Manawatu = 15
Wellington = 58
Nelson = 14
West Coast = 5
Blenheim = 7
Christchurch = 59
Oamaru/Timaru = 13
Dunedin = 22
Invercargill = 13
Wairarapa = 7

The participants were randomly selected from the regional telephone directories (white pages). One number was selected on every fourth page of the directory. Using Excel, a random number between 1 and 4 pages was generated and a name (number) was drawn from the page chosen, e.g., page 2. Because a phone book has four columns in each page, a random number was generated between columns 1 and 4 of the page chosen. Based on 50 names per column, a random number was generated between 1 and 50 and the name (number) was chosen accordingly. The process was repeated until enough names (numbers) had been generated.

Survey instrument

The interview tool comprised a structured questionnaire based on Department of Health 1990 study. The questionnaire was modified and divided into two parts. The first part included risk perceptions questions involving pesticides only. The second part prescribed specific questions relating to 1080. The second part repeated many of the questions in the first part but the reference to 1080 was changed to pesticides (see Appendix 9c). The revised questionnaire took approximately 10 minutes to read.

Ethical approval (Departmental level) was obtained from the University of Otago Ethics Committee before the survey was conducted. The completed questionnaires have been stored at the University of Otago for a period of five years as a requirement of the Ethics approval. The revised questionnaire was pilot tested in the Wellington region. There were no problems encountered in understanding the questions asked, although one respondent found the questionnaire long and decided to stop before finishing the interview.

Interview process

A screening sheet (see Appendix 9b) for the telephone interviewers was also developed. Two contractors were trained to make the calls in all the non-Wellington regions and experiences encountered in the Wellington region, e.g., how to politely introduce yourself to the participants, not to use the word 'survey', if necessary, but instead use alternative words, such as "study", were shared to the interviewers to give them some general ideas on the nature of the survey.

The instruction sheet developed for the interviewers contained the following information. Each survey form was prepared and the telephone number called. People aged 18 and over within the dwelling were eligible for interview. If there was no answer, the number being called was written on the box allotted on the first page of the survey form. One call back was made to telephone numbers where no contact was made. The call back was made on a different day in a different time period. Up to two call backs were made to the selected respondent if the interview was not completed on the first call. The call back was made on a different day in a different time period. If unsuccessful, this call was recorded as "no contact". All people called who refused to participate were recorded "refused to participate". The telephone directories used in making the calls were listed in the telephone survey form (Appendix 9c).

Bias

The likelihood of bias was reduced by random sampling. Each person was chosen entirely by chance (see Selection criteria). The questionnaire was trialled in the Wellington region to ensure that participants understood the questions. The questionnaires were coded (see Appendix 9c) and encoding was developed with the statistician (G. Purdie) and the validity of the codes was tested by verifying whether or not the codes were statistically analysable. This was done by taking few samples and entering the codes on the data entry programme (see Data entry). The interviewers were trained how to enter the codes on the data entry programme.

Response rate

There was a 94.8% response rate to this survey. A 100% response rate was achieved in all regions with the exception of Wellington (59%) and Manawatu (87%). The response rate in the Wellington region was lower when compared with the other regions. Reasons for this were varied, such as participants refused to participate, very busy, not interested at all, and unavailability. This author (NF) noted that the word "survey" appeared to be unattractive to participants. Few participants said that they were not interested on any type of survey, while those who answered that they were busy and asked what would be the convenient time to call back said they were not interested.

Data entry

A data entry programme was developed using Microsoft Access 2000. The programme was developed with the assistance of a statistician (G. Purdie) to ensure that the correct coding is entered into each question. Questions 9 and 20 were not answerable by 'yes' or 'no' and were coded as free text.

Contractors were trained to enter the data. Responses were recorded initially on the survey form and then the data were entered on the programme. During the data entry process, it was found out that there was no field created for 'main 1080 concern'. Interviewers provided the data as 'write ins', and these were later entered on to the database by the researcher (NF) prior to statistical analysis.

Validation of data

One hundred samples were randomly selected using Microsoft Excell. These samples were compared with the data entered on to the data entry package and were considered to be accurate representation of the data obtained from the survey questionnaires.

Statistical method

Full analysis of the data was undertaken using the Statistical Analysis System (SAS). The Chi-square test was utilised in determining the statistical significance of the data. The Chi-square test was appropriate because it is often used to analyse categorical data (Downie 1983; Harraway 1992) and the samples were independent for testing association in between samples in a two-way table. For a similar reason, the Chi-square test was used for the one-way tables.

Data analysis

Unanswered questions were not analysed because only frequencies of responses were computed for the variables.

Answers coded as free text (Q9 and Q20) were further grouped as follows for further analysis. Answers on Q9 "who was spraying" were coded as Council – 1; Neighbour – 2; Others – 3 and Q9 "what was being sprayed" were coded as 1 for weed killer, general spray, including garden and domestic sprays; 2 for orchard, vineyard and farm; and 3 for others. There were no answers for "where was being sprayed". For Q20, answers were coded as 1 – human health effects including long-term effects, birth defects; 2 – environmental effects including soil; 3 – animal effects; and 4 – others. Non-response for these free text questions was too high (93% of the data are missing) to allow for any meaningful analysis to be further carried out.

Among the demographic variables used in the study, only age and gender were compared against the 2001 Census of Population and Dwellings (Department of Statistics 2001) to see if respondents have projected the actual population or a random selection of participants was achieved. Analysis showed that males, 18-24 years were relatively higher than the other age groups compared with what should have been actually sampled. As suggested by the statistician (R. Namay), ethnicity and region were not included because based on expert opinion, for some variables such as Maori and regional benchmarks, there was considerable bias observed (more than 15%) in the survey estimates. Potential issues raised were the number of benchmark variables and what can be done to lessen the non-sampling error of source.

Aggregation was performed on some of the variables to carry out meaningful analyses. Those who were aware that they have issues/concern with pesticides were categorised as having "pesticides concern". All other responses ("no opinion", "no concern", "don't know") have been aggregated to form a second group of respondents. The same aggregation method was used in relation to those having "1080 concern".

Multiple ethnicities were a problem. Without aggregation of ethnicities, some ethnic group counts are too low to allow for a meaningful statistical significance analysis. Ethnicity was aggregated to form the following groups: Maori/Pacific Islander, NZ European and Asian/Others.

Furthermore, a "domicile" variable with two categories was created. The categories were "City/Suburb" dwellers and "Town/Country" dwellers. Also a new variable pertaining to "knowledge of 1080 usage" in the area was formed. Two groups defined the variable formed as

those "aware" that 1080 is used in their area and those who "don't know" or "claim that it was not used".

The number of respondents of "among those with 1080 concern" (N=171) has been filtered from among those "1080 aware" as it is logical to assume that only those who were "1080 aware" would have some "1080 concern" (Table 13).

Table 13

"1080 Concern" and Knowledge of 1080 Usage

"1080 Concerns"	Knowledge of usage	
	Aware (%)	No/don't know (%)
With concerns	8	46

N = 171

Results and Discussion

According to the definition of the Food and Agriculture Organisation (FAO) International Code of Conduct on the Distribution and Use of Pesticides, a pesticide is "any substance or mixture of substances intended for preventing, destroying, or controlling any pests, including vectors of human or animal disease, unwanted species of plants or animals causing harm during or otherwise interfering with production, processing, storage, transport or marketing of food, agricultural commodities, wood and wooden products or animal feedstuffs, or which may be administered to animals for the control of insects, arachnids or other pests in or on their bodies. The term includes substances intended for use as a plant-growth regulators, defoliant, desiccant, or fruit tinning agent for preventing of premature fall of fruit and substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport." (Kaloyanova and El Batawi 1991: 1).

Based on the FAO definition, 1080 is classified as a pesticide. However, from a layperson's point of view, pesticides would generally mean those substances which, for instance, are being used as weed killer, or home garden sprays. Hence, from this survey, specific questions were asked relating to 1080 to obtain the public perception with respect to this compound.

Table 14

Distribution of Biggest/Main Pesticide Concern

"Biggest/Main Concern"	Percentage	Chi-Square
Animal effects	63	P <0.0001*
Environmental effects	16	
Long-term effects	21	

N = 281
** Significant at 1% level

As shown in Table 14, there was a strong association ($p<0.0001$) noted when respondents were asked about their "biggest/main concern" with regard to the use of pesticides in the environment. The majority of the respondents (63%) claimed that their "biggest/main concern" about the use of pesticides relates to danger to animals. This was followed by concerns due to its long-term effects (21%) and from a public health point of view was considered to be of direct relevance to this study. The views expressed by Dunlap and Beus (1992) that threat from pesticides are in agreement with this study that threat from pesticide use was not well understood, has delayed, long term and potentially fatal consequences. However, what specific pesticides respondents' were worried about cannot be identified from this survey.

Table 15

Public's opinion with a selection of statements about pesticide usage

Statements	Agree (%)	Disagree (%)	No Opinion (%)	Chi-Square
a) "The public knows enough about the health risks of pesticides".	31	65	4	P< 0.0001*
b) "There is not enough available information about the health risks of using pesticides."	49	43	8	P< 0.0001*
c) "The controls on the use of pesticides are adequate".	35	43	22	P< 0.0001*
d) "Not enough care is taken when people use pesticides."	69	19	12	P< 0.0001*
e) "There is too much fuss made about the risk from pesticides".	25	70	5	P< 0.0001*
f) "All pesticides should be banned."	8	82	10	P< 0.0001*
g) "The long term health risks of pesticides are worrying."	67	24	9	P< 0.0001*

N = 476 except statement (g) where N = 475

** Significant at 1% level

The survey results are in agreement with the 1990 study where 89% of the respondents disagreed with an absolute ban of all pesticides while there was a split between whether respondents "agree" (35%) or "disagree" (43%) that the controls on the use of pesticides were adequate (Table 15).

For each statement asked with respect to pesticide usage in Table 15, a significant difference ($p<0.0001$) was observed among the "agree", "disagree", and "no opinion" respondents. People who think that "too much fuss is made about the risk of pesticides" accounted for about 25% of the respondents while 67% of the respondents were of the opinion that "the long-term effects of pesticides were worrying." A high proportion (65%) of respondents disagreed that "the public knows enough about the health risks of pesticides". Similarly, a majority of respondents tend to

agree that "not enough care is taken when people use pesticides" (69%) while 49% were of the view that "not enough available information about the health risks of using pesticides" and 82% disagreed "that all pesticides should be banned."

Table 16

Relationship between "pesticide concerns" and "1080 concerns"

"Pesticides Concerns"	"1080 Concerns"		Chi-Square
	With concerns (%)	No/don't know (%)	
With concerns	44	19	P <0.0001*
No/don't know	10	27	

** Significant at 1% level

N = 320

It can be deduced from Table 16 that those with "pesticide concern" were those of "1080 concern" as well. A strong association (P <0.0001) was observed between the ways the respondents answered the question on "1080 concern" vs the way they answered the "pesticide concern" question. A high percentage (82%) of those with "1080 concern" also had "pesticide concern". Conversely, around 70% of those with "pesticide concern" have "1080 concern" as well.

Table 17

Demographic analysis of groups who are concerned about pesticides

Characteristics	"Pesticide concern"		Chi-Square
	With concerns (%)	No/don't know (%)	
Educational Qualification	N = 427		P = 0.17
1 – 2 years school	10	6	
Qualification [1]	8	6	
School Certificate	17	9	
University Degree	25	11	
University 1 year	4	4	
Domicile	N = 477		
City & Suburbs	6	3	P = 0.73
Town & Country	56	35	
Ethnicity	N = 477		
Maori/Pacific Islander	5	5	P = 0.28
NZ European	50	31	
Asian/Others	6	3	
Age (years)	N=474		
18 –24	3	4	P < 0.0001**
25 –34	9	6	
35 - 44	15	7	
45 –54	14	6	
55 and up	22	14	
Gender	N = 469		
Male	23	19	P=0.0013**
Female	40	18	

[1] Trade qualification, technical qualification or some other qualifications

** Significant at 1% level

The concerns of the different population subgroups were generally quite similar. It appears that those who obtained a University degree have much more "1080 concern" than those who finished lower qualifications (Table 18), who tended to have less concerns. A similar trend was noted to respondents who have a "pesticide concern" (Table 17). Bord and O'Connor (1992) and Dunlap and Beus (1992) suggested that the well educated appeared to be more anti-pesticide than their counterparts. This statement appears to concur with the findings of this survey.

There was a modest gender difference found in this survey with respect to their belief about 1080 concerns (significant at 5% level, P=0.0286). Females were likely to be more concerned (32%) than males (22%) (Table 18). This finding was supported by a survey carried out where women were more opposed to the use of cyanide than men (Sheppard and Urquhart 1991). Of the general sociodemographic variables that have been studied, there was some evidence that gender and age may influence evaluations of risk, although the precise interpretation to be placed upon such findings was uncertain. Several studies found that women perceived more threat to the environment than men (Schmidt and Gifford 1989; Pilisuk *et al.* 1987; Fischer *et al.* 1991).

Respondents aged 55 and above were "more concerned" with 1080 (18%) than their younger counterparts (Table 18). Similarly, the same trend was observed in relation to those who were "pesticide concerned" with respect to gender and age (Table 17).

The findings from this current survey appear to be consistent with the findings by Anon (1978) and Dunlap and Beus (1992) that those living in "city and suburbs" have low percentage of 1080 concerns (5%) (Table 18) and because they are less 1080 concerned, they may favour the use of 1080. Those who were classed as "town and country dwellers" (49%) were more concerned and would probably not support the use of 1080. This rationale is consistent with Nelkin (1989) and Howe (1990) that people's distance from the source of risk and the consequences also appeared to influence risk perception. Pesticides followed a similar profile where those living in "town and country" were more of concerned than those living in "city and suburbs" (Table 17). This finding is inconsistent with Whitford (1993) where the author has concluded that the non-agricultural population was more inclined to focus negatively on the potential risks of pesticides. Pesticides followed a similar profile as shown in Table 17.

Respondents from this study who suggested that they have "no/don't know 1080 concerns" (41%) live in "town and country" and the "city and suburbs" dwellers (5%) were the groups that were accounted for (Table 18). The same trend was observed in "no/don't know pesticide concerns" as shown in Table 17. The findings may concur with Whitford (1993) on the assumption that those living in "town and country" may engage in some form of farming activities. Farmers were inclined to form a positive attitude about pesticides because they are familiar with risk and because the benefits of preventing crop destruction from pests can be observed easily and immediately.

When the respondents were filtered to only those who are aware of 1080, no association was noted between "1080 concern" and all the demographic variables, namely age, educational qualification, ethnicity and domicile (Table 18). It is interesting to note that the educational qualification, domicile, age and ethnicity do not play a critical factor about the level of "1080 concern" among

the respondents. However, gender does matter as demonstrated by the 5% level of significance (P=0.0286) observed between them although the association was modest (Table 18).

Table 18

Demographic analysis of groups who are concerned about 1080

Characteristic	"1080 Concerns"		Chi-Square
	With concerns (%)	No/don't know (%)	
Educational Qualification	N = 284 [b]		P = 0.6885
1 – 2 years school	7	6	
Qualification [a]	9	9	
School Certificate	11	9	
University Degree	23	17	
University 1 year	4	5	
Domicile	N = 320 [b]		
City & Suburbs	5	5	P = 0.2438
Town & Country	49	41	
Ethnicity	N = 305 [b]		P = 0.8851
Maori/Pacific Islander	3	3	
NZ European	45	38	
Asian/Others	6	5	
Ages	N = 317 [b]		P = 0.5519
18 –24	3	3	
25 –34	6	6	
35 - 44	12	8	
45 –54	15	10	
55 and up	18	19	
Gender	N = 312 [b]		
Male	22	25	P=0.0286*
Female	32	21	

[a] Trade qualification, technical qualification or some other qualifications

* Significant at 5% level

[b] "1080 aware"

Table 19

How "1080 Concern" affects the knowledge of 1080 usage in local area

"1080 Concerns"	Knowledge of usage		Chi-Square
	"Aware" (%)	"No/don't know" (%)	
With concerns	8	46	P = 0.6504
No/don't know	6	40	

N= 320 ("1080 aware")

No association was noted between having or no "1080 concern" and knowledge of whether or not 1080 is being used in their locality (Table 19). It appears from this finding that the level of 1080 concern among respondents was not affected by whether or not they were aware of 1080 being used in their area. As can be seen, those who were aware of knowledge of 1080 use has only accounted for 8% (with "1080 concern") as opposed to 6% for the "no/don't know" respondents.

Table 20

How "1080 concern" affects the perception on 1080 handling

Perception "1080 Concerns"	"1080 Concern"		Chi-Square
	"Aware" (%)	"No/don't know" (%)	
1080 handling perception	15	25	P <0.0001**
No opinion	39	21	

** Significant at 1%level
N = 320 ("1080 aware")

There was a strong association (P<0.0001) noted between "aware" or "no/don't know" and the way the respondents perceived whether or not controls on the use of 1080 were adequate and whether or not enough care was being taken when people use 1080 (Table 20). The significant association has demonstrated that respondents' awareness of 1080 being used in their locality affects their perception on 1080 use.

Moreover, an association (P = 0.0003) was also noted between having or not having "1080 concern" and the way respondents feel about whether or not the public knows enough about the health risks of 1080 and whether or not there is not enough available information about the health risks of using 1080 (Table 21). These two factors play a significant role in affecting the way respondents expressed their view as being "1080 concerned".

Table 21

How "1080 concern" affects the perceptions on public's 1080 risk awareness

Risk Awareness	"1080 Concern"		Chi- Square
	"With concerns" (%)	"No/ don't know" (%)	
"Aware"	20	28	P= 0.0003**
"No/no opinion"	33	19	

** Significant at 1% level

N = 320 ("1080 aware")

A strong association (P<0.0001) was found between the "biggest/main concern" and those who expressed "1080 concern" about the use of 1080 in the environment (Table 22). The small P-value means that the people do not evenly have the same main concern. Close examination of those with "1080 concern" shows that the major concern that stands out from this group was the effect of 1080 on animals (49%) (Table 22). Long-term effects (20%) and environmental effects (15%) were the next major concerns. Acute effects were relatively of less concern (10%).

The set of concerns evoked by the questionnaire suggested that danger to animals clearly topped the list accounting for 49% and 63% for 1080 and pesticides, respectively. It is known that 1080 is very toxic to dogs as only a tiny amount is sufficient to produce a lethal effect as mentioned in section 4.1.1. A number of PHUs have reported complaints about dogs' deaths (Appendix 7).

Table 22

Distribution of Biggest/Main "1080 Concern"

"Biggest/Main Concern"	Percentage	Chi-Square
Acute effects	10	P <0.0001**
Animal effects	49	
Environmental effects	15	
Long-term effects	20	
Other effects	6	

** Significant at 1% level
Among "1080 concern" = 137

Table 23

How respondent's "1080 concern" perceived their source of drinking water supply

Water supply	Percentage	Chi-Square
Town supply	87	P <0.0001**
Ground (bore)	5	
Tank water	7	
Don't know	1	

** Significant at 1% level

Among "1080 concern" = 171

There was also a strong association (P<0.0001) noted between the "1080 concern" group and their source of drinking water (Table 23) which illustrates that people do not evenly have the same concern. For the same group, the main source of water was the town supply (87%). The other sources were proportionally small compared to the biggest source of drinking water. Ground (bore) water accounted for 5%, tank water (untreated) was 7% and the "don't know" group was 1%.

Table 24

Public's opinion with a selection of statements about 1080 usage

Statements	"Agree" (%)	"Disagree" (%)	"No Opinion" (%)	Chi-Square
a) "The public knows enough about the health risks of 1080". [1]	27	66	7	P<0.0001**
b) "There is not enough available information about the health risks of using 1080." [1]	45	43	12	P<0.0001**
c) "The controls on the use of 1080 are adequate". [1]	34	32	34	P< 0.8203
d) "Not enough care is taken when people use 1080." [2]	31	30	39	P< 0.0918
e) "There is too much fuss made about the risk from 1080". [2]	24	62	14	P<0.0001**
f) " 1080 should be banned." [2]	26	48	26	P<0.0001**
g) "The long term health risks of 1080 are worrying." [2]	48	22	30	P<0.0001**

[1] N = 318 ("1080 aware")

[2] N = 317 ("1080 aware")

** Significant at 1% level

When a specific question was asked about 1080, there were 34% of the respondents who "agreed" that there were adequate controls on the use of 1080 while 32% "disagreed", and 26% of the respondents "agreed" that 1080 should be banned as opposed to 48% who "disagreed" (Table 24). It appears from this survey that although there were people who were opposed to its use, almost half of people surveyed have supported its continued use.

The group of respondents with "1080 concern" (N = 171) was further investigated. There were only 17 people who said they get (or sometimes get) their meat from the farm and only two of these respondents thought that the meat was contaminated, hence no further analysis was done on this group. Only 13 of those with "1080 concern" get (or sometimes get) their meat from hunting so

this group was also not further investigated. Only one respondent said he/she gets milk from the farm so no further investigation was done either.

Long-term effects of both pesticides and 1080 (Tables 14 and 22, respectively) were the next most common category that concerned the respondents followed by environmental effects. Long-term effects of 1080 was the primary focus of this study as there were no known studies to date as to whether or not humans are susceptible to the overt effects of this compound. A 1990 poll indicated that 75% of the American public now share the perception that pesticides posed serious hazard to humans and the environment (Whitford 1993).

Each statement was analysed statistically and p-values were based on whether respondents "agree", "disagree", and "no opinion" expressed on specific statements asked during the survey (Table 24). Across the three categories, the differences were statistically significant ($P<0.0001$) showing strong associations between the ways the respondents answered the question on 1080 usage. A high proportion disagreed that 1080 should be banned (48%) while a high proportion (48%) agreed that the long-term effects of 1080 were worrying. A low proportion (27%) agreed that "the public knows enough about the health risks of 1080", 45% agreed that "there is not enough available information about the health risks of using 1080". When asked whether "the controls on the use of 1080 are adequate", there was an almost even split between those who "agreed" (34%), "disagreed" (32%), and the "no opinion" accounted for 34%. Similarly, the same trend was noted with respect to "not enough care is taken when people use 1080".

Table 25

Summary of people's awareness about public protest about 1080 usage

Protests	Percentage	Chi-Square
Danger to animals	52	P <0.0001**
Harm to environmental	13	
Long-term effects	15	
Acute effects	8	
Others	12	

** Significant at 1% level

N = 48

There were only 48 respondents who answered the statement with respect to their awareness of any public protest about the use of 1080 in their area. Public protest concerning danger to animals

accounted for 52% and long-term effects and harm to the environment were about 15% and 13%, respectively. A low percentage (8%) of public protests with respect to acute effects of 1080 was noted. A strong association ($P<0.0001$) was noted between "1080 usage" and public protests (Table 25).

There was no further investigation carried out as only 23 respondents had "1080 concern" in relation to ethnicity and culture. Various opinions were expressed by respondents about this question including:

- Untested over time/would like more research done on it
- Danger to animals/living things and environment
- Long-term effects on human health and environment
- Harmful effects on pregnant women and birth defects
- Stays long in soil and it does not breakdown
- Harm/risks to health
- Not enough care or control is taken/flagrant use
- Whanau and heritage is at stake if 1080 is used

Summary

Risk perception studies examine the judgements people make when are asked to characterise and evaluate hazardous activities (Slovic 1987), as demonstrated in this survey.

The long-term effects of 1080 and pesticides were consistently of major concern as raised by the respondents. Attitudes to "1080 concerns" tend to vary according to the educational qualification, domicile, age and gender of the person concerned. The most concerned tends to be expressed by females, older people, those with University degrees and those living in town and country. The same trend was observed with regard to pesticides.

A significant association was observed between "1080 and pesticides concern" and gender which indicates that males and females expressed their views differently with respect to their concerns about 1080 and pesticides use. A significant association was also noted in relation to age and 'pesticides concern'.

A large proportion of respondents disagreed that the public knows enough about the health risks of 1080 and pesticides and almost an equal split between respondents who agree and disagree that not enough available information about the health risks of 1080 and pesticides. Despite of these

perceptions, the majority of respondents did not appear to support the ban of either 1080 or pesticides use.

Appendix 9b. Screening sheet

"Good morning/afternoon, my name is _____ from the University of Otago. We are carrying out a nationwide survey on people's attitudes towards the use of pesticides to control vermin. The results from this survey will update the findings of a similar survey done by the Ministry of Health in 1990. This project has been approved by the University of Otago Ethics Committee."

Q.A "My sampling requires me to interview people aged 18 and over. Do you belong to this age group?

IF YES, GO TO Q.B. IF NOT OLD ENOUGH, ASK TO SPEAK TO A PERSON OVER 18. REINTRODUCE THE SURVEY IF NECESSARY. GO TO Q.B. IF NO ONE ELSE IS ELIGIBLE, USE THE FOLLOWING THANK YOU AND TERMINATE.

"Thank you very much for your time, but I can only interview people aged 18 years and over. Goodbye."

Q.B

IF NOT PRESENT

↓

"When would be the best time for me to call back to speak to him/her?

RECORD ON THE SAMPLING SHEET

SAY: "The questions I am going to ask will take about 10 minutes or less to answer. Could you spare me that time now?"

IF BUSY OR RELUCTANT, SAY: "If you cannot spare that time right now, I would very much like to make a time to call you back. It is important that we talk to a good cross-section of people on these issues.

FOR PERSEASION IF NECESSARY: "People who have taken part so far have found it an interesting survey to answer."

NO

↓

TRY FOR AN APPOINTMENT AND RECORD DETAILS ON THE QUESTIONNAIRE, FOR TELEPHONING.

If refused: Thank them for their time.

YES

↓

PROCEED TO THE QUESTIONNAIRE

Appendix 9c. Public perception of risk from pesticides and 1080

QUESTIONNAIRE

Q.1 "In the last 12 months, have you personally come into contact with any pesticides?" (circle ONE only)

Yes – 1 No – 3 Don't know - 5

Q.2 "Do you have any concerns about coming into contact with pesticides?" (*circle ONE only*)

Yes – 1 No – 3 Don't know – 5 GO TO Q6

Q.3 "What is your biggest single main concern about the use of pesticides in the environment? (*circle ONE only. Code to the best match answer given*).

Acute health effects from the use of pesticides – 1
Long –term effects of pesticides– 2
Harm to environment - 3
Danger to animals - 4

Q.4 "Have you personally suffered any illness that, in your opinion, was caused by pesticides?" (*circle ONE only*

Yes – 1 No – 3 Don't know - 5

Q.5 "Have any members of your family suffered any illness that, in your opinion, was caused by pesticides?" (*circle ONE only*

Yes – 1 No – 3 Don't know - 4

Q.6 "Now I'm going to read out some statements and I'd like you to tell me whether you agree, disagree, or have no opinion with each one. Do you agree, or disagree that …" (*read out for each statement, and circle the answer as you go*).

	Agree	Disagree	No opinion
a) "The public knows enough about the health risks of pesticides".	1	3	5
b) "There is not enough available information about the health risks of using pesticides."	1	3	5
c) "The controls on the use of pesticides are adequate".	1	3	5
d) "Not enough care is taken when people use pesticides."	1	3	5
e) "There is too much fuss made about the risk from pesticides".	1	3	5
f) "All pesticides should be banned."	1	3	5
g) "The long term health risks of pesticides are worrying."	1	3	5

Q.7 "Which of these four best describes the place where you live?"
(read all four options before circling the one option chosen)

"Outside a city or large town" 1
"Within a city or large town" 2
"In a small town" 3
"In the country" 4

DO NOT READ OUT: Other (Specify) .....

Don't' know = Y Refused = Z

Q.8 "Please tell me which of these four statements best describes your knowledge of pesticide spraying carried out where you live, or near where you live, by people outside of your household?'
(read all four options before circling the one option chosen)

"You know that other people have used pesticide sprays where you live or near where you live" .....1 → GO TO Q.9

"or you think that other people may have used pesticide sprays: 2

"or you're not sure if other people have used pesticide sprays or not" ..3

"or you know that other people have not used pesticide sprays where you live or near where you live".....4 → GO TO Q11

DO NOT READ OUT:.....Don't know 5
Refused 6

Q.9 "Can you describe who was spraying, what was being sprayed and where was being sprayed?" (*Write down answer*)

_____
_____
_____
_____

Q.10 "Do you have any idea, how often these pesticides are being used?"
(circle ONE only)

Monthly = 1 Quarterly = 2 Every 6 months = 3 Other (Specify) 4
No/Not sure = 5

Q.11 "Is there anything else you want to say about pesticide or sprays?" (*circle ONE only*)

Yes = 1 .....
Nothing else = 2 Don't know = 5

"I'm now going to ask you specific questions relating to 1080, a known pesticide."

Q.12 "Can you tell me what 1080 is used for?" (*Tick ALL that apply*)

❑ Kill possums ❑ Kill rabbits ❑ Kill wallabies
❑ Don't know Other:.....

Q.13 "Is 1080 being used in your area?" (*circle ONE only*)

Yes – 1 Not sure – 2 No – 3 Don't know - 4

Q.14 "How is it used in your area?" (*circle ONE only*)

Aerial application – 1 Ground application – 2 Don't know - 3

Q.15 Do you have any concerns about the use of 1080?" (*circle ONE only*)

Yes – 1 Not sure – 2 No – 3 Don't know - 4

↓
GO to Q17

Q.16 "What is your biggest single main concern about the use of 1080 in the environment?

Acute effects from the use of 1080 = 1
Long –term effects of 1080 = 2
Harm to environment = 3
Danger to animals = 4
Other = 5: _____

Q.17 "Are you aware of any public protest about the use of 1080 in your area?" (*circle ONE only*)

Yes – 1 Not sure – 2 No – 3 Don't know - 4

↓
GO to Q19

Q.18 "Can you please briefly summarise what people are protesting about?" (*circle ONE only*)

Acute effects from the use of 1080 – 1
Long –term effects of 1080 – 2
Harm to environment - 3
Danger to animals - 4
Other

Q.19 "In relation to your ethnicity and culture, do you have any specific concerns regarding the use of 1080?" (*circle ONE only*)

Yes – 1 Not sure – 2 No – 3 Don't know - 4

GO to Q21

Q.20 "Can you please briefly tell me your concerns?" (*write down answer*)

_____

_____

Q.21 "In the last 12 months, have you personally been exposed to 1080?"

Yes = 1 Not sure – 2 No – 3 Don't know - 4

GO to Q23

Q.22 "Please tell me how you were exposed."
(*circle ONE only*)
Drinking water = 1 Food =2 Air borne dust = 3
Other (Specify) _____ = 4

"Now I'm going to ask you specific questions relating to your sources of drinking water and food".

Q.23 "Where does your drinking water supply come from? (*circle ONE only*)

Town drinking-water supply =1 Tank water (not treated) = 2
Ground (bore) water = 3 Other = 4 Don't know = 5

Q.24 "Do you collect your milk from a farm?" (*circle ONE only*)

Yes = 1 No = 2 Sometimes = 3 Don't know = 3

Q.25 "Is there a possibility that cows in area that have been contaminated with 1080?" (*circle ONE only*)

Yes = 1 Not sure – 2 No – 3 Don't know - 4

Q.26 "Do you obtain your meat supply from a farm?" (*circle ONE only*)

Yes =1 No=2 Sometimes = 3 Don't know = 4

Q.27 "Is there a possibility that the animal's meat were contaminated with 1080?" (*circle ONE only*)

Yes = 1 Not sure – 2 No – 3 Don't know - 4

Q.28 "Do you obtain your meat supply from hunting?" (*circle ONE only*)

Yes =1 No=2 Sometimes = 3 Don't know = 4

Q.29 What sort of animals do you hunt? (*tick ALL that apply*)

❑ Rabbit ❑ Deer ❑ Pigeon ❑ Duck❑ Pig ❑ Goat
Other: .....

Q.30 "Is there a possibility that these hunted animals have been contaminated with 1080?"

Yes = 1 Not sure – 2 No – 3 Don't know - 4

Q.31 "Now I'm going to read out some statements and I'd like you to tell me whether you agree, disagree or no opinion with each one. These questions are similar to an earlier question. The only difference is that the reference to pesticides has been changed to 1080. Do you agree, or disagree that ..." *(read out for each statement, and circle the answer as you go).*

	Agree	Disagree	No opinion
a) "The public knows enough about the health risks of 1080".	1	3	5
b) "There is not enough available information about the health risks of using 1080."	1	3	5
c) "The controls on the use of 1080 are adequate".	1	3	5
d) "Not enough care is taken when people use 1080."	1	3	5
e) "There is too much fuss made about the risk from 1080".	1	3	5
f) "1080 should be banned."	1	3	5
g) "The long term health risks of 1080 are worrying."	1	3	5

Q.32 "And finally, just a few questions about yourself to help us analyse the data. I am going to read out a list of age groups. Please stop me when I get to the age group you fall into." (READ OUT & CIRCLE ONE ONLY).

"18 – 24 years?" --- 1 "45 – 54 years?" ----4

"25 – 34 years?" ----2 "55 or over?"----------5

"35 – 44 years?" ----3 DO NOT READ OUT: Refused = 6

Q.33 "What kind of work do you do?" _____

Q.34 "Does this work involve handling 1080?"
❑ Yes ❑ No → GO TO Q37

Q.35 "in what industry is that? (*write down answer*)

(IF IT IS IS RELATED TO 1080, e.g., MIXING & HANDLING OF 1080 CONCENTRATE SOLUTION, MANUFACTURING OF 1080 BAITS, APPLICATION OF BAITS, LOADING & HANDLING OF TOXIC BAITS, ETC, ASK THE NEXT QUESTIONS 36 a) -c*). Tick the ONE box that applies in each question.* IF NOT RELATED TO 1080 GO TO Q37

Q.36 a) "Do you wash your hands and other parts of the body that you think have been exposed to 1080 before going home?"
❑ Yes ❑ No ❑ Sometimes

Q 36 b) "Do you take your working clothes with you at home?"
❑ Yes ❑ No: GO TO Q 36 d)
❑ Sometimes

Q 36 c) "If yes or sometimes, how are they washed?
❑ Wash separately ❑ Wash with other clothes
❑ Dry clean ❑ Other _____

Q 36 d) "Are there any children staying with you?"
❑ Yes ❑ No

Q.37 "About your schooling and education. Did you pass:
(Tick ONE box that applies)

❑ School Certificate or its overseas equivalent
❑ One or two full years at school after your School Certificate year
❑ One fully year of university study after leaving school"
❑ University degree or diploma
❑ Trade qualification, technical qualification or some other qualification

Q.38 "Are there any children under the age 16 living in your household?
(circle ONE only)

Yes – 1 No - 2

Q.39) "To which of these groups do you consider you most belong?"
(*read out all answers and tick as many that apply*)

❑ Maori
❑ New Zealand European
❑ Samoan
❑ Cook Island Maori
❑ Tongan
❑ Niuean
❑ Chinese
❑ Indian
❑ Other (such as Dutch, Japanese, Tokelauan). Please specify _____

Don't know – Y Refused = Z

Q.40) (*circle sex of respondent*) Male – 1 Female – 2

Q. 41) (*circle telephone book you are using*)

Northland = 01
Auckland = 02
Waikato, King Country
Thames Valley = 03
Bay of Plenty = 04
Gisborne = 05
Hawkes Bay = 06
Taranaki = 07
Wanganui = 08
Manawatu = 09
Wairarapa = 10
Wellington = 11
Nelson = 12
West Coast = 13
Blenheim = 14
Christchurch = 15
Oamaru/Timaru = 16
Dunedin = 17
Invercargill = 18

Thank you for participating to this survey. Your participation is most appreciated and will help us update our information on how the public perceives pesticides.

Appendix 10. References for postal and telephone surveys

Anon. (1978). *Predator Damage in the West: A Study of Coyote Management Alternatives*. US Fish and Wildlife Service. Department of the Interior. 168 pp.

Bord, R.J., O'Connor, R.E. (1992). Determinants of risk perceptions of hazardous waste site. *Risk Analysis* 12(3): 411-416.

Bruhn, C.M. (1992). Consumer concerns and educational strategies: focus on biotechnology. *Food Technology* 46(3): 80-97.

Carle, B., Charron, S., Milochevitch, A., Hardeman, F. (2004). An inquiry of the opinions of the French and Belgian populations as regards risk. *Journal of Hazardous Material* 111: 21-27.

Coronado, G.D., Thompson, B., Strong, L., Griffith, W.C., Islas, I. (2004). Agricultural task and exposure to organophosphate pesticides among farmworkers. *Environmental Health Perspectives* 112(2): 142-147.

Curl, C.L., Fenske, R.A., Kissel, J.C., Shirai, J.H., Moate, T.F., Griffith, W., Coronado, G., Thompson, B. (2002). Evaluation of take-home organophosphorus pesticide exposure among agricultural workers and their children. *Environmental Health Perspectives* 110(12): A787-A792.

Department of Health. (1990). *Public Perception of Risk from Chemicals*. Department of Health, Wellington. 53 pp.

Department of Statistics. (2001). *2001 Census of Population and Dwellings*. Department of Statistics, Wellington. pp. 68-87, 256-257.

Downie, N.M., Heath, R.W. (1983). *Basic Statistical Methods*. Harper and Row Publishers. New York. pp. 225-239.

Dunlap, R.E. (1991). Trends in public opinion toward environmental issues: 1965-1990. *Society and Natural Resources* 4: 285-312.

Dunlap, R.E., Beus, C.E. (1992). Understanding public concerns about pesticides – an empirical examination. *The Journal of Consumer Affairs* 26(2): 418-438.

Finucane, M.L., Slovic, P., Mertz, C.K., Flynn, J., Satterfield, T.A. (2000). Gender, race, and perceived risk: the 'white male' effect. *Health, Risk & Society* 2(2): 159-172.

Fischer, G.W., Morgan, M.G., Fischhoff, B., Nair, I., Lave, L.B. (1991). What risks are people concerned about? *Risk Analysis* 11: 303-314.

Fitzgerald, G., Wilkinson, R., Saunders, L. (2000). Public perceptions and issues in possum control. In: Montague, T., ed. *Possum in New Zealand: Biology, Impact and Management of an Introduced Marsupial*. Maanaki Whenua Press, Lincoln. pp. 187-197.

Flynn, J., Slovic, P., Mertz, C.K. (1994). Gender, race and perception of environmental health risks. *Risk Analysis* 14(6): 1101-1108.

Garry, V.F., Harkins, M., Erickson, L.L., Long-Simpson, L.K., Holland, S.E., Burroughs, B.L. (2002a). Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA. *Environmental Health Perspectives* 110(3): 441-449.

Garry, V.F., Harkins, M., Lyubomov, A., Erickson, L., Long, L. (2002b). Reproductive outcomes in the women of the Red River Valley of the North. I. The spouses of pesticide applicators: pregnancy loss, age at menarche, and exposures to pesticides. *Journal of Toxicology and Environmental Health*, Part A (65): 769-786.

Hamilton, L.C. (1985). Concern about toxic wastes: Three demographic predictors. *Sociological Perspectives* 28(4): 463-486.

Hammitt, J.K. (1990). Risk perceptions and food choice: an exploratory analysis of organic-versus conventional-produce buyers. *Risk Analysis* 10: 42-51.

Harraway, J. (1992). *Introductory Statistical Methods and the Analysis of Variance*. University of Otago Press, Dunedin. pp. 136-140.

Health and Safety in Employment Act 1992. New Zealand.

Hernandez-Valero, M.A., Bondy, M.L., Spitz, M.R., Zahm, S.H. (2001). Evaluation of Mexican American migrant farmworker work practices and organochlorine pesticide metabolites. *American Journal of Industrial Medicine* 40(5): 554-560.

Hood, E. (2002). Bringing home more than a paycheck. *Environmental Health Perspectives* 110(12): A765.

Horn, C., Kilvington, M. (2002). *Maori and 1080*. Maanaki Whenua Landcare Research. 17 pp.

Howe, H.L. (1990). Public concern about chemicals in the environment: Regional differences based on threat potential. *Public Health Reports* 105(2): 186-195.

Kaloyanova, F.P., Batawi, M.A. (1991). *Human Toxicology of Pesticides*. CRC Press, Inc. Boca Raton, Florida, p. 1.

Loewenherz, C., Fenske, R.A., Simcox, N.J., Bellamy, G., Kalman, D. (1997). Biological monitoring of organophosphorus pesticide exposure among children of agricultural workers in central Washington State. *Environmental Health Perspectives* 105: 1344-1353.

Lu, C., Fenske, R.A., Simcox, N.J., Kalman, D. (2000). Pesticides exposure of children in an agricultural community evidence of household proximity to farmland and take-home exposure pathways. *Environmental Research* 84: 290-302.

MacGregor, D., Slovic, P., Morgan, M.G. (1994). Perception of risks from electromagnetic fields: A psychometric evaluation of a risk-communication approach. *Risk Analysis* 14(5): 815-828.

Maderthaner, R., Swaton, E., Guttman, G., Otway, H.J. (1978). The effect of distance upon risk perception. *Journal of Applied Psychology* 63: 380-382.

McCauley, L.A., Lasarev, M.R., Higgins, G., Rothlein, J., Muniz, J., Ebbert, C., *et al.* (2001). Works characteristics and pesticide exposures among migrant agricultural families: A community-based research approach. *Environmental Health Perspectives* 108: 533-538.

McStay, J.R., Dunlap, R.E. (1983). Male-female specific differences in concern for environmental quality. *International Journal of Women's Studies* 6(4): 291-301.

Mills, P.K., Zahm, S.H. (2001). Organophosphate pesticide residues in urine of farmworkers and their children in Fresno County, California. *American Journal of Industrial Medicine* 40: 571-577.

Ministry of Health (1995b). *Model Permit Conditions for the Use of Sodium Monofluoroacetate (1080)*. Ministry of Health, Wellington. 12 pp.

Morgan, D.R. (1998). Community participation in research to improve the efficiency of ground-based possum control. *Proceedings of the 11th Vertebrate Pest Conference*, Bunbury, Western Australia. pp. 93-98.

National Possum Control Agencies (NPCA). (Undated). *1080 is Not Kid's Stuff.* National Possum Control Agencies, Wellington. 6 pp.

Nelkin, D. (1989). Communicating technological risk: The social construction of risk perception. *Annual Review of Public Health* 10: 95-113.

O'Connor, C.E., Eason, C.T., Fountain, J.S. (2000). "Assessing exposure risks to 1080 workers in New Zealand". Landcare Research Contract Report LC9900/98 (unpublished), prepared for the Department of Conservation and the Animal Health Board. 19 pp.

O'Connor, C.E., Fountain, J.S., Eason, C.T. (2001). "1080 worker exposure". Landcare Research Contract Report LC0001/56 (unpublished), prepared for the Department of Conservation and the Animal Health Board. 9 pp.

Olin, S.S., Sonawane, B.R. (2003). Workshop to develop a framework for assessing risks to children from exposure to environmental agents. *Environmental Health Perspectives* 111(12): 1524-1526.

Parliamentary Commissioner for the Environment (PCE). (1994). *Possum Management in New Zealand.* Office of the Parliamentary Commissioner for the Environment, Wellington. 196 pp.

Parliamentary Commissioner for the Environment (PCE). (1998). *Possum Management in New Zealand: Critical Issues in 1998.* PCE Progress Report No. 1. Office of the Parliamentary Commissioner for the Environment, Wellington. 9 pp.

Pilisuk, M., Parks, S., Hawkes, G. (1987). Public perception of technological risk. *The Social Science Journal* 24: 403-413.

Potter, M.F., Bessin, R.T. (2000). Termites and public attitudes. *Pest Control Technology* 28(2): 39-99.

Rohrmann, B. (1994). Risk perception of different societal groups: Australian findings and cross-national comparisons. *Australian Journal of Psychology* 46(3): 150-163.

Savitz, D.A., Arbuckle, T., Kaczor, D., Curtis, K.M. (1997). Male pesticide exposure and pregnancy outcome. *American Journal of Epidemiology* 146: 1025-1036.

Schmidt, F.N., Gifford, R. (1989). A dispositional approach to hazard perception: Preliminary development of the environmental appraisal inventory. *Journal of Environmental Psychology* 9: 57-67.

Schwatz, S.P., White, P.E., Hughes, R.G. (1985). Environmental threats, communities and hysteria. *Journal of Public Health Policy* 6: 58-77.

Sheppard, R.L., Urquhart, L.M. (1991). *Attitudes to Pests and Pest Control Methods: Results from a Sample Survey of the NZ Population* in February 1991, Research Report No. 210, Canterbury, Agrobusiness and Economics Research Unit. Lincoln University. 69 pp.

Simcox, N.J., Fenske, R.A., Wolz, S.A., Lee, I.C., Kalman, D.A. (1995). Pesticides in household dust and soil: Exposure pathways for children of agricultural families. *Environmental Health Perspectives* 103: 1126-1134.

Slovic, P. (1987). Perception of risk. *Science 236*: 280-285.

Slovic, P., Fischhoff, B., Lichtenstein, S. (1981). Perceived risk: Psychological factors and social amplifications. *Proceedings Royal Society London* A (376): 17-34.

Slovic, P., Kraus, N.N., Lappe, H., Letzel, H., Malmfors, T. (1989). Risk perception of prescription drugs: Report on a survey in Sweden. *Pharmaceutical Medicine* 4: 43-65.

Wessely, S. (2005). Risk, psychiatry and the military. *British Journal of Psychiatry* 186: 459-466.

Whitford, F. (1993). Pesticide facts and perceptions. *Journal of Extension* 31: 1-12.

Whitmore, R.W., Immerman, F.W., Gamann, D.E., Bond, A.E., Lewis, R.G., Schaum, J.L. (1994). Non-occupational exposures to pesticides for residents of two U.S. cities. *Archives of Environmental Contamination and Toxicology* 26(1): 47-59.

Zahm, S.H., Ward, M.H. (1998). Pesticides and childhood cancer. *Environmental Health Perspectives Supplements* 106(S3): 893-908.

Zimmerman, R. (1993). Social equity and environmental risk. *Risk Analysis* 13(6): 649-666.