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Internal Memo
Ministry of Health

To: Sally Gilbert
David Ogilvie

From: Naty Foronda

Subject: Review of maximum acceptable value (MAV) for sodium fluoroacetate (1080)

Date: 10 August 2011

For Your: ACTION (X) DECISION (X) INFORMATION (X)

The Environmental Risk Management Authority's (now the Environmental Protection Agency) decision on reassessment of 1080 was finalised in August 2007. Dr Michael Taylor made a submission during the reassessment process and one of the items raised was the forthcoming review of the provisional MAV in the Drinking water Standards New Zealand given the more recent (and the latest) toxicology information on the potential adverse health effects of 1080. The purpose of this memo is recommend a PMAV including the rationale in the derivation of that value. A short value is also being proposed.

Principal study and supporting studies

Eason et al. (2001) conducted a 90 day subchronic study in which three groups of 10 male and 10 females 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 once daily for 90 days. A group of 10 male and 10 female rats were administered with water only and served as the control group. The control and 0.25 mg/kg/day groups included 10 additional rats of each sex that were treated for 90 days, then maintained without treatment for a further 56-day recovery period.

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 no-observed-adverse-effect-level (NOAEL)[1] for rats administered with 1080 via oral gavage for 90 days was 0.075 mg $kg^{-1}day^{-1}$. The authors also noted increases in heart weight in both male and female Sprague-Dawley rats when compared with controls. 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.

Dose response modelling of the data for testicular (males) and myocardial toxicity (males and females) was conducted to derive a benchmark dose for 1080 (Foronda et al. 2007a). A benchmark dose ($BMDL_{10}$ is the lower confidence limit of the dose that gives a 10% excess in abnormal responses above the spontaneous background level) of 0.10 mg/kgbw/day was derived and used for further quantification in this assessment.

Supporting studies

[1] NOAEL is **t**he 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 2000).

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 7^{th} 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 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 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.

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. There has been little reliable information on 1080's action and toxicity in the larger domestic animals (Annison *et al*. 1960).

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).

Uncertainty Factors

An uncertainty factor of 3000 was used: 10 to account for interspecies extrapolation, 10 for differences in human sensitivity, 10 for use of a subchronic study for a chronic RfD derivation, and 3 for the lack of reproductive/developmental studies and toxicity studies in a second species.

Tolerable Daily Intake (TDI)

It is proposed that the $BMDL_{10}$ 0.10 mg/kg/day be used in deriving the TDI rather than the NOAEL as the BMD approach uses all of the experimental data to fit one or more dose response curves (Foronda et al 2007a). The TDI therefore equates to 0.10 mg/kg/day/3000 = 0.00003 mg/kg/day (0.03 µg/kg/day).

Oral TDI

Critical Effect	Experimental Doses*	UF	MF	RfD
Cardiomyopathy in females and males; altered spermatogenesis, severe degeneration of seminiferous tubules of the testes in males	$BMDL_{10}$: 0.10 mg/kg/day	3000	1	3E-5 mg/kg/day
90 day Rat Oral Study (gavage)	LOAEL: 0.25 mg/kg/day			
Eason et al. (2001)				

The US EPA has derived the following reference dose (RfD)

Oral RfD *

Critical Effect	Experimental Doses*	UF	MF	RfD
Increased heart weight in females and males; decreased testis weight and altered spermatogenesis in males	NOAEL: 0.05 mg/kg/day	3000	1	2E-5 mg/kg/day
13-Week Rat Oral Study (gavage)	LOAEL: 0.20 mg/kg/day			
U.S. EPA, 1988				

* RfD, ADE, ADI have similar meaning and intent as the TDI.

EPA's (formerly ERMANZ) derivation of Acceptable Daily Exposure (ADE)*

The chronic exposure threshold was the Acceptable Daily Exposure of 0.02 µg/kg bw/day. This value was used to derive separate potential daily exposures (PDE) for different routes:

PDE_{food} = 0.006 µg/kg bw/day

PDE_{water} = 0.01 µg/kg bw/day

$PDE_{inhalation}$ = 0.002 µg/kg bw/day

PDE_{dermal} = 0.002 µg/kg bw/day

EPA has not derived an "official" TEL for 1080 yet. The hazardous Substances (Sodium Fluoroacetate) Transfer Notice 2005 established a TEL water of 3.5 µg/l. This was based on the PMAV established by the Ministry, rather on the derivation of an ADE and PDEwater. The EPA proposes that this value is retained pending revision of the PMAV by the Ministry.

Recommendations

1) Provisional MAV

The BMDL computed for male cardiomyopathy (0.10 mg/kg body weight/day) and for testicular effects (0.11 mg/kg body weight/day) were chosen as these effects were considered to be the most sensitive end points (Foronda et al. 2007b). The proposed PMAV was calculated as follows:

PMAV = $(BMDL_{10}/UF)$ * body wt* proportion of total intake)/(daily intake of DW)

0.10 mg/kg/3000 x 70 kg x 0.5/2L =

= 0.00058 mg/L (rounded to 0.0006 mg/L)

Where:
$BMDL_{10}$ = 0.10 mg/kg
Average quantity of water consumed by an adult = 2 L per day
Average weight of adult = 70 kg
Proportion of total intake allocated to drinking-water = 0.8
Uncertainty factor = 3000 (10 for intraspecies variation, 10 for interspecies variation, 10 for use of a subchronic study for a chronic TDI derivation, and 3 for incompleteness of database)

2) **Short-term PMAV**

Since it is recognised that there is a chance that members of the public might be exposed to high concentrations of 1080 over a short period without the chronic PMAV being exceeded, setting an ARfD appears to be appropriate. Solecki et al (2005) developed a list of possible relevant end

points that are relevant in setting ARfD, such as for instance developmental effects, eg malformations and other effects on the offspring. ARfD values that were derived from embryo/feto toxicity in rats or rabbits are considered appropriate to sufficiently protect women of childbearing age including the developing organism. However, knowledge on the mode of action of an acute exposure during a sensitive window of fetal development and of the postnatal consequences of fetal observations is currently very limited.

While an ARfD based on developmental (embryo/foetal) effects would be appropriate for women of child-bearing age, it is recognised that the same value may be overly conservative with respect to other subgroups in the population. Depending on the type of effect seen and the species evaluated, the use of an ARfD based on a developmental effect, e.g., skeletal or soft tissue malformations, could be inappropriate for children aged 1 to 6 years; as they are unlikely to be at risk for the developmental toxicity observed. In this situation, separate modelling with respect to acute dietary intake of residues can be performed taking into account age-specific acute consumption data. Alternatively, it might be necessary to address higher sensitivity of children to other forms of acute toxicity by testing during early life-stages.
The WHO Guidelines (2011) say: "Cyanide is rapidly detoxified, and exposure spread throughout the day will further reduce the potential for effects. **This health-based value would be suitable for use for a limited period of up to 5 days**, which is the longest period likely to be required under the circumstances of such an emergency. However, it is probable that, in most circumstances, this value will be highly conservative for short-term exposure."

A developmental toxicity study (Eason et al. 1999) in pregnant Sprage-Dawley rats were orally given a single daily dose of 1080 solution at 0, 0.1, 0.33 or 0.75 mg/kg/day (26 female rats in each group) from day 6 through to day 17 of gestation and euthanised on day 20. Skeletal abnormalities were found in fetuses exposed at 0.33 and 0.75 mg/kg/day groups. The abnormalities included abnormal development of the forelimbs, characterised by bent scapula, humerus and radius or ulna, and observed in 24%, 12% and 8% litters respectively. These changes were treatment-related, and were classified as irreversible alterations of skeletal development (malformations). At 0.33 and 0.75 mg/kg/day, bent ribs were observed in 20% and 52% of litters respectively. Unossified sternebrae were also observed in 72% of litters at 0.75 mg/kg/day. Bent or wavy ribs and unossified sternebrae were classified as variations rather than malformations because these effects were considered to be reversible. No clinical symptoms of maternal toxicity were observed at any dose. Decreased maternal and foetal body weight was observed at the highest dose tested of 0.75 mg/kg/day. No external or visceral soft tissue abnormalities were observed in fetuses at any dose. The no-observed –effect level (NOEL) for maternal toxicity was 0 .33 mg/kgbw/day and a NOAEL of 0.1 mg/kgbw/day based on irreversible skeletal malformations were reported.

In a developmental pilot study (Eason et al. 1999) in five rats per treatment group dosed orally with 1080 solution at 0, 0.05, 0.1, 0.5, or 1.0 mg/kgbw/day, maternal toxicity (weight loss and 60% mortality) and decreased litter size were observed at 1.0 mg/kgbw/day. There were no effects on uterine parameters (gravid uterine weight, number of implantations, resorptions and live and dead fetuses) at all dose levels. The NOEL was 0.5 mg/kgbw/day based on gross pathological examination of the female rats (the fetuses were not examined).

An ARfD of 0.0003 mg/kg bw was estimated on the basis of a NOAEL of 0.1 mg/kg bw per day for teratogenicity in developmental toxicity study in rats and using an uncertainty factor of 300.
For the purposes of setting a short term PMAV, a TDI was derived using

Acute PMAV

The derivation of acute PMAV is done in the normal manner and allocating 100% of the ARfD to drinking water. Derivation was calculated as follows:

$PMAV_{acute}$ = (NOAEL /UF) * body wt* proportion of total intake)/(daily intake of DW)
= (0.10/300)* 70 *1)/2
= 0.035 mg/L

where:
NOAEL = 0.10 mg/kg
Average quantity of water consumed by an adult = 2 L per day
Average weight of adult = 70 kg
Proportion of total intake allocated to drinking-water = 1
Uncertainty factor = 300 (10 for intraspecies variation, 10 for interspecies variation, and 3 for incompleteness of database)

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Document 2

Pesticides (15 of them) in the 2008 DWSNZ with a PMAV set by the MoH

Prepared by David Ogilvie, 3 Dec 2018

Azinphos methyl – no longer on ACVM Register

A tolerable daily intake approach was used by the MoH for the derivation of the provisional MAV for azinphos methyl in drinking-water, as follows:

$$\frac{0.125 \text{ mg/kg body weight per day} \times 70 \text{ kg} \times 0.1}{2 \text{ L} \times 100} = 0.00438 \text{ mg/L (rounded to 0.004 mg/L)}$$

where:

- No-Observable-Adverse-Effect Level = 0.125 mg/kg body weight per day
- Average weight of adult = 70 kg
- Average quantity of water consumed by an adult = 2 L per day
- Proportion of tolerable daily intake allocated to drinking-water = 10%
- Uncertainty factor = 100.

Bromacil – still on ACVM Register

The MAV is provisional because it was developed by the MoH in-house rather than by WHO. A tolerable daily intake approach has been used for the derivation of the MAV for bromacil in drinking-water, as follows:

$$\frac{10 \text{ mg/kg body weight per day} \times 70 \text{ kg} \times 0.1}{2 \text{ L} \times 100} = 0.35 \text{ mg/L (rounded to 0.4 mg/L)}$$

where:

- No-Observable-Adverse-Effect Level = 10 mg/kg body weight per day
- Average weight of adult = 70 kg
- Average quantity of water consumed by an adult = 2 L per day
- Proportion of tolerable daily intake allocated to drinking-water = 10%
- Uncertainty factor = 100.

Diuron - still on ACVM Register

A tolerable daily intake approach has been used by the MoH for the derivation of the PMAV for diuron in drinking-water, as follows:

$$\frac{0.625 \text{ mg/kg body weight per day} \times 70 \text{ kg} \times 0.1}{2 \text{ L} \times 100} = 0.02 \text{ mg/L}$$

where:

- No-Observable-Adverse-Effect Level = 0.625 mg/kg body weight per day
- Average weight of adult = 70 kg
- Average quantity of water consumed by an adult = 2 L per day
- Proportion of tolerable daily intake allocated to drinking-water = 10%
- Uncertainty factor = 100.

Hexazinone - still on ACVM Register
A tolerable daily intake approach was used by the MoH to derive the provisional MAV for hexazinone in drinking-water, as follows:

$$\frac{\text{10 mg/kg body weight per day x 70 kg x 0.1}}{\text{2 L x 100}} = \text{0.35 mg/L, rounded to 0.4 mg/L}$$

where:
- No-Observable-Adverse-Effect Level = 10 mg/kg body weight per day.
- Average weight of adult = 70 kg
- Average quantity of water consumed by an adult = 2 L per day
- Proportion of tolerable daily intake allocated to drinking-water = 10%
- Uncertainty factor = 100.

Metalaxyl - still on ACVM Register
A tolerable daily intake approach was used by the MoH for the derivation of the provisional MAV for metalaxyl in drinking-water, as follows:

$$\frac{\text{3 mg/kg body weight per day x 70 kg x 0.1}}{\text{2 L x 100}} = \text{0.105 mg/L (rounded to 0.1 mg/L)}$$

where:
- No-Observable-Adverse-Effect Level = 3 mg/kg body weight per day.
- Average weight of adult = 70 kg
- Average quantity of water consumed by an adult = 2 L per day
- Proportion of tolerable daily intake allocated to drinking-water = 10%
- Uncertainty factor = 100.

Metribuzin - still on ACVM Register
A tolerable daily intake approach was used by the MoH for the derivation of the provisional MAV for metribuzin in drinking-water, as follows:

$$\frac{\text{2 mg/kg body weight per day x 70 kg x 0.1}}{\text{2 L x 100}} = \text{0.07 mg/L}$$

where:
- No-Observable-Adverse-Effect Level = 2 mg/kg body weight per day
- Average weight of adult = 70 kg
- Average quantity of water consumed by an adult = 2 L per day
- Proportion of tolerable daily intake allocated to drinking-water = 10%
- Uncertainty factor = 100.

Oryzalin - still on ACVM Register
A tolerable daily intake approach was used by the MoH for the derivation of the provisional MAV for oryzalin in drinking-water, as follows:

$$\frac{12 \text{ mg/kg body weight per day} \times 70 \text{ kg} \times 0.1}{2 \text{ L} \times 100} = 0.4 \text{ mg/L}$$

where:
- No-Observable-Adverse-Effect Level = 12 mg/kg body weight per day
- Average weight of adult = 70 kg
- Average quantity of water consumed by an adult = 2 L per day
- Proportion of tolerable daily intake allocated to drinking-water = 10%
- Uncertainty factor = 100.

Oxadiazon - still on ACVM Register
A tolerable daily intake approach was used by the MoH for the derivation of the PMAV for oxadiazon in drinking-water, as follows:

$$\frac{5 \text{ mg/kg body weight per day} \times 70 \text{ kg} \times 0.1}{2 \text{ L} \times 100} = 0.175 \text{ mg/L (rounded to 0.2 mg/L)}$$

where:
- No-Observable-Adverse-Effect Level = 5 mg/kg body weight per day
- Average weight of adult = 70 kg
- Average quantity of water consumed by an adult = 2 L per day
- Proportion of tolerable daily intake allocated to drinking-water = 10%
- Uncertainty factor = 100.

Picloram - still on ACVM Register
A tolerable daily intake approach was used by the MoH for the derivation of the provisional MAV for picloram in drinking-water, as follows:

$$\frac{0.07 \text{ mg/kg body weight per day} \times 70 \text{ kg} \times 0.1}{2 \text{ L}} = 0.245 \text{ mg/L (rounded to 0.2 mg/L)}$$

where:
- Tolerable Daily Intake = 0.07 mg/kg body weight per day
- Average weight of adult = 70 kg
- Average quantity of water consumed by an adult = 2 L per day
- Proportion of tolerable daily intake allocated to drinking-water = 10%.

Pirimiphos methyl - still on ACVM Register
The provisional MAV for pirimiphos methyl was calculated by the New Zealand Ministry of Health as follows:

$$\frac{0.03 \text{ mg/kg} \times 70 \text{ kg} \times 0.1}{2 \text{ L}} = 0.105 \text{ mg/L (rounded to 0.1 mg/L)}$$

where:
- Acceptable daily intake = 0.03 mg/kg body weight
- Average weight of adult = 70 kg
- Proportion of acceptable daily intake allocated to drinking-water = 0.1
- Average quantity of water consumed by an adult = 2 L/day.

Pirimisulfuron methyl - still on ACVM Register
A tolerable daily intake approach was used by the MoH for the derivation of the provisional MAV for pirimisulfuron methyl in drinking-water, as follows: (also called primisulfuron methyl)

$$\frac{0.25 \text{ mg/kg body weight per day} \times 70 \text{ kg} \times 0.1}{2 \text{ L}} = 0.9 \text{ mg/L}$$

Where:
- No-Observable-Adverse-Effect Level = 0.25 mg/kg body weight per day
- Average weight of adult = 70 kg
- Average quantity of water consumed by an adult = 2 L per day
- Proportion of tolerable daily intake allocated to drinking-water = 10%.

Terbacil - still on ACVM Register
The provisional MAV for terbacil in drinking-water was derived by the MoH as follows:

$$\frac{1.25 \text{ mg/kg body weight per day} \times 70 \text{ kg} \times 0.1}{2 \text{ L} \times 100} = 0.044 \text{ mg/L (rounded to 0.04 mg/L)}$$

where:
- No-observable-adverse-effect level = 1.25 mg/kg-day based on the absence of increase in thyroid/body weight ratio, a slight increase in liver weights, and an elevated alkaline phosphatase level, in a 2-year dog feeding study
- Average weight of an adult = 70 kg
- Proportion of tolerable daily intake allocated to drinking-water = 0.1
- Average quantity of water consumed by an adult per day = 2 L
- Uncertainty factor = 100.

Thiabendazole - still on ACVM Register

A tolerable daily intake approach was used by the MoH for the derivation of the provisional MAV for thiabendazole in drinking-water, as follows:

$$\frac{3 \text{ mg/kg body weight per day} \times 70 \text{ kg} \times 0.1}{2 \text{ L} \times 30} = 0.35 \text{ mg/L (rounded to 0.4 mg/L)}$$

where:

- No-Observable-Adverse-Effect Level = 3 mg/kg body weight per day
- Average weight of adult = 70 kg
- Average quantity of water consumed by an adult = 2 L per day
- Proportion of tolerable daily intake allocated to drinking-water = 10%
- Uncertainty factor = 30.

Triclopyr - still on ACVM Register

The provisional MAV for triclopyr in drinking-water was derived by the MoH using a tolerable daily intake approach as follows:

$$\frac{3 \text{ mg/kg body weight/day} \times 70 \text{ kg} \times 0.1}{2 \text{ L/day} \times 100} = 0.105 \text{ mg/L (rounded to 0.1 mg/L)}$$

where:

- No-observable-adverse-effect level = 3 mg/kg body weight per day from a two year feeding study in rats
- Average weight of adult = 70 kg
- Average quantity of water consumed by an adult = 2 L per day
- Proportion of tolerable daily intake allocated to drinking-water = 0.1
- Uncertainty factor = 100 (for intra and inter-species variation)

1080 - still on ACVM Register

The provisional MAV for 1080 was calculated by the New Zealand Ministry of Health using an NOAEL derived from a Department of Conservation teratology study of rats (Eason, 1999) as follows:

$$\frac{0.1 \text{ mg/kg} \times 70 \text{ kg} \times 0.5}{2 \text{ L} \times 500} = 0.0035 \text{ mg/L}$$

where:

- No-Observable-Effect Level = 0.1 mg/kg body weight per day
- Average weight of adult = 70 kg
- Average quantity of water consumed by an adult = 2 L per day
- Proportion of lowest lethal dose allocated to drinking-water = 0.5
- Uncertainty factor = 500 (10 for intraspecies variation, 10 for interspecies variation, 5 for the inadequacy of the studies and database).

MINISTRY OF HEALTH
MANATŪ HAUORA

New Zealand Government

Volume 3 Datasheets – Chemical and physical determinands

Part 2.3: Pesticides

2019

2.3 Pesticides

Introductory notes

1. Pesticides can have more than one common name, trade name and chemical name. The CAS Registry Number (Chemical Abstracts Systematic names) is a single identifier aimed to remove any ambiguity arising from the various nomenclatures. An internet site for finding pesticide names for a CAS number is **http://www.alanwood.net/pesticides/index_rn2_frame.html**. Or to find a CAS number for a pesticide: **http://www.alanwood.net/pesticides/index_cn_frame.html**.

2. The Drinking-water Standards for New Zealand (DWSNZ) define a MAV 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. For carcinogenic chemicals, the MAVs set in the DWSNZ generally represent a risk of one additional incidence of cancer per 100,000 people ingesting the water at the concentration of the MAV for a lifetime of 70 years.

   The World Health Organization (WHO) states that a drinking-water guideline value (equivalent to our MAVs) normally represents the concentration of a constituent that does not result in any significant risk to health over a lifetime of consumption.

3. **USEPA**

   (a) **MCL**: Some datasheets include the USEPA's MCL. Title 40, Protection of Environment, Chapter I: Environmental Protection Agency, Part 141, National Primary Drinking Water Regulations, § 141.1 40 CFR Ch. I (7–1–02 edition) defines MCL (maximum contaminant level) as the maximum permissible level of a contaminant in water which is delivered to any user of a public water system.

   (b) **RfD**: Some datasheets also include the reference dose (usually meaning the chronic reference dose) or RfD, which the USEPA defines as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime".

   An ARfD or acute reference dose, is defined as the maximum quantity of an agricultural or veterinary chemical that can safely be consumed as a single, isolated, event. Note that the 2001 JMPR defined the acute reference dose as "The acute RfD of a chemical is an estimate of the amount of a substance in food and/or drinking-water, normally expressed on a body-weight basis, that can be ingested in a period of 24 hours or less without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation".

(c) **HHBPs**: The USEPA maintains a table of Human Health Benchmarks for Pesticides that includes RfDs and ARfDs for (currently) 363 pesticides. The HHBPs were originally developed in 2012. The table includes a column for "acute or one-day HHBPs", another for "chronic or lifetime (non-cancer) HHBPs", and one for "carcinogenic HHBPs". HHBPs are the concentrations in water at or below which adverse health effects are not anticipated from one-day or lifetime exposures. HHBPs are derived for the most sensitive population group. Details can be accessed at **http://www.epa.gov/sites/production/files/2015-10/documents/hh-benchmarks-techdoc.pdf** or **http://iaspub.epa.gov/apex/pesticides/f?p=HHBP:home**.

The acute HHBP = [aRfD (mg/kg bw/day) x BW (kg) x 1,000 (µg/mg)] / [Drinking Water Intake (L/day)] where BW = 10 kg for children and 66 kg for females 13–49 years and Drinking Water Intake = 1 L/day for children and 2 L/day for females 13–49 years. In essence, these can be considered to be one day MAVs.

The chronic HHBP = [cRfD (mg/kg bw/day) x BW (kg) x 1,000 (µg/mg) x 0.2 RSC] / [Drinking Water Intake (L/day)] where BW = 70 kg for general population and 66 kg for females 13–49 years and Drinking Water Intake = 2 L/day for general population as well as for females 13–49 years and RSC = Relative Source Contribution assumed as 20 percent. This calculation is basically the same as that used by the WHO in deriving their guideline values, and hence our MAVs.

The formula for deriving carcinogenic HHBP = [10–6 or 10–4/Drinking Water Unit Risk (ppb-1), where Drinking Water Unit Risk (ppb-1) = [CSF (per mg/kg/day) x 2(L/day)]/[70 kg x1000 (µg/mg)].

Because pesticides should only be found rarely in New Zealand waters, and for short periods, the acute one day HHBP (where available) has been included in the datasheets.

(d) **DWEL**: The USEPA also uses the concept of Drinking Water Equivalent Level or DWEL, which is defined as "a lifetime exposure concentration protective of adverse, non-cancer health effects, that assumes all of the exposure to a contaminant is from drinking water". The DWEL is calculated by multiplying the oral chronic RfD (mg/kg/d) by 70 (kg body weight) divided by 2 (L/day consumption).

The USEPA review their MCLs, DWELs and RfDs regularly. The 2012 values can be found at: **http://water.epa.gov/action/advisories/drinking/upload/dwstandards2012.pdf.**

(e) **Carcinogenicity**: The USEPA classification of carcinogenicity as at 24 September 2008, has been included where available. See latest list at **http://envirocancer.cornell.edu/turf/chemseval.pdf**. This also explains their classification groups.

4. The Australian guideline values for pesticides are not always based on health issues. For pesticides that are not approved for use in water or in water catchments, the guideline value is often set at or about the analytical limit of determination. Where a pesticide is approved for use in water or in water catchments, the guideline value is set at a level consistent with good management practice and which would not result in any significant risk to health of the consumer over a lifetime of consumption. These datasheets only include their health based guideline values, see **http://www.nhmrc.gov.au**.

5. The Australian Government's Department of Health and Ageing, Office of Chemical Safety and Environmental Health has a document that lists the Acceptable Daily Intakes (ADIs)* for Agricultural and Veterinary Chemicals, where "the acceptable daily intake (ADI) for humans is considered to be a level of intake of a chemical that can be ingested daily over an entire lifetime without any appreciable risk to health. It is calculated by dividing the overall NOEL from the animal studies by a safety factor. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to humans, variation between humans, the completeness of the toxicological data base and the nature of the potential adverse effects". Their ADIs (which are updated regularly) appear in these datasheets. See **http://www.health.gov.au/internet/main/publishing.nsf/Content/ocs-adi-list.htm**. They also publish Acute Reference Doses for Agricultural and Veterinary Chemicals (called the ARfD List), see **http://www.health.gov.au/internet/main/publishing.nsf/content/ocs-arfd-list.htm**.

   Note: The acceptable daily intake (ADI) is similar in definition and intent to terms such as reference dose (RfD), reference concentration (RfC) and tolerable daily intake (TDI). They are 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).

6. A MAV had been developed for most of the early pesticides because of their usually general and high level of toxicity and/or persistence. Many of these products now have restricted use in New Zealand or have been withdrawn. Despite this, most of these MAVs have been retained because traces of some of these older pesticides can still be found in the soil or possibly groundwater.

   Most pesticides included in this section of the datasheets do not have a MAV but are registered for agricultural use in New Zealand and appear on the NZFSA's complete database of Agricultural Compounds and Veterinary Medicines (ACVM) as at 2009 (see **https://eatsafe.nzfsa.govt.nz/web/public/acvm-register** and select entire register). Many of these are fairly new products with a much more specific application, are usually a lot less persistent, and are mostly used at a much lower dose. Many of these are yet to be evaluated in the WHO *Guidelines for Drinking-water Quality*.

7. The WHO has developed a classification of pesticides by hazard, where:
   - Class IA is extremely hazardous
   - Class IB is highly hazardous
   - Class II is moderately hazardous
   - Class III is slightly hazardous

   See The WHO Recommended Classification of Pesticides by Hazard. **http://www.who.int/ipcs/publications/pesticides_hazard/en/**.

8. Pesticides can participate in a number of transformation processes resulting in a large number of degradation products. The AWWA Research Foundation produced in 2008 "*Pesticide Degradates of Concern to the Drinking Water Community*": 143 pages. See **http://www.waterrf.org/PublicReportLibrary/2938.pdf**.

   They report that 92 pesticide degradates have been detected in the environment with 29 detected in groundwater and 27 detected in surface waters. Degradates of alachlor, acetochlor, atrazine, cyanazine, dichloropropene, dicamba and 2,4-D were likely to be the greatest concern to water supplies in the USA, whereas in the UK they were cyanazine, isoproturon and flufenacet. All are used in New Zealand.

9. DWI (2010) published a 478-page report "A Desk Study on Pesticide Metabolites, Degradation and Reaction Products to Inform the Inspectorate's Position on Monitoring Requirements", DWI Project: 70/2/232. See **http://dwi.defra.gov.uk/research/completed-research/2000todate.htm**.

10. "Review of Trends in Agricultural Pesticide Use in New Zealand" (1999) MAF Policy Technical Paper 99/11 (**www.maf.govt.nz/mafnet/rural-nz/sustainable-resource-use/resource-management/pesticide-use-trends/PesticideTrends.pdf**) discusses how pesticides were used in New Zealand up to 1998.

11. IUPAC (2003) Technical Report: "Significance of impurities in the safety evaluation of crop protection products", includes:

    > There may be substantial differences in the chemical composition of technical-grade products of the same active ingredient manufactured under different conditions, from different raw materials, or by different routes of synthesis. Resulting differences in impurity content may significantly affect the toxicological properties of pesticide products.

    See *Pure Appl Chem* 75(7) 2003, pp 937–73, for details of the more significant impurities. Available at: **http://old.iupac.org/publications/pac/2003/pdf/7507x0937.pdf**.

12. Dow Chemical Company maintains a "Product Safety Assessment Finder" on their website: **http://www.dow.com/productsafety/assess/finder.htm**.

13. ESR coordinates a survey of pesticides in groundwater throughout New Zealand. The survey has been completed every four years since 1990 with 2014 being the seventh. The report for the 2014 survey covers 165 groundwaters; pesticides were detected in 28 wells (17 percent), with 10 of these having two or more pesticides. Seven pesticides were detected in one well and 21 different pesticides were detected. Herbicides were the most frequently detected group with four insecticides and two fungicides also detected. There were 31 detections (61 percent) of triazine herbicides with terbuthylazine being the most frequently detected (16 detections). There were four pesticide detections exceeding 0.001 mg/L. One sample exceeded the MAV: dieldrin was detected at 0.000043 mg/L, slightly in excess of the MAV of 0.00004 mg/L. The next highest detection relative to the MAV was terbuthylazine at 17 percent of the MAV with the remainder of detections being less than 5 percent of the MAV. For details, see: Humphries B, Close M (2015) *National Survey of Pesticides in Groundwater 2014*, Client Report No CSC 15003, 33 pp. **http://www.marlborough.govt.nz/Environment/Groundwater/~/media/Files/MDC/Home/Environment/Groundwater/2015%20Reports/National_Survey_of_Pesticides_in_Groundwater_Report_final.pdf**.

14. The most commonly used pesticides in New Zealand up to 2004 (excluding domestic) appear in the following table. Source: Manktelow et al 2005, Trends in Pesticide Use in New Zealand 2004: Report to the Ministry for the Environment, Project SMF4193 – modified – copied from "Literature Review of Organic Chemicals of Emerging Environmental Concern in Use in Auckland", Auckland Regional Council, Technical Report No. 028, December 2008, 193 pp. **http://www.arc.govt.nz/albany/fms/main/Documents/Plans/Technical%20publications/Technical%20reports/1-50/TR2008-028%20-%20Literature%20Review%20of%20Organic%20Chemicals%20of%20Emerging%20Environmental%20Concern%20in%20Use%20in%20Auckland.pdf**.

    The table does not include mineral oils (ca. 25 t/y). A number of other pesticides are used in domestic, roadside and specialty applications, including pyrethroids, neonicotinoids, and anticoagulant rodenticides. Some of these, while used in much lower volumes, are likely to be more hazardous to the environment.

Chemical compound type (FAO category)	Active ingredient	Percentage of sales	Mode of action
phenoxy hormones	MCPA, 2,4-D, mecoprop, MCPB	25 percent	synthetic auxin (herbicides)
dithiocarbamates	mancozeb, metiram, thiram, ziram	11 percent	lipid synthesis inhibitors (fungicides)
phosphonyls	glyphosate, glufosinate-ammonium	8.4 percent	amino acid inhibitor (herbicides)
triazines	terbuthylazine, hexazinone, atrazine, simazine, propazine	7.6 percent	photosynthesis inhibitors (herbicides)
plant growth regulators	hydrogen cyanamide, ammonium thiosulphate, chlomequat-chloride, mepiquat-chloride	6.9 percent	growth inhibitors/ retardants (herbicides)
inorganics	copper compounds, sulphur compounds, phosphorous acid	6.9 percent	mostly fungicides
organophosphates	diazinon, methamidophos, chlorpyrifos, fenamiphos, pirimiphos-methyl, phorate	3.6 percent	neurotoxic (insecticides)
chloroacetanilides	acetochlor, alachlor, propachlor	3.0 percent	seedling shoot inhibitors (herbicides)
other fungicides	captan, chlorothalonil, metalaxyl-m, tolylfluanid	2.4 percent	fungicides
urea derivatives	isoproturon, linuron	2.0 percent	photosynthesis inhibitors (herbicides)
other hormone types	triclopyr, pichloram	1.3 percent	synthetic auxin (herbicides)
dinitroanilines	trifluralin	0.4 percent	–
N-methyl carbamate insecticides	aldicarb, carbaryl, carbofuran, formetanate HCl, methiocarb, methomyl, oxamyl, pirimicarb, propoxur and thiodicarb	0.4 percent	inhibition of the acetylcholinesterase enzyme

15. Some physical data have been included for some pesticides. The following discussion has mostly been taken from **http://npic.orst.edu/ingred/ppdmove.htm and http://pubs.usgs.gov/circ/2005/1291/** (accessed 2013).

The soil half-life is a measure of the persistence of a pesticide in soil. Pesticides can be categorised on the basis of their half-life as non-persistent, degrading to half the original concentration in less than 30 days; moderately persistent, degrading to half the original concentration in 30 to 100 days; or persistent, taking longer than 100 days to degrade to half the original concentration. A "typical soil half-life" value is an approximation and may vary greatly because persistence is sensitive to variations in site, soil, and climate.

Note: The United Nations Environment Programme (UNEP), Secretariat of the Stockholm Convention on Persistent Organic Pollutants, as amended in 2009, Annex D (b) Persistence:

(i) evidence that the half-life of the chemical in water is greater than two months, or that its half-life in soil is greater than six months, or that its half-life in sediment is greater than six months; or

(ii) evidence that the chemical is otherwise sufficiently persistent to justify its consideration within the scope of this convention.

This definition is consistent with the European Union definition for a very persistent pesticide of a half-life in soil of greater than six months (Regulation EC No 1107/2009 concerning the placing of plant protection products on the market).

Two of the parameters used most often to describe the partitioning of a compound among environmental media are (1) the Henry's Law constant (KH), which describes partitioning between air and water, and (2) the soil organic carbon-water partition coefficient (Koc), which describes partitioning between water and the organic matter in soil or sediment.

A pesticide with a high KH is volatile and thus, primarily tends to reside in and be transported by air. As a result, such compounds are rarely retained for long in streams or soil, but if they reach groundwater, they may remain for substantial periods of time because there is comparatively little exposure to the atmosphere.

The sorption coefficient (Koc) describes the tendency of a pesticide to bind to soil particles. Sorption retards movement, and may also increase persistence because the pesticide is protected from degradation. The higher the Koc, the greater the sorption potential, ie, the lower the mobility. Koc is derived from laboratory data. Many soil and pesticide factors may influence the actual sorption of a pesticide to soil. Because they associate more strongly with organic matter than with water, pesticides with high Koc values are sometimes referred to as hydrophobic. Compounds with low Koc values (which therefore tend to favour water over organic matter) are described as hydrophilic. As a result of their affinity for organic matter, the more persistent hydrophobic pesticides are likely to accumulate not only in soils and sediments, but also in fish, birds, mammals, and other biota. Pesticides with high Koc values are typically not very water soluble and will preferentially adhere to soils rather than be dissolved in water. This means that pesticides in this class are unlikely to be carried offsite in run-off as dissolved substances; instead, they are transported on sediment particles. For example DDT with a Koc of 100,000 adheres strongly to soil. Diazinon has a Koc of 1,580 and is readily transported as the free substance dissolved in water. The California Department of Pesticide Regulation has determined that pesticides with a Koc less than 1,900 have potential to contaminate groundwater.

The GUS or Groundwater Ubiquity Score is an empirically derived value that relates pesticide persistence (half-life) and sorption in soil (sorption coefficient, Koc). The GUS may be used to rank pesticides for their potential to move toward groundwater. The pesticide movement rating is derived from the GUS. GUS = log10 (half-life) x [4 – log10 (Koc)]. Movement ratings range from extremely low to very high. Pesticides with a GUS less than 0.1 are considered to have an extremely low potential to move toward groundwater. Values of 1.0–2.0 are low,

2.0–3.0 are moderate, 3.0–4.0 are high, and values greater than 4.0 have a very high potential to move toward groundwater.

16. **Threshold values indicating potential for groundwater contamination by pesticides**: The USEPA developed the following values in 1986 (taken from **http://psep.cce.cornell.edu/facts-slides-self/facts/pest-gr-gud-grw89.aspx**):

Chemical or physical property	Threshold value
Water solubility	greater than 30 mg/L
Henry's Law constant	less than 10-2 atm/m3 mol
Kd	less than 5, usually less than 1 or 2
Koc	less than 300 to 500
Hydrolysis half-life	more than 25 weeks
Photolysis half-life	more than 1 week
Field dissipation half-life	more than 3 weeks

The likelihood of a pesticide to volatilise is a function of both its vapour pressure and its solubility. This function is expressed by Henry's Law constant. (Unfortunately there are many different ways to express Henry's Law constant, and many different units are used.)

Kd = the concentration of chemical adsorbed divided by the concentration of chemical dissolved. The major drawback of using Kd to predict leaching of pesticides is that it is highly dependent on soil characteristics. Organic matter is the most important soil constituent determining pesticide retention. It therefore is useful to adjust the Kd value by the percent organic carbon in the soil. This yields another adsorption coefficient, Koc, which is relatively independent of soil type. Koc = Kd divided by the percent organic carbon in the soil.

17. An excellent primer on toxicology has been prepared by the Australian Pesticides and Veterinary Medicines Authority (APVMA). See **http://apvma.gov.au/node/1036**.

18. Neonicotinoids (or neonics) are a class of neuro-active insecticides chemically similar to nicotine. These compounds account for about 25 percent of the current (2013) global insecticide market. The neonicotinoids include (on ACVM Register as at October 2013):

acetamiprid (yes)	clothianidin (yes)
dinotefuran (no)	imidacloprid (yes)
nitenpyram (yes)	nithiazine (no)
thiacloprid (yes)	thiamethoxam (yes)

On 24 May 2013, the European Commission imposed a number of use restrictions on neonicotinoid insecticides, which are suspected to be a contributing factor of bee colony collapse disorder. The European Commission has adopted a proposal (Regulation (EU) No 485/2013) to restrict the use of three pesticides belonging to the neonicotinoids family (clothianidin, imidacloprid and thiametoxam) for a period of two years from December 2013. See: **http://ec.europa.eu/food/animal/liveanimals/bees/neonicotinoids_en.htm**.

Clothianidin is a primary metabolite of thiamethoxam. The chloronicotinyl insecticides (thiamethoxam, clothianidin, imidacloprid) are more toxic than the cyano substituted (thiacloprid, acetamiprid). See also: FERA (2013) Neonicotinoid Pesticides and Bees, The Food and Environment Research Agency (UK), 133 pp. **http://www.fera.defra.gov.uk/scienceResearch/scienceCapabilities/chemicalsEnvironment/documents/syngentaNeonicotinoidReportJan13.pdf**.

19. Drinking water standards in England and Wales are now set out in European and UK legislation. They are called Prescribed Concentrations or Values (PCVs) and many are different from WHO's Guideline Values. See: DWI (2010) The Water Supply (Water Quality) Regulations 2010, *Water, England and Wales* 994 (W.99): 42 pp. **http://dwi.defra.gov.uk/stakeholders/legislation/wsr2010wales.pdf**.

20. Many vertebrate toxic agents (VTAs) are used in New Zealand. Datasheets have been prepared for brodifacoum, bromadiolone, chloralose, 3-chloro-p-toluidine hydrochloride, cholecalciferol, coumatetralyl, difethialone, diphacinine, flocoumafen, norbormide, PAPP, phosphine, pindone, strychnine and 1080.

21. **Triazole derivatives**: These are generally considered to comprise triazole alanine (TA), 1,2,4-triazole (1,2,4-T), triazole acetic acid (TAA) and triazole lactic acid (TLA). They are common metabolites of the triazole-containing fungicides which includes the following 18 triazole active fungicides:

    bromuconazole, cyproconazole, difenoconazole, epoxiconazole, fenbuconazole, fluquinconazole, flusilazole, flutriafol, ipconazole, metconazole, myclobutanil, paclobutrazol, penconazole, propiconazole, prothioconazole, tebuconazole, tetraconazole, triticonazole.

    Others that are sometimes mentioned are azaconazole, hexaconazole, triadimefon, triadimenol and uniconazole.

    An abbreviated datasheet for the triazoles has been included. For further detail, refer to the individual fungicide datasheets.

Contents

The datasheet for *Bacillus thuringiensis israelensis* is included in the Bacteria datasheets. Abamectin and streptomyces – see actinomycetes (bacteria section) for brief discussion.

If a pesticide does not appear in the contents list, do 'a find': for example, a pesticide frequently called dacthal or DCPA appears here as chlorthal-dimethyl.

1080

CAS No. 62-74-8 for the sodium salt. The IUPAC and CAS name is sodium fluoroacetate. Also called fluoroacetic acid, sodium monofluoroacetate, sodium fluorethanoate and 2-fluoroacetic acid. The name of 1080 resulted from an invoice number at an early research station in the US!

CAS No. 144-49-0 refers to the fluoroacetate ion.

Maximum Acceptable Value (provisional)

Based on health considerations, the concentration of 1080 in drinking-water should not exceed 0.0035 mg/L. The MAV in the 1995 DWSNZ had been 0.005 mg/L.

1080 is not mentioned in the WHO Guidelines.

Sources to water

1080 is a highly toxic poison (rodenticide) used for the control of possums, deer, rats and rabbits. It was introduced increasingly during the 1940s and 1950s as a more effective and humane alternative to strychnine. It may enter source waters as a result of aerial application.

1080 occurs naturally in several plants, such as tea; recent studies at Lincoln University have detected natural traces of 1080 in puha. It has been found in more than 40 West Australian plants; possums in New Zealand come from the eastern seaboard of Australia and are more susceptible to the toxin, unlike their West Australian cousins who are more resilient. It has been used overseas in sewers and ships to control rats.

New Zealand uses approximately 80 percent of the world's production of manufactured 1080 amounting to 3.2 tonnes of raw product in the period 1 July 2001 to 30 June 2002. Following a re-assessment by ERMA in August 2007, 1080 continues to be registered for use in New Zealand; it is a Class B, restricted use poison, and a license is required for its use.

The Parliamentary Commissioner for the Environment (PCE 2011) reviewed the use of 1080 in New Zealand.

To monitor 1080 operations, more than 500 water samples have been taken in the target area over the last five years. Less than 2 percent of them (10 samples) have contained detectable concentrations of 1080. All of these samples were well below the tolerable exposure limit (TEL) of 3.5 micrograms of 1080 per litre of water (0.0035 mg/L) set in the reassessment. The highest concentration detected was 0.3 micrograms per litre (0.0003 mg/L) of water. The TEL is set at a level that is

protective of human health. None of the samples taken from areas in drinking water catchments have shown any measurable amounts of 1080, ie, <0.0001 mg/L (EPA 2013).

The Environmental Risk Management Authority, now called the Environmental Protection Agency (EPA), has delegated the function of granting permissions for the use of selected VTAs to Medical Officers of Health and Health Protection Officers who are also warranted HSNO enforcement officers and have completed relevant Ministry of Health courses. In addition to granting permission, the delegation also includes adding, deleting or otherwise varying any condition on a permission; and/or revoking a permission. See MoH (2013).

Forms and fate in the environment

While 1080 is comparatively rapidly eliminated from living animals, it can persist in carcasses for many months in cool or dry conditions where it will break down more slowly and may pose a risk to scavenging dogs. Undigested baits in carcasses remain toxic for prolonged periods (Eason 2002).

Studies show that 1080 can be metabolised by soil micro-organisms. Sodium monofluoroacetate derived from baits will be dispersed by water since it is highly water soluble and mobile. If heavy rainfall follows the use of 1080 baits, leaching to unmeasurable concentrations (<0.0001 mg/L) may precede biodegradation. In comparison to cereal bait, 1080 is retained in carrot baits and will only slowly leach from carrots into the soil. In mild weather or warm conditions, such as 11 to 20ºC and 8 to 15 percent moisture, 1080 may be significantly defluorinated in one to two weeks. In less favourable conditions breakdown might take several weeks, and in extreme cold and drought 1080 residues might persist in baits or in the soil for several months (from Eason 2002).

1080 can be translocated from water or soil to plants and then defluorinated. It is absorbed by aquatic organisms but it is not bioaccumulated. NSW Government (2013) reports that fish and some crustaceans (eg, water fleas Daphnia sp.) are relatively tolerant to 1080, whereas some aquatic insects (eg, mosquito larvae) are susceptible. Some aquatic plants, such as duckweed (Spirodela oligorrhiza), have been found to be sensitive.

Water solubility is very high, about 100 percent.

A nationwide water testing programme carried out between 1990 and 2003 showed that only 5 percent of over 1,450 water samples tested had detectable traces of 1080. These levels were transient and associated with the visible presence of baits in small streams. The 1080 levels ranged from 0.0002 to 0.009 mg/L (Booth et al 1997; Eason 2002; ERMA 2007a).

If released to soil, fluoroacetic acid is expected to have very high mobility based upon an estimated Koc of 1.4. The pKa of fluoroacetic acid is 2.59, indicating that this compound will primarily exist in the dissociated form in the environment and anions generally do not adsorb more strongly to organic carbon and clay than their neutral

counterparts. Fluoroacetic acid may volatilise from dry soil surfaces based upon its vapour pressure. Fluoracetic acid has been identified as one which could be removed by biological sewage treatment provided suitable acclimatisation can be achieved, suggesting that the compound may be subject to biodegradation in terrestrial or aquatic systems. If released into water, fluoroacetic acid is not expected to adsorb to suspended solids and sediment based upon the estimated Koc. The pKa value indicates fluoroacetic acid will exist almost entirely in the ionised form at pH values of 5 to 9 and therefore volatilisation from water surfaces is not expected to be an important fate process. An estimated BCF of 3 suggests the potential for bioconcentration in aquatic organisms is low. Hydrolysis is not expected to be an important environmental fate process since this compound lacks functional groups that hydrolyse under environmental conditions (EAWAG accessed February 2015).

Typical concentrations in drinking-water

The P2 Chemical Determinand Identification Programme did not find 1080 at detectable concentrations (limit of detection = 0.0001 mg/L) (ESR 2001).

Removal methods

No information is available about methods for removing 1080 from water.

Recommended analytical techniques

Referee method

Derivatisation with dicyclohexylcarbodiimide and gas chromatography with electron capture detection (Ozawa and Tsukioka 1987, *Anal Chem* 59: 2914–17).

Some alternative methods

No alternative methods have been recommended for 1080 because no methods meet the required criteria.

Health considerations

Animal studies have shown that 1080 is absorbed rapidly and excreted as unchanged fluoroacetate and a range of metabolites.

1080 poisoning results from the transformation of fluoroacetate into fluorocitrate within cell mitochondria. Acute poisoning is characterised by a symptom-free latent period of half to two hours or longer between ingestion and onset of symptoms (nausea, vomiting, diarrhoea and hyperactive behaviour leading to convulsions, coma

and cyanosis). Ventricular fibrillation is noted commonly and is the primary cause of death. Early symptoms include alteration of heart sounds and premature, weak contractions.

The LD_{50} (dose required to kill half a sample human population) is 2.0 mg/kg bw. Therefore a 70 kg person would need to drink 70,000 litres of water containing 0.002 mg/L of 1080, in one sitting, to absorb a fatal dose. [Note: 0.002 mg/L is half the MAV, rounded up.] Even allowing a significant safety margin (typically applied to allow for sensitivity in the general population and uncertainty in the toxicological studies), a safety factor of 1,000 would still require a person to drink at least 70 litres of water containing 0.002 mg/L of 1080 before being considered at risk (DoC 2004).

The oral RfD was calculated at 0.00002 mg/kg/d (USEPA 1993) based on increased heart weight in females and males; decreased testis weight and altered spermatogenesis in males in a 13-week rat oral study (gavage); NOAEL = 0.05 mg/kg/d.

Eason and Turck (2002) found from animal toxicology studies commissioned by DoC and the AHB that 1080 was teratogenic, a male reproductive toxin and a myocardial toxin in rats.

The No Observable Effect Level (NOEL) for toxicity in rats (0.075 mg/kg-day) indicates that regular intake of 1080 contaminated water could cause sub-lethal effects. Based on this NOEL, a 70 kg person would need to drink 2,680 litres of water containing 0.002 mg/L of 1080 per day, for an extended period of time, for sub-lethal effects to occur. Allowing a safety margin of 1,000, a person would need to drink their entire daily intake of two litres a day of water from a contaminated source, for a period of weeks, to be considered potentially at risk. Similarly, a pregnant woman would need to drink at least three litres a day, all of her daily intake, during the first 90 days of pregnancy, to receive a daily intake one thousand times less than the NOEL (0.1 mg/kg-day) for developmental toxicity in rats (Eason and Turck 2002, and Tremblay et al 2002, in DoC 2004).

Work by Foronda et al (2007) found the BMD_{10} and $BMDL_{10}$ for cardiomyopathy and testicular effects were 0.21 mg/kg bw and 0.10 mg/kg bw, respectively. These values are proposed for use in the eventual determination of the tolerable daily intake (TDI) for 1080. Based on the best fit of modelled dose–response data, a TDI of 0.03 µg/kg bw/day was proposed for human health risk assessment of 1080 (Foronda et al 2007a).

Assessment thresholds were established (ERMA 2007a) for acute, subchronic and chronic exposure to 1080. The acute threshold applied was the estimated minimum lethal dose (MLD) in humans 0.7 mg/kg bw. The subchronic exposure threshold established was the acceptable operator exposure (AOEL) of 0.2 µg/kg bw/day (appropriate only for workers). The Department of Labour's biological exposure index for 1080 in urine was used for analysis of some data.

The chronic exposure threshold was the Acceptable Daily Exposure of 0.02 µg/kg bw/day. This was used to derive separate potential daily exposures (PDE) for different routes:

- PDE_{food} = 0.006 µg/kg bw/day
- PDE_{water} = 0.01 µg/kg bw/day
- $PDE_{inhalation}$ = 0.002 µg/kg bw/day
- PDE_{dermal} = 0.002 µg/kg bw/day

Derivation of Maximum Acceptable Value

The provisional MAV for 1080 was calculated by the New Zealand Ministry of Health using an NOAEL derived from a Department of Conservation teratology study of rats (Eason 1999) as follows:

$$\frac{0.1 \text{ mg/kg} \times 70 \text{ kg} \times 0.5}{2 \text{ L} \times 500} = 0.0035 \text{ mg/L}$$

where:

- no observable effect level = 0.1 mg/kg body weight per day
- average weight of adult = 70 kg
- average quantity of water consumed by an adult = 2 L per day
- proportion of lowest lethal dose allocated to drinking-water = 0.5
- uncertainty factor = 500 (10 for intraspecies variation, 10 for interspecies variation, 5 for the inadequacy of the studies and database).

The MAV in the 1995 DWSNZ had been derived by the MoH as follows:

$$\frac{0.5 \text{ mg/kg} \times 70 \text{ kg} \times 0.2 \times 2.5}{2 \text{ L} \times 2{,}000} = 0.005 \text{ mg/L}$$

where:

- lowest lethal dose in humans = 0.5 mg/kg body weight
- average weight of adult = 70 kg
- average quantity of water consumed by an adult = 2 L per day
- proportion of lowest lethal dose allocated to drinking-water = 0.2
- uncertainty factor = 2,000 (10 for intraspecies variation, 2 for interspecies variation, 10 for the inadequacy of the studies and database, 10 for nature and a severity of effect)
- arbitrary factor = 2.5 (the determination was done by a very conservative process which gave a result similar to that found in tea as it is normally consumed. Tea leaves are a natural source of 1080. Consequently, the 2.5 factor was applied for common sense reasons).

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