



*Maximum Residue Limits (MRLs) for  
Agricultural Compounds in Food: The Purpose  
and Procedure for Determining MRLs*

NZFSA Public Policy Paper 16/07

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# 1 Introduction

Whenever the New Zealand Food Safety Authority (NZFSA) proposes to alter the current edition of the New Zealand (Maximum Residue Limits of Agricultural Compounds) Food Standard (the MRL Standards), an explanation of the proposal and a request for submissions is sent to interested stakeholders and published in major newspapers. This document is intended to provide background information for that consultation process, which happens several times a year. This document covers:

- what MRLs are,
- how MRLs are determined,
- how MRLs are assessed (e.g. so public health is protected), and
- how the MRL Standards work.

Submission made on behalf of an organisation should include the position within the organisation of the person making or signing the submission, and an indication of the extent of consultation, discussion and support within the organisation for the opinions and advice expressed.

If you wish to request a change to the level of a proposed MRL or suggest other amendments to the proposal, please provide justification and technical data in support of your argument. All submissions are considered and analysed before a recommendation is made to the Minister for Food Safety, who makes the final decision on issuing the MRL Standards. Relevant new information received by NZFSA may alter the advice given to the Minister for Food Safety.

You can find out whether any new MRLs are currently being proposed, and the closing date for submissions, by checking the 'Consultation' page of the 'Policy & Law' section of the [NZFSA website \(www.nzfsa.govt.nz/policy-law/consultation/index.htm\)](http://www.nzfsa.govt.nz/policy-law/consultation/index.htm), or by contacting NZFSA directly.

All submissions are subject to the Official Information Act 1982. Therefore, if you consider that all or part of your submission should be treated as confidential, please make this clear when making your submission. Submissions should be sent to:

MRL Amendments

Policy Group

New Zealand Food Safety Authority

PO Box 2835, WELLINGTON

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Facsimile: (04) 894 2583, Phone 04 894 2692

## 2 Background

### 2.1 What are MRLs?

Maximum Residue Limits (MRLs) indicate the maximum legal levels at which residues of agricultural compounds and veterinary medicines may be present in food for sale in New Zealand. The purpose of an MRL is to ensure that the methods of food production keep agricultural compound residues in food as low as reasonably achievable, thereby minimising risks to public health.

MRLs are primarily a tool for monitoring the use of agricultural compounds against good agricultural practice (GAP). GAP is not explicitly defined or regulated, but is the generally-accepted means of producing safe primary produce. GAP is about ensuring that chemical residues in food are as low as practicable, without compromising the ability of the chemical to successfully do what is intended.

In New Zealand, MRLs are set under the Food Act as food standards, namely the New Zealand (Maximum Residue Limits of Agricultural Compounds) Food Standards. These Standards amended a number of times each year to reflect changes in the use of agricultural compounds in the production of food. The current Standards are on the NZFSA website: <http://www.nzfsa.govt.nz/policy-law/legislation/food-standards/index.htm>

### 2.2 What is the Legislative Framework?

The MRL Standards are issued by the Minister for Food Safety under Section 11C of the Food Act 1981. The MRL Standards has been amended regularly since 1999, when it became the base standard for agricultural compound residues in foods as a parallel standard with regulation 257 of the Food Regulations 1984, which have since been revoked. The frequency of these amendments reflects new agricultural compounds coming on the market and changes in the registered uses of compounds already available.

NZFSA now administers the MRL Standards but the final decision on any changes to the Standards rests with the Minister for Food Safety. When amending or issuing any food standard, including the MRL Standards, the Minister must take into account the following:

- The need to protect public health
- The desirability of avoiding unnecessary restrictions on trade

- The desirability of maintaining consistency between New Zealand's food standards and those applying internationally
- New Zealand's obligations under any relevant international treaty, agreement, convention, or protocol, and, in particular, under the Australia-New Zealand Joint Food Standards Agreement
- Such other matters as the Minister considers appropriate.

Although residues of agricultural compounds in food for sale are regulated under the Food Act, the sale and use of the compounds themselves is regulated under the Agricultural Compounds and Veterinary Medicines Act 1997 (the ACVM Act). When an agricultural compound is registered under the ACVM Act, conditions are placed on the use of that product to ensure food residue limits are not exceeded.

The MRL Standards do not cover incidental contaminants that are not sold for use as agricultural compounds, such as heavy metals and natural toxicants. These are regulated in the joint Australia New Zealand Food Standards Code.

MRLs are excluded from the joint Australia New Zealand food standards-setting system, as MRLs which apply to the use of compounds to control pests, diseases and growing conditions are specific to each country.

## 3 How are MRLs set?

There are two stages to determining an appropriate MRL. First, good agricultural practice (GAP) must be determined. Second, evidence that the residues arising from appropriate GAP are unlikely to pose any human health risks is required. Once the appropriate MRL has been determined, other matters are taken into account such as avoiding trade restrictions, maintaining consistency and meeting international obligations (see criteria in section 2.2). The MRL is then set at a level that supports GAP and allows for the monitoring of compliance with GAP.

### 3.1 Determining the Appropriate Good Agricultural Practice

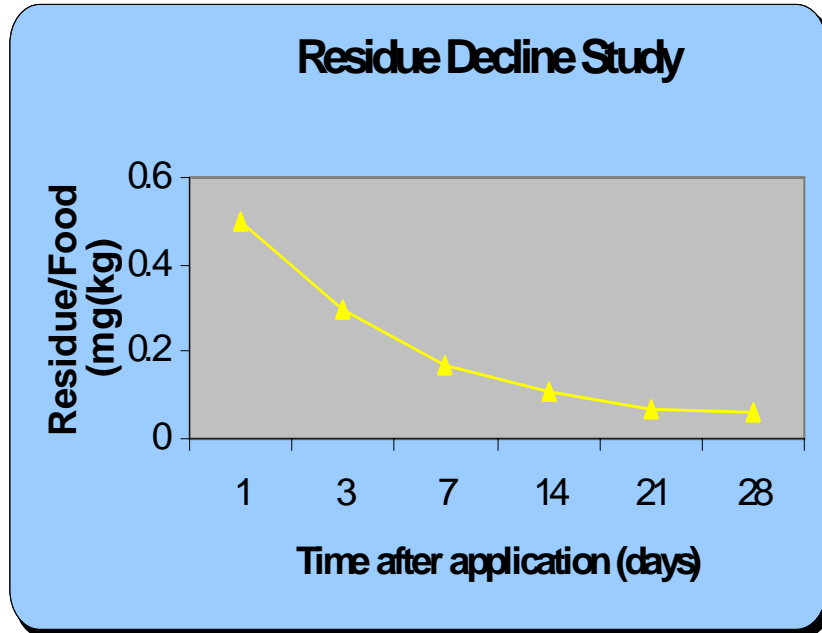
Use of agricultural compounds is quite different when being used in or on animals as opposed to plants. Animals are often treated individually when suffering specific conditions (although they may also be treated as a group), whereas for plants, a grower's entire crop is usually treated. Additionally, farmers can be more flexible when withholding animals from slaughter, whereas plants must be harvested at a certain times of the year (e.g. when appropriately ripe). This means that determining GAP and therefore MRLs for animals and plants follows a slightly different process.

#### 3.1.1 Agricultural Chemicals

Plants are very dependent on the season and food-producing plants are usually harvested at a specific time of the year (e.g. when ripe). Agricultural chemicals are an important component of pest and disease management programmes and may need to be used at various stages of crop development. For agricultural chemicals, GAP encompasses a range of application rates and frequencies up to the highest authorised use, applied in a manner that is effective but leaves the smallest residue practicable in the crop at harvest.

When registering an agricultural chemical, data are considered from residue studies that represent the range of growing conditions in the field. In each residue decay trial, samples of the crop are taken and analysed at regular intervals from the time of the application of the agricultural chemical until harvest. These data are presented in a graph similar to the one in Figure 1 below (the values used in this diagram are for illustration purposes only and are not intended to reflect a real situation):

Figure 1

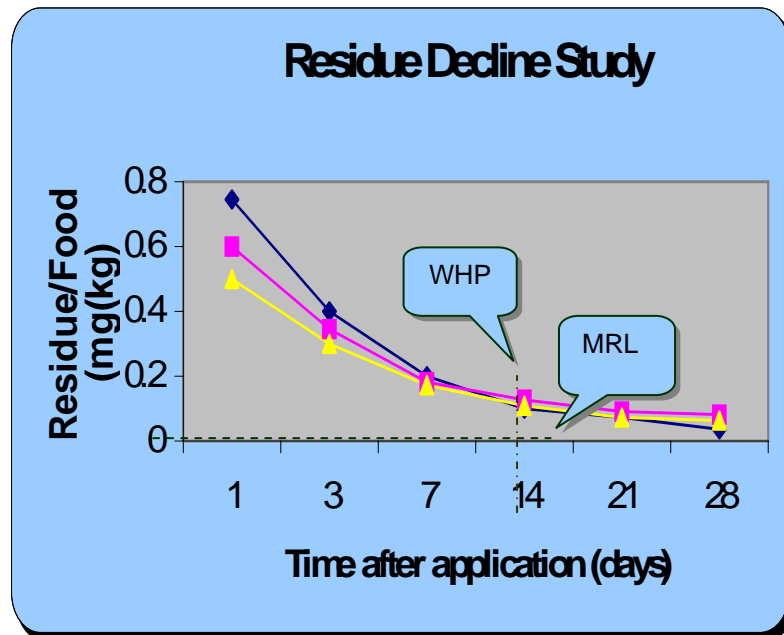


The withholding period (WHP) between the last application of the agricultural chemical and harvest is established to suit the particular pesticide and its efficacy profile in order to allow the longest interval between treatment and harvest that is compatible with good protection of the crop until harvest. In this way, residues are minimised without compromising efficacy. The residue trial data can then be used to determine what maximum residue levels are likely to remain in the crop or plant at harvest. The proposed MRL is based on these expected levels.

For example, if after application, an insecticide's residue decays until after 14 days, it is no longer present on the crop in sufficient amounts to control insect pests, then to protect the crop, the product needs to be applied every two weeks at an appropriate rate until harvest. The minimum WHP for that product on those fruit is likely to be 14 days and the fruit should not be harvested any less than 14 days after the last application of the insecticide. Using the hypothetical graphs in Figures 1 and 2, as the withholding period is 14 days, the residue after this time is 0.15 mg/kg. It should be noted that normally a number of residue decay trials are undertaken to provide confidence of the likely residues in the crop at harvest (see Figure 2 below). The proposed MRL is therefore based on a slightly higher value to take into account variations. In this case it would be likely to be set at 0.2mg/kg.

This value would only be breached if a product was not being used appropriately (e.g. the crop was harvested too soon and thus the WHP was not followed, or the application rate of the insecticide was too high).

Figure 2



In addition to this, there are times due to grower practices which mean a WHP may not be based on its efficacy. In such cases GAP may be dictated by this practice. An example is picking of strawberries during the harvesting period. As strawberries are only ripe for a short period of time, they need to be picked frequently. Hence, a short WHP may be required.

The MRL is the regulatory limit by which compliance with GAP can be *monitored*. However, it is not the tool by which the use of the agricultural compounds is *controlled*. This is done by placing controls on the agricultural chemical's registration (which is one of the main tools used by NZFSA to ensure their appropriate use). Compliance with the MRL follows naturally from compliance with the application rate, timing and WHP.

From the above, it can be seen that there is usually no direct relationship between the MRL for an agricultural chemical and its Potential Daily Exposure level ( $PDE_{(food)}$ ) determined from toxicological studies. However, the MRL is part of a system intended to keep residues of agricultural compounds as low as reasonably achievable and intake of those residues below a level likely to cause harm. See section 4.1 Protection of Public Health for an explanation of how health considerations are managed.

### 3.1.2 Veterinary Medicines

Because food-producing animals are not 'harvested' at set times of the year as plants are, there is more flexibility in determining GAP. Therefore the MRL for a veterinary medicine can be simply set at a level that will ensure the  $PDE_{(food)}$  for that compound will not be exceeded. The WHP is then set to ensure compliance with that MRL. So, whereas agricultural chemical MRLs arise out of GAP set on

the basis of efficacy, for some veterinary medicines, GAP is dependent on compliance with the MRL, which is dependent on the  $PDE_{(food)}$ . However, it is more usual for veterinary medicine MRLs to be set in a similar way to those for agricultural chemicals. The major difference is that good practice in the use of a veterinary medicine is that a WHP is set as short as possible to allow maximum flexibility for the farmer to send stock to slaughter when the market offers the best return on meat, or to ensure the least disruption to the milking regime (the discarding of quantities of milk can create environmental concerns).

Some veterinary medicines are flushed out of the animal's system so quickly that WHPs of days make no sense as sometimes residues have dropped below the level of detection within hours. Additionally, some veterinary medicines are identical to substances naturally occurring in animals. Residues of these substances can only be detected indirectly as transiently elevated levels in the animal.

The decline in residue levels in animals are determined from at least one trial, involving several animals, run under controlled conditions. From the resultant residue decay curve, a WHP can be determined to ensure that a proposed MRL is unlikely to be breached. However, when assessing residues in animals, the potential for livestock to be exposed to compounds applied to animal housing or remaining in forage crops and other sources of animal feeds is also considered.

## 4 Assessing MRL Proposals

When proposing an amendment of the MRL Standards, or indeed any standard under the Food Act, the following criteria are considered:

- the need to protect public health
- avoiding unnecessary restrictions to trade
- maintaining consistency between New Zealand food standards and those applying internationally
- the need to meet New Zealand's international obligations.

### 4.1 Protection of Public Health

Protection of public health is achieved under the risk assessment/risk management framework (i.e. determining the level of risk posed by identified hazards and then managing that risk). However, as a general rule, the conditions placed on the use of agricultural compounds are designed to ensure that residues are at the lowest level that can be achieved without compromising the product's intended purpose. Exposure to those compounds through consumption of food should not exceed the  $PDE_{(food)}$ , if one has been established by the Environmental Risk Management Authority (ERMA), or international standards for Average Daily Intakes (ADIs).

Where a risk to public health from exposure to an agricultural compound residue is identified, the mechanism for managing that risk is not usually through the MRL itself, but rather through the conditions placed on registration of products containing those chemicals. These conditions control the use of the agricultural compounds. The MRL is used to monitor compliance with those conditions (although selling food that breaches an MRL is also an offence).

#### 4.1.1 Risk Assessment

Risk assessment for agricultural compound residues consists of assessing the toxicological risk of exposure to those residues and identifying the consumption levels that the compounds should not exceed. Usually this assessment is undertaken by ERMA under the Hazardous Substances and New Organisms Act 1996 (the HSNO Act).

NZFSA's Agricultural Compound and Veterinary Medicines (ACVM) Group reviews the residue data against the limits set by ERMA and combines this with known or expected consumption patterns to

estimate potential daily intakes of the agricultural compounds. From this comparison, the ACVM Group can determine the acceptability of any proposed product use on food crops.

All companies wishing to market agricultural compounds for use in New Zealand must have their products approved under the ACVM Act and ensure that they are also covered by an approval under the HSNO Act. This process ensures that before a compound is imported, manufactured or used in New Zealand, it has been through a complete review and evaluation supported by data presented to international standards.

Significant scientific data are required to show that the compound can be used in a manner that does not have an adverse effect on public health. Where appropriate, the data should be generated in accordance with international guidelines, such as the OECD's Guidelines for the Testing of Chemicals and Good Laboratory Practice (GLP). Among other things, the studies must include data on acute toxicity, reproductive toxicity, (effect of the compound on reproduction), carcinogenicity, mutagenesis (ability of the compound to cause cancer or mutations), metabolism in plants and animals and environmental fate.

Risk assessment in the development of MRLs is based on:

- hazard identification - identification of known or potential adverse health effects in humans produced by agricultural compounds which may be present in a particular food
- hazard characterisation - evaluation of the nature of the adverse effects associated with agricultural compounds present in food, the level of the residue that is required to cause that effect, and also the level that clearly does not cause the effect. This is also referred to as the 'dose-response assessment' for chemical hazards
- exposure assessment - evaluation of the likely intake of agricultural compounds via food, as well as exposures from other sources where relevant
- risk characterisation - estimation of the severity and occurrence of known potential adverse health effects in a given population, based on hazard identification, hazard characterisation, and exposure assessment.

#### **4.1.2 Hazard Identification and Characterisation**

The metabolism and toxicological data supplied by applicants is evaluated to identify any adverse health effect that could occur if consumers were exposed to excessive levels of the agricultural compound. Hazard characterisation is carried out to estimate the level of exposure to a compound below which no adverse effects are expected.

In risk assessment, potential health hazards need to be identified first. In the hazard identification phase of the risk assessment, the results from each toxicity study are examined, with a focus on the relationship between chemical dose and toxic effect. Each study uses a range of chemical doses and measures the number and types of different toxicological responses in laboratory animals. From this, the dose producing no toxic effect in the study demonstrating the highest sensitivity is identified. This is the No Observed Adverse Effect Level (NOAEL). The NOAEL is divided by uncertainty factors to give a margin of safety, which usually includes a factor of 10 to account for potentially greater sensitivity of humans as compared with laboratory animals, and an additional factor of 10 to protect sensitive individuals. In this way the ADI is determined from the NOAEL. More information on the ADI is provided in Appendix 2.

### 4.1.3 Exposure Assessment

The  $PDE_{(food)}$  is used for dietary intake calculations where a value has been set. The  $PDE_{(food)}$  is a value set by ERMA and represents the proportion of the acceptable daily exposure to a substance via the food route as relevant to the New Zealand population. The methodology for calculation of these values is set out in the Hazardous Substances (Classes 6, 8, and 9 Controls) Regulations 2001 and can be found at: [www.legislation.govt.nz](http://www.legislation.govt.nz).

NZFSA estimates exposure to agricultural compound residues using the internationally accepted approach to calculate the National Estimated Daily Intake (NEDI). The NEDI is calculated by multiplying the Supervised Trial Median Residue (STMR) by the estimated New Zealand daily per capita consumption of the crop. Estimates of dietary intake are based on the 1997 New Zealand National Nutrition Survey (or other data as appropriate). This assessment takes account of high risk consumers and sensitive population groups (e.g. children).

- $NEDI = S (F_i \times STMR_i)$

where

- S = the sum of (for all foods);
- $F_i$  = New Zealand per capita food consumption for each given food commodity with that residue in it; and
- $STMR_i$  = the median residue observed in supervised trials for the food that  $F_i$  applies to.

The NEDI also takes other factors into account, such as levels of residues in edible portions and effects of processing, when this gives a more accurate estimate of exposure. In the past, exposure was estimated using the Theoretical Maximum Daily Intake (TMDI) model, which is the sum of the

established or proposed MRL (or permissible proportions) multiplied by the estimated average New Zealand daily per capita consumption for each food commodity.

- $TMDI = S (F_i \times MRL_i)$

where

- $S$  = the sum of (for all foods)
- $F_i$  = New Zealand per capita food consumption for each given food commodity with that residue in it.

This was a very simple and straightforward approach but it greatly overestimates the true level of exposure to the population. It is very rare that residues will ever approach the MRL and often no residues whatsoever are detected. The NEDI is a more accurate estimate of actual exposure and therefore a more useful tool in determining whether residues pose any risks to public health. When assessing public health risks, NZFSA's ACVM Group calculates the NEDI and compares this with the  $PDE_{(food)}$ .

An agricultural compound's use pattern is deemed acceptable provided that the NEDI, based on typical residues remaining in food produced in accordance with GAP, is not more than the  $PDE_{(food)}$ . This approach also factors in dietary considerations for different consumption patterns of children and other population sub-groups to ensure that sensitive populations are protected.

#### 4.1.4 Risk Characterisation

A risk characterisation is the expression of health risk in quantitative or qualitative terms. In this case, the expression is the proportion of the  $PDE_{(food)}$  represented by the NEDI. The health risks from agricultural compounds, and most other chemicals that are not regarded as primary carcinogens, have been shown in extensive toxicity testing to have a threshold dose below which no adverse effects are expected. The risk characterisation therefore relies on the  $PDE_{(food)}$  as the benchmark for protection of public health. As already discussed under the hazard identification step, the  $PDE_{(food)}$  adds a large margin of safety, resulting in a level well below that observed to cause any toxic effects in animal studies. Additionally, the actual intake of agricultural compound residues is overestimated because it is extremely unlikely that each and every item of food consumed over an individual's lifetime will have been treated with a particular compound.

### 4.1.5 Risk Management

Until ERMA has set an appropriate  $PDE_{(food)}$  for any given agricultural chemical, an appropriate ADI is used in the absence of a  $PDE_{(food)}$ . The ADI value is used in exactly the same way as the  $PDE_{(food)}$ , however as a default position, NZFSA bases assessments on 50% of the ADI value.

#### Management of Toxicological Risks

MRLs for particular plant compounds are not *based* on the  $PDE_{(food)}$ . However it is true that no MRL would be acceptable unless its potential daily intake was no more than the  $PDE_{(food)}$ . The toxicology and residue data for those compounds have been assessed and conditions are placed on their registration to ensure that the MRLs are not exceeded. Such conditions may include limiting the permissible uses of the compound or extending the WHP.

#### Other means of Protecting Human Health

Other human health-related risks arising from the use of agricultural compounds are managed through separate processes. For example, risks of promoting the development of antibiotic resistant human pathogens through inappropriate use of antibiotics are managed through the conditions placed on the registration of veterinary antibiotics.

If a product is also a prescription medicine under the Medicines Act, it may not be registered as an agricultural compound until the Director-General of Health has granted consent. This gives the Ministry of Health the opportunity to identify public health hazards other than potential residues and indicate the kinds of controls that would be needed to manage the risks. The Ministry of Health has the function of improving, promoting, and protecting public health.

If a product is also a hazardous substance, it cannot be registered as an agricultural compound until approval has been granted under the HSNO Act by ERMA. The purpose of the HSNO Act is 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. ERMA considers the potential exposure to a hazardous substance through all exposure routes, including ingestion of food, and may impose, limits in air, water, soil and on surfaces that must not be exceeded when the substance is used.

NZFSA imposes conditions on the use of agricultural compounds (which could include limiting who can use a product and under what circumstances) to ensure that any identified risks are adequately managed. Where a risk identified by NZFSA, the Ministry of Health or ERMA cannot be managed adequately via a wide range of possible conditions then the product would not be registered, even though a MRL may have been set for its active ingredient.

## 4.2 Implications for Trade

### Domestic Food Production

Domestic food production and trade is usually facilitated by new MRLs. The proposed MRLs permit residues up to the specified level, which in turn reflects GAP or appropriate use in food-producing plants and animals.

### Imported Foods

Under the MRL Standards, imported food commodities may comply with either the appropriate Codex MRL, the limits specified in the MRL Standards, or the 0.1 mg/kg default level. Although additional MRLs do not necessarily affect imports, they could ease the importation of some foodstuffs because the new MRLs complement the Codex permission.

### Exported Foods

New Zealand MRLs do not apply to exports. However, food produced with agricultural compounds used in accordance with GAP is unlikely to breach New Zealand MRLs, irrespective of whether the food is sold domestically or exported. Export food commodities must also comply with requirements of the country importing the produce. Occasionally, MRLs are set lower than GAP requires. This can ensure international market access for the food commodities listed.

## 4.3 Consistency with International Food Standards

There is no requirement that the MRLs for New Zealand domestic production are the same as those set by other countries or international bodies (e.g. Codex). However, maintaining consistency with food standards applying internationally is an important aspect of New Zealand food standards development. New Zealand's approach to MRL setting is aligned with international practice, and recognises Codex MRLs for imported food.

## 4.4 Implications for International Obligations

MRLs for agricultural compounds fall outside the scope of the joint Australia New Zealand food standard-setting system. This is because the MRLs reflect agricultural practices specific to the New Zealand climate, production systems and local pest and disease pressures.

Although the proposed MRLs are for foods sold domestically, under the Trans Tasman Mutual Recognition Arrangement (TTMRA) between Australia and New Zealand, New Zealand manufacturers

can export foods to Australia if they meet New Zealand domestic requirements. Equally, foods meeting Australian domestic food requirements may be imported into New Zealand from Australia.

New MRLs are consistent with New Zealand's obligations under the World Trade Organization (WTO) Agreement on the Application of Sanitary and Phytosanitary Measures (the SPS Agreement). The MRLs are recommended on the basis of internationally approved protocols and criteria that are accepted by the WTO. In addition, under the MRL Standards, imported food commodities may comply with either the appropriate Codex MRL or the New Zealand standard. As a matter of course, New Zealand MRLs are notified internationally under the SPS Agreement.

## Appendix 1: Glossary of Terms

### Relevant Agencies

- *ACVM Group*: Agricultural Compounds and Veterinary Medicines Group - The section of NZFSA responsible for the registration of agricultural compounds
- *Codex*: Codex Alimentarius Commission
- *EMEA*: European Agency for the Evaluation of Medicinal Products
- *ERMA*: Environmental Risk Management Authority
- *FAO*: Food and Agriculture Organization of the United Nations
- *FSANZ*: Food Standards Australia New Zealand - a bi-national independent statutory authority that develops food standards for composition, labelling, contaminants, and microbiological limits, that apply to all processed foods produced or imported for sale in Australia and New Zealand
- *JECFA*: Joint FAO/WHO Expert Committee on Food Additives
- *JMPR*: Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues
- *NZFSA*: New Zealand Food Safety Authority
- *OECD*: Organisation for Economic Cooperation and Development
- *TTMRA*: Trans Tasman Mutual Recognition Arrangement
- *USEPA*: United States Environmental Protection Agency
- *WHO*: World Health Organization
- *WTO*: World Trade Organization

### Technical Terms

- *ADI*: Acceptable Daily Intake - the daily intake which, during an entire lifetime, appears to be without appreciable risk on the basis of all the known facts at the time

- *GAP*: Good Agricultural Practice
- *GEMS*: Global Environment Monitoring System - Food Contamination Monitoring and Assessment Programme
- *GLP*: Good Laboratory Practice
- *MRL*: Maximum Residue Limit
- *NEDI*: National Estimated Daily Intake
- *NOAEL*: No Observed Adverse Effect Level
- *NOEL*: No Observed Effect Level
- $PDE_{(food)}$ : Potential daily exposure via food
- *STMR*: Supervised Trial Median Residue
- *TMDI*: Theoretical Maximum Daily Intake
- *WHP*: Withholding Period

## Appendix 2: Establishing an ADI, ADE, or PDE<sub>(food)</sub>

The lowest 'no observed adverse effect level' (NOAEL) or 'no observed effect level' (NOEL) is taken from a consideration of all the toxicological studies submitted in support of the registration of a substance. For most compounds where the long-term (chronic) hazard is of concern, long-term or lifetime feeding studies are the most appropriate. For those compounds that pose a short-term (acute) hazard, short-term studies are the most appropriate.

The ADI is defined by the WHO (*The WHO Environmental Health Criteria Series, No. 70: Principles for the Safety Assessment of Food Additives and Contaminants in Food*, Geneva: World Health Organization, 1987) as being:

*'the daily intake which, during an entire lifetime, appears to be without appreciable risk on the basis of all the known facts at the time'*

Without appreciable risk is further defined by the WHO to mean:

*'the practical certainty that injury will not result even after a lifetime of exposure'*

The Acceptable Daily Exposure (ADE) is estimated by ERMA NZ in the same way as the Average Daily Intake (ADI), and essentially has the same definition. The difference between the ADI and the ADE is that the ADE is to cover intakes of a substance from all routes of exposure (including dermal and inhalation exposures), whereas the ADI refers to oral intakes only. Usually, because the same data is used to estimate the ADE, the numerical value of the ADE will be the same as that of the ADI.

The Potential Daily Exposure from food (PDE<sub>(food)</sub>) is estimated from the ADE for a substance, based on the likely routes of exposure to that substance, and the likely contribution of the route of exposure to the overall exposure of an individual. In no case may the sum of all exposure routes (PDE<sub>(total)</sub>) exceed the ADE. In the absence of any specific data enabling the establishment of specific contributions to the overall exposure of an individual to a substance, the PDE<sub>(food)</sub> is normally assumed to be 50% of the ADE.

Usually, two 'uncertainty' factors (or 'safety' factors) are applied to the NOAEL to establish the ADI or ADE. The first factor (the NOAEL divided by 1 to 10) is to accommodate the variation between species in susceptibility. This factor allows for the possibility that people may be even more sensitive to the toxic effects of the chemical than the most sensitive test species.

The second factor is to accommodate the variation within the human species - the human population is far more diverse and lives longer in a far more complex environment than do laboratory animal populations. The second factor (NOAEL divided by 1 to 10 again) allows for the possibility that some

individuals within the general population may be more sensitive to the toxic effects of the chemical than the majority of the population. Young children are often considered to be part of this group of particularly sensitive individuals.

A further uncertainty factor (NOAEL divided by 1 to 10 a third time) may be used if the toxicological data package is deficient in some way (but still allows a proper assessment of the substance), or some other circumstance indicates that an even greater margin is required (such as the severity of a known toxic effect at higher dose levels).

Therefore, the ADI or ADE equals the NOAEL divided by the combined factor, usually 100 or 1000, depending on the specific details presented in the toxicological evaluation.