Australian Government

Australian Pesticides and Veterinary Medicines Authority

Residues (Part 5A)

This guideline describes the general requirements for submitting residue data for the registration of agricultural chemical products, including the establishment of maximum residue limits (MRLs) and withholding periods.

The data submitted is evaluated by the Australian Pesticides and Veterinary Medicines Authority (APVMA). Where relevant, we may take other information into consideration, including recommendations made by other governments and internationally recognised organisations. Evaluations are subject to peer review. We seek public comment when a product containing a new active constituent is considered for registration for the first time or when a product containing an APVMA-approved active constituent is first considered for registration for use in food-producing crops or animals.

Final recommendations for MRLs are entered into the Agricultural and Veterinary Chemicals Code Instrument No. 4 (MRL Standard) 2012. The MRL standard includes tables listing the MRLs of agricultural and veterinary chemicals, tables listing the portion of the commodity to which the MRL applies, residue definitions and uses of substances where MRLs are not necessary. Where appropriate, the APVMA promulgates the MRLs into the Australia New Zealand Food Standards Code – Standard 1.4.2 – Maximum Residue Limits (Australia Only). These standards are referenced by various state and territory laws.

MRLs may be subject to reconsideration, which could be prompted by a change in use of a chemical or by availability of new data.

Further information can be found on the Organisation for Economic Co-operation and Development (OECD) website (under Publications on pesticide residues) and the Food and Agriculture Organization of the United Nation's website (under AGP–JMPR Guidance and related documents).

1. General instructions

1.1. Residue data

Both the field and laboratory phases of residue studies conducted in Australia, and used to support the establishment of MRLs in food and feed commodities, must be generated in accordance with the OECD principles of good laboratory practice (GLP).

Applicants conducting GLP-compliant residue trials in Australia should refer to the OECD's publication, No.1: Principles of good laboratory practice.

For a study conducted in Australia to be GLP-compliant, it must be undertaken by a facility that is accredited and within the Australian GLP compliance monitoring program. The National Association of Testing Authorities (NATA) is the sole Australian organisation responsible for monitoring compliance with the OECD principles of GLP. Additional information on GLP accreditation in Australia is available from NATA. Overseas studies must be conducted by facilities covered by the relevant country's GLP compliance monitoring program.

Certain residue trials are exempt from GLP requirements:

- A submission to the APVMA after 1 January 2003 may contain non–GLP compliant studies but only if those studies were started in Australia before 1 January 2003; or, for overseas studies, only if the studies were started before 1 January 2003 and conducted in accordance with the standards in place in the relevant country at the time when the studies were initiated.
- Characterisation of test items (active ingredients or formulation) for use in GLP studies do not need to be conducted according to the OECD principles of GLP, but it is recommended that a laboratory accredited to ISO/IEC 17025 by NATA or a NATA mutual recognition partner be used. Note: Some member states of the European Union may require that characterisation of test items be in accordance with GLP. Applicants intending to submit residue data to both the APVMA and those member states may wish to comply with the standards applied by the member states to the characterisation of test items.
- The GLP requirement is not mandatory for studies in support of permits; however, it is strongly recommended.

1.2. Residue guidelines

The APVMA, in cooperation with peak industry bodies, has prepared a series of residue guidelines addressing specific residue requirements. Some of those guidelines are referred to in the explanatory sections of this document. They should be consulted and followed where relevant.

2. Outline of data requirements and application format

This section describes the data requirements for Part 5A – Residues of an application for agricultural chemical products.

2.1. Residue studies

Data should show whether, and at what level, residues occur in edible crops, fodder, animal tissues, milk and eggs.

The formulation to be sold in Australia should be subjected to trials that address the maximum use rate. You may also run a concurrent trial using a rate of 1.5 to 2 times the maximum recommended application rate at one of the trial locations.

Experiments should show the rate of disappearance of residues and/or the interval that elapses before the residues substantially disappear.

You should plan the trials with care so that the results will enable the necessary MRLs and withholding periods to be recommended with confidence. The APVMA should not be called upon to extrapolate or otherwise place undue dependence on inadequate data. Residue trials should therefore be extensive enough to provide the opportunity for all probable sources of variation to be expressed.

You should produce residue data from home garden applications and/or argument to justify the safety of the proposed use for products intended for application in the home garden to food crops, and for which no MRL and withholding period has been established for the same use pattern in broad-scale agriculture.

2.1.1. Data requirements for Part 5A – Residues

- Table of contents
- Summary of residue studies
- Residue database form
- Crop residues
  - Crops for human consumption
  - Crops used as livestock feed

- Livestock, poultry, egg and milk residues
  - From direct application (not relevant for agricultural chemicals)
  - From feeding of treated crops (animal transfer data)
  - Wool residues (if applicable)
- Analytical methods
- Fate of residues during storage, processing and cooking
- Maximum residue limits
  - Australia
  - Other countries
  - Codex
  - Applicant's proposed MRL
- Applicant's proposed withholding periods

2.2. Residue trials

You must provide full details of trial procedures, including data on variables that might influence the decline of residues. Each study reported must include an abstract summarising the methodology and the results.

Each application should contain a summary of the residue application. Normally the summary should not extend beyond a few pages, and we prefer tables as a means of condensing information. You are also required to submit:

- a residue database form providing an overview of the trial submitted
- a residue database trial summary.

Further information is provided in the guideline Reporting of residue trials.

2.2.1. Residue database form – overview of trial submitted

These forms should include all residue trials (Australian and overseas) submitted. Complete a separate sheet for each Australian residue trial or for overseas trials if no Australian trials are submitted. The format may be modified to suit individual company practice, but all of the information must be provided. Use tabular format where possible.

- Identifying information:
  - Trial reference, volume and page number
  - Year
  - Location
  - Dose rate
  - Number of applications and intervals
- Date
- Crop or animal
- End-use product name
- Active constituent
- Formulation type and level of active constituent
- Recommended dose rate
- MRL proposed
- Withholding period proposed

2.2.2. Residue database – trial summary

- Date
- End-use product name
- Active constituent
- Formulation type and level of active constituent
- Trial reference and page number in submission
- Location of trial [insert district and state]
- Recommended dose rate [insert label recommendation]

- Dose rate used [insert rate used in trial]
- Method of application [include equipment and spray volume used in trial, as applicable]
- Number of applications/intervals [insert number of treatments in the trial and the intervals between (days)
- Crop and area treated, or number and species of animals treated
- Product(s) and portion(s) analysed
- Identifying information:
  - Date of application
  - Date of sampling
  - Interval (days)
  - Residues found (mg/kg)
- Analytical method no./ref
- Limits of detection
- Method recoveries
- Metabolites included in analyses
- Organisation performing field trial (including officers' names)
- Laboratory performing analyses(including officers' names)
- Date of analyses

2.3. Data requirements

2.3.1. Crop residue data

Crop field trials (also referred to as supervised field trials) are conducted to determine the magnitude of the pesticide residue in or on raw agricultural commodities, including feed items, and should be designed to reflect pesticide use patterns that lead to the highest possible residues. The objectives of crop field trials are to:

- quantify the expected range of residue(s) in crop commodities following treatment according to the proposed or established good agricultural practice
- determine, when appropriate, the rate of decline of the residue(s) of plant protection product(s) on commodities of interest
- determine residue values such as the supervised trial median residue and the high residue for conducting dietary risk assessment and calculating the dietary burden of livestock
- derive MRLs.

The guideline, Residue trials to obtain permanent maximum residue limits for crops, provides information on conducting crop residue trials.

2.3.2. Livestock residue data

Residue data are required for pesticides that are to be applied to livestock premises, regardless of whether livestock are likely to be present at the time of application. Data should be presented to show the levels of residues in commodities from livestock and poultry normally held in such premises. Those commodities include meat, fat of meat, edible offal, eggs and milk.

Further information is provided in the guideline, Control of pest species in animal housing.

2.3.3. Animal transfer data

Residue data are required for pesticides applied to crops that may later be fed to livestock and/or poultry (such as pasture, forage crops, silage, hay and grain) or that may be eaten by grazing livestock (failed crops or crop stubble). Such data are necessary to enable the establishment of MRLs in livestock and livestock products. The data should indicate the levels of residue in the crop concerned, and in commodities from livestock and poultry that would normally eat such plant material. Those commodities include meat, fat of meat, edible offal, eggs and milk.

Guidance on the conduct of animal transfer studies is provided in the guideline Animal transfer studies and in the Food and Agriculture Organization's guidelines on pesticide residue trials.

Important points to consider in designing these studies are:

- using animals in store condition (avoid animals that are rapidly gaining weight, if possible)
- feeding animals on a maintenance diet
- if possible, confirming that residue levels in animals have reached plateau
- where appropriate, performing depletion studies.

2.3.4. Metabolism studies

The APVMA also evaluates metabolism and kinetics data. Refer to the metabolism and kinetics section of the regulatory guidelines for more information.

2.3.5. Overseas residue data

You may submit relevant data from residue trials carried out overseas in support of an application. However, in most cases you will be expected to conduct, at a minimum, confirmatory tests under typical conditions of use in Australia to indicate the levels of residues under local conditions, and to validate any extrapolation from the overseas data. Australian residue data are required for agricultural chemicals whose use patterns or conditions of use in Australia are different from those overseas.

2.3.6. Extrapolation from one species to another

Data on residue levels in one species of plant or animal do not necessarily represent the residue levels that might reasonably be expected to occur in distinctly different species. In the case of plants, we will give consideration to the use of satisfactory data from several crops in a crop group to reflect the position on another member of that group, or even to a very similar crop in another group, provided use patterns are comparable. We will examine each case on its merits, which will include consideration of the similarities in the metabolic pathways for these chemicals.

The Codex classification of foods and animal feeds has been developed by the Codex Committee on Pesticide Residues for international use. It provides lists of crops and raw agricultural commodities that are considered essentially similar for the purposes of recommending MRLs.

Overseas residue data may assist in extrapolating Australian data from one crop when MRLs are sought for an allied crop. If overseas data show that residues are substantially similar for a number of related crops, this could provide a good case for extrapolating Australian data on one or two crops to other similar crops in a crop group.

2.3.7. Herbicide tolerant crops

Herbicide-tolerant crops are developed to be treated over the top with a relevant herbicide during an application window that is wider than would be the case in a non-herbicide-tolerant crop. The application of a herbicide over the top of a herbicide-tolerant crop may present increased risk with regard to residues.

The trait conferring herbicide tolerance may alter the way in which the herbicide is transformed into a residue. Those transformation pathways may be quite different to the pathways in a conventional crop. OECD test guideline 501 clearly describes the situations under which additional metabolism studies need to be conducted for a herbicide-tolerant crop to determine if the residue definition resulting from the application of a herbicide over the top of a herbicide-tolerant crop is different from the definition that results from use in a non-herbicide-tolerant crop. See the OECD residue chemistry test guidelines for more information.

Herbicide-tolerant crops may modify the behaviour of the chemical degradation pathways, which therefore affects the residue profile. The pathways may respond differently to variations in formulation, application timing and application rates compared to those of conventional crops. The arguments that may be made for a non-herbicide-tolerant crop do not apply to herbicide-tolerant crops and use of a herbicide over the top. Assessment of residue data has established that the differences in residue concentrations of a herbicide used over the top of a herbicide-tolerant crop when compared to a non-herbicide-tolerant crop can be significant, and therefore residue data will be required to support these uses.

Comparability of formulation, application timing and use rates are not considered sufficient grounds on which to make a determination on the adequacy of an existing MRL. Data or scientific argument that may be provided for a non-herbicide-tolerant crop is not acceptable for a herbicide-tolerant crop due to possible variations in the response of the herbicide-tolerant plant to the herbicide.

The guideline, Residue trials to obtain permanent MRLs for crops, outlines the numbers of trials that are required for different crops for the purposes of setting an MRL.

As with efficacy and crop safety trials, the APVMA requires residue trials to be conducted on the specific herbicide-tolerant crop for which use over the top is being sought, and in locations that are representative of the main growing regions in Australia. Data from trials conducted with superseded commercial herbicide-tolerant traits or varieties are not acceptable. The maximum use pattern (as per the label) must be trialled and samples collected in accordance with the guidance on residue trials to obtain permanent MRLs for crops. If the directions for use specify a variety of application timings, each trial must include a number of treatment regimens to ensure that the maximum residue scenario is addressed.

You should contact the APVMA and discuss the trial protocol if you are unsure about the required number of confirmatory trials. If the commercially available herbicide-tolerant crop is considered to be a major crop, the GLP requirement will apply.

2.4. Residue analytical method

You must provide complete details of the analytical methods used for determining residues in the trials conducted. The methods should:

- possess a suitable degree of specificity for the agricultural chemical in question
- have a limit of analytical quantitation at a level considerably lower than any MRL proposed for finite residues (refer to the guideline, Maximum residue limit proposals 'at or about the limit of analytical quantitation')
- be substantiated by adequate evidence in the form of blanks, recovery data and extraction data to show that the method is effective for determining residues in the substrates analysed and at the levels under consideration. If the analytical method involves an instrumental determination such as spectrophotometry, high-performance liquid chromatography or gas–liquid chromatography, specimen output charts showing blank determinations and recovery determinations should be provided to assist in evaluating the method.

It is important to relate the residue analytical procedures applied in the particular trial to those provided in the supporting documentation. The detailed method of analysis should be clearly identified with a distinctive reference number. The same reference number must then be specified in the section providing the relevant trial data, with an indication that this was the analytical method used to determine the residues.

Because methods can be modified over time, problems arise when, in a subsequent application, reference is simply made to previously submitted methodology. The complete method must again be described in a new application.

A method of analysis suitable for routine monitoring and for regulatory control should be submitted. In some cases, the method may be the same as the method used for determining the residues in the trials conducted for the purposes of requesting an MRL. In other cases a separate method may be required for regulatory purposes.

Further information is given in the guideline, Residue analytical method.

2.5. Post-harvest applications

If post-harvest application is proposed, good agricultural practice dictates that withholding periods will not be practicable, and hence will not be approved in other than exceptional circumstances.

The information required will include multiple replications to show variability of the residue. Replication within one trial will not be sufficient. You should conduct multiple trials under different conditions, including using different operators and equipment. Any indication of residue breakdown with time, with manufacturing processes, or with domestic use is of significance and should be reported.

Further information is given in the guideline Crops – post-harvest applications except fumigants and grain protectants.

2.6. Fate of residues during processing and cooking

You should provide any available information about the effect of processing and cooking on the level of residues at harvest, slaughter, and other relevant times, so that the likely pesticide intake in diets can be estimated. Details should be inclusive of all components of the residue definition.

In some circumstances, you will need to provide information on the level of residues in the food as consumed (for example, the residue levels in banana pulp as compared to the whole commodity). This could be required for a first application, or at a future time if the use pattern is expanded to include further crops, or in situations where the acceptable daily intake is a low number in relation to the residues of intake of the whole commodity.

Further information is given in the guideline, Processing studies.

2.7. Fate of residues during storage

Storage stability data representative of the proposed uses of the product are required for treated food commodities in order to ensure that MRLs are based on accurate knowledge of the residue level in a commodity.

If residue samples are always analysed within 30 days of their storage in frozen conditions, applicants can omit conducting a freezer storage stability study provided justification is given, for example basic physical chemical properties data show residues are not volatile or labile.

Further information is given in the guideline, Stability of residues during storage.

2.8. Nomination of maximum residue limits and withholding periods

You should nominate a proposed complete use pattern, including withholding periods and proposed MRLs. The pertinent withholding period and residue restraints to be included on proposed labels should be selected from those specified in the relevant Agricultural Labelling Code.

When conducting trials where a finite residue occurs, and/or when a withholding period is necessary, the sampling regime should be spread across the time range within which the withholding period is expected to occur. It is essential to sample at the recommended withholding period; otherwise, the withholding period will be set at the next longest sampling time.

For further information, refer to the guidelines, Withholding periods and Maximum residue limit proposals ‘at or about the limit of analytical quantitation’.

2.9. Establishment of maximum residue limits

The use pattern of an end-use product influences the level and nature of residues that will occur in food. Applications should therefore include the complete, detailed use pattern proposed for the product, including rate, timing (including interval between treatments) and number of applications, and withholding periods. You are also required to nominate MRLs for the active constituents contained in the product. The MRLs nominated must be compatible with the proposed use pattern of the product and based on the Codex nomenclature for commodities.

Regardless of the apparent lack of toxicity of residues, human intake of agricultural chemicals should be kept to a minimum consistent with effective use. If the residue level immediately after application is unacceptably high, the use pattern will have to be re-examined or rejected.

Further information is given in the guideline, Definition of residues for the purpose of setting a maximum residue limit.

2.9.1. Maximum residue limits ‘at or about the limit of analytical quantitation’

If use of the end-use product according to the proposed use pattern (which includes the withholding period) is shown not to give rise to detectable residues in food, an MRL will normally be recommended ‘at or about the limit of analytical quantitation’. Such use patterns (including the withholding period) must be compatible with good agricultural practice.

If the end-use product is to be used on this basis, the residue trials must show the rate of decline and ultimate reduction of residue levels to the point at which they are in fact ‘at or about the limit of analytical quantitation’.

Acceptable evidence may include reliable and extensive data from overseas experiments that demonstrate the absence of residues of the parent compound or its toxicologically significant metabolites following application as proposed. However, data from locally conducted trials may still be necessary.

For further advice, refer to the guideline, Maximum residue limit proposals 'at or about the limit of analytical quantitation'.

2.9.2. 'Finite' maximum residue limits

If use of the end-use product according to the proposed use pattern (which includes the withholding period) is shown to give rise to detectable residues in food, you will need to establish a 'finite' MRL.

This will always be the case when residues are present in the crop at harvest or in an animal at slaughter.

2.10. Compounds for which maximum residue limits are not necessary

Wherever possible, you should propose an entry for inclusion in Table 1 (Maximum residue limits of agricultural and veterinary chemicals and associated substances in food commodities) of the MRL standard.

A proposal for a Table 5 (Uses of substances where maximum residue limits are not necessary) entry in the MRL standard will only be considered if you can clearly demonstrate that a Table 1 entry is not practicable for some stated, and supported, reason. Merely requesting a 'Table 5 entry' or 'exemption from an MRL' will not be considered adequate. You should also provide the proposed wording for the entry in Table 5.

In order to substantiate the proposal, you must:

- submit appropriate detailed residue data, or
- present sound scientific argument as to why such data are not necessary.

2.11. Special requirements for seed dressings

Seed dressings for use on cereal seeds are subject to special requirements laid down by the former Standing Committee on Agriculture. Evidence of their fate when fed to livestock, including poultry, must be presented. Detailed information on these requirements can be found in the guideline, Animal feeding studies for seed dressings.

3. Other related studies

If data are required to show that the use of agricultural chemicals is not likely to affect the taste of produce (organoleptic tests) or have any effect on subsequent processing (such as brewing, wine fermentation or cheese manufacture), you should include those data in the efficacy and safety (Part 8) section of your application.

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2	8 June 2016	Clarification of terminology in heading 2.3.7 to reflect the text and intent of the operational notice that this section replaced
1	1 July 2014	First version

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator of agricultural and veterinary (agvet) chemical products.

We acknowledge the traditional owners and custodians of country throughout Australia and acknowledge their continuing connection to land, sea and community. We pay our respects to the people, the cultures and the elders past, present and emerging.