TOXICOLOGY AND RESIDUE REQUIREMENTS FOR HERBICIDES

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Summary. The National Health and Medical Research Council's (NH&MRC) toxicology and residue requirements for herbicides are amongst the most stringent in the world. Considerable toxicological data is necessary to assess the toxic potential of a herbicide to users and consumers prior to its release into the marketplace. From this data acceptable daily intakes (ADIs) and poisons schedules are established. Appropriate residue data enables establishment of maximum residue limits (MRLs). Residue trials involve the generation of large amounts of information to assess whether potentially hazardous residues may occur. Alachlor and dinoseb are recent examples of herbicides where the NH&MRC recommendations have been amended.

INTRODUCTION

Federal clearance of a new herbicide for use in Australia requires submission of a considerable package of toxicology and residue data to the National Health and Medical Research Council (NH&MRC). This data is reviewed by expert Committees of the NH&MRC to assess the safety of the herbicide to applicators and consumers of any produce which may contain residues. This paper will review the NH&MRC requirements for toxicology and residue data for new herbicides.

TOXICOLOGY REQUIREMENTS

The current NH&MRC requirements for toxicology testing of new herbicides are specified in the Department of Primary Industry document PB310B-Requirements for Clearance of Agricultural Chemicals. The broad areas in which testing is required are:

1. Toxicokinetic studies
2. Acute toxicity testing
3. Sub-chronic toxicity studies
4. Chronic toxicity studies
5. Oncogenicity (carcinogenicity) studies
6. Reproduction and developmental toxicity (teratology) studies
7. Genotoxicity (mutagenicity) studies

From these studies and using all the information available from human exposure it is possible to assess the toxic potential of a chemical. This information enables us to answer commonly asked questions such as:-

"Does the chemical cause cancer in exposed persons?"
"If I am exposed to the chemical will this affect the development of my children?"
"Does exposure to the chemical make you ill?"

Few people are aware that the NH&MRC requirements are internationally recognised as being amongst the most stringent in the world.

One of the main outcomes of the review of the toxicology data is the establishment of an acceptable daily intake (ADI). The ADI is usually defined as the daily intake which, during an entire lifetime, appears to be without

appreciable risk on the basis of the available information at the time. It is derived from the "no-effect-level" (NEL) which is the highest dose in the animal studies which result in no toxic effects. Safety factors are then applied to the NEL to arrive at an ADI. Generally, the lowest safety factor used is 100, which indicates the large margins of safety applied to such chemicals. The use of a chemical is only considered acceptable when human exposure does not exceed the ADI.

A further important outcome of the review of the toxicology data is the establishment of a poisons schedule. The schedule is a general indicator of the toxic potential of a chemical. Herbicides are usually scheduled as:

Exempt	-	very low hazard potential
Schedule 5	-	low hazard potential
Schedule 6	-	moderate toxicity
Schedule 7	-	dangerous poison

These schedules also dictate the availability of a chemical, i.e. exempt substances are available without restriction whilst schedule 7 substances are highly restricted (e.g. to authorized persons only). In addition, from its review of the toxicology data, the NH&MRC recommends first aid and safety directions for the chemical. These appear on labels to assist the user in reducing exposure where necessary and when accidental or deliberate poisoning occurs.

RESIDUE REQUIREMENTS

Residue data are required to be submitted to the NH&MRC for determination of a maximum residue limit (MRL). The MRL is defined as the maximum concentration for a chemical residue resulting from the use of a chemical according to good agricultural practice. It is a legal limit and not a measure of safety of a chemical. However, MRLs are not established if use of a chemical will result in residues, the consumption of which will cause the ADI to be exceeded.

The current NH&MRC requirements for residue trials are specified in PB310B. For herbicides, trials are required to demonstrate whether residues will occur in crops for human consumption or potential animal feed (e.g pasture, straw) following use of the chemical under good agricultural practice (GAP). Information required from these trials is listed in Table 1. Guidelines for the undertaking of residue trials for the NH&MRC are published by the Department of Primary Industry as document PB412. This document is a modification of guidelines developed by the FAO/WHO Codex Committee on Pesticide Residues.

Table 1. Information requirements for residue trials

1. <u>General information on the supervised trail</u>

- Pesticide (active constituent and trade name)
- Formulation (including concentration)
- Trial number and type (field/glasshouse/other)
- Commodity
- Varieties
- Test location (district and site)
- Soil characteristics, pH, physical and chemical properties
- Name (and signature) of the person(s) responsible for the trial and for collecting the sample.

2. Application data for field trials

- Crop planting or sowing date
- Description of plot plan/crop layout/cropping system
- Plot size or number of plants per plot/unit area
- Number of plots per treatment
- Target pest or disease (if any)
- Method of application and equipment
- Number of applications and application date(s)
- Application details (overall, banded, etc.)
- Does rate - active ingredient/ha
  - weight/volume of formulation/ha
  - applied dilution
- Climatic conditions during and after applications, preferably for the whole period of the trial
- Other pesticides applied to trial plots with relevant details, as above
- Cultural treatments before, during and after applications - include irrigation and fertilizer information
- Growth stage at (last) treatment

3. Sampling data

- Growth stage at sampling - normal harvest data
- Method of sampling
- Sampled part(s)
- Number of samples taken per test/treatment replication
- Number of units in sample, if relevant (e.g. lettuce, pome fruit)
- Sample weight and preparation (trimming/washing/other, if common practice in preparing the commodity)
- Control/treated
- Date of sampling with time interval between last application and sampling
- Storage conditions before shipment
- Date shipped
- Method of packaging

As indicated previously, apart from residues in crops, consideration must be given to residues of the herbicide in potential animal feed. Thus, residue data must be generated for animals following the feeding of residues to which animals may be exposed. Whilst there are no guidelines to assist in the planning of these trials the information requirements are generally as for those listed in Table 1. In addition consideration needs to be given to the following points:

- an adequate number of animals must be included at each dose rate
- the dose rate is the maximum residue to which animals may be exposed and twice this level
- any potential for accumulation must be examined
- the analytical method must be capable of detecting plant metabolites in animal tissue.

An important aspect of undertaking trials is to ensure that the reporting is adequate to enable independent evaluation of the data by the NH&MRC. A standard format for reporting trials has been devised and is included in PB412. This format ensures that the information required in Table 1 is appropriately reported. In addition, submission of data to the NH&MRC requires a summary of each trial and a summary of all experiments to be

provided. When considering undertaking a residue trial, one important overriding requirement is to ensure that the worst possible situation likely to be encountered has been examined so that the figure obtained is truely the maximum residue limit. Special consideration must therefore be given to those factors which can be most significant in affecting residue levels. Some of these are listed in Table 1, but emphasis must be placed on:

- rate of application
- time and number of treatments
- climatic conditions

Other less obvious factors such as previous use of the chemical on the trial plot and its persistence must also be taken into account. Lastly, it is normally required that residues are followed to the limit of analytical determination. However, this will often be limited by the growth of the crop and the closeness of application to harvest.

Despite the availability of guidelines for the undertaking and reporting of residue trials there continues to be a significant number of submissions to the NH&MRC which are deficient for one or more reasons. Some of the most common problems are:

- mean residue figures are supplied but not the individual figures
- the quoted analytical method determined metabolites but no metabolite figures are reported
- codes are inadequate to correlate treated plots, samples and analyses
- analytical methods and recovery data are absent
- a summary instead of full details of the trial is provided.

One question that often arises is how to reduce the cost of undertaking residue trials. Basically, the best method of keeping total costs to a minimum is to ensure that the trial is correctly undertaken. Before commencement of the trial all aspects must be considered, particularly the perceived outcome. Unfortunately, trials are often undertaken in such a manner that aspects such as the final withholding period are neglected. The withholding period is determined by the period between application and sampling (usually harvest) and must reflect normal agricultural use of the chemical. Nevertheless, it is possible to make some savings by combining efficacy and residue trials. With some foresight, the efficacy trial can provide a concurrent control and at least one dose rate for a residue trial. However, caution must be exercised to ensure that all the endpoints for both trials continue to be met.

Submission of toxicology and residue data to the NH&MRC is an ongoing requirement. Where this data indicates a potential hazard then appropriate amendments to recommendations are usually necessary. The following are two recent examples where the NH&MRC has amended recommendations following review of further information.

Alachlor. Following a review of further toxicological data for this widely used pre-emergence herbicide it was determined that alachlor was carcinogenic in animals, producing lung tumours in mice, and stomach, thyroid and nasal turbinate tumours in rats. In addition, it produced irreversible ocular lesions (uveal degeneration syndrome) in rats. Based on this information it was agreed that use of alachlor was a potential hazard to applicators. It is important to note that a complete review of available residue data indicated that residues of alachlor would not occur following use according to good agricultural practice. Thus, it was not considered that there was a

significant risk to consumers. Following this review of the toxicology and residue data, the NH&MRC announced in July 1986 that alachlor would be recommended to be schedule 7 (dangerous poison) with the MRLs to be withdrawn as of the end of 1986.

Dinoseb. This chemical was widely used as a pre and post-emergence herbicide against broad-leaf and annual weeds in pea and peanut crops. Toxicological data confirmed that dinoseb caused sterility in animals and was also shown to be teratogenic. A no-effect-level was not established for adverse reproductive effects and dinoseb was also associated with the development of cataracts in three different species of animals. Based on this information the NH&MRC in December 1986 recommended that sales of dinoseb should cease immediately and that it should be available for approved research purposes only. Again, it is important to recognize that this action was based on a potential hazard to applicators as residues should not occur following use according to good agricultural practice.

These examples serve to emphasize the importance of the toxicological and residue data in delineating the potential hazard from chemicals. This is particularly true for herbicides which are very widely used in Australia. In conclusion, the main message is that such chemicals must be used properly. Withholding periods and use patterns must be adhered to so that unacceptable residues will not occur and result in unnecessary exposure to consumers; safety directions must be observed so that applicators are not unnecessarily exposed to any chemical.

FURTHER READING

1. Department of Primary Industry, 1981. Guidelines on Residue Trials PB412, AGPS, Canberra.

2. Department of Primary Industry, 1985. Requirements for clearance of Agricultural Chemicals PB310B, AGPS, Canberra.

3. National Health and Medical Research Council, 1986. Standard for Maximum Residue Limits of Pesticides, Agricultural Chemicals, Feed Additives, Veterinary Medicines and Noxious Substances in Food, AGPS, Canberra.

4. National Health and Medical Research Council, 1986. Standard for the Uniform Scheduling of Drugs and Poisons, AGPS, Canberra.