Australian Government
Australian Pesticides and Veterinary Medicines Authority

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Metabolism and kinetics (Part 4)

Metabolism studies are used to assess the nature and disposition of chemical residues in, or on, food or feed commodities. The composition of the residues (the parent compound and/or metabolites) and where they occur in a crop or farm animal must be known so that supervised residue trials, processing trials and analytical methods deal with the relevant residues.

You should compare the metabolites that are formed in crops, experimental animals and target animals. Discuss similarities and differences in the degradation of the chemical in the light of the residues that may be present in food commodities for human consumption in order to determine appropriate residue definitions. These studies are also used to help determine analytical methods for determining residue levels. Metabolism studies should also provide information on residues that have the potential to pass into a processed commodity (for example, a water-soluble conjugate has a higher potential to contaminate sugar or wine).

If a metabolite appears in plants and is not present in animals, additional toxicological data on it may be required. Animal metabolites are normally considered as being covered by the toxicological studies on the parent compound because the metabolites will be formed during the feeding studies.

1. General instructions

You are required to do plant metabolism studies when the active ingredient of your product will be used on edible (human and animal) crops. Animal metabolism and kinetic studies are required for any proposed use. Data are required for both laboratory animals and livestock (the target animals).

Of the various types of study:

- metabolism studies in plants show the chemical transformations and distributions that take place after exposure to an agricultural chemical
- metabolism studies in animals are used to assess the fate of the administered chemical, including the chemical identification and location of the residue
- toxicokinetic or pharmacokinetic studies allow the quantification and determination of the time-course of absorption, distribution, biotransformation and excretion of xenobiotic chemical agents in animals.

These studies are often conducted using radiolabelled substances and should be conducted according to recognised test protocols, including those of the Organization for Economic Co-operation and Development (OECD), the European Union, the Food and Agriculture Organization or the United States Environment Protection Agency. If you will do studies using non-standard testing protocols, you should seek advice from us about the suitability of those studies for registration purposes.

Metabolism studies should be performed on animal species and crops representative of those on which the product is to be used or on species likely to come in contact with the material, such as animals grazing or fed treated crops.

If your original detailed studies are performed using laboratory animals, you will need to show that similar metabolic pathways are followed in animals exposed to the chemical or its residues and whose meat, milk and eggs are destined for human consumption.

There should be a comparison of the metabolites that are formed in experimental animals and target animals or crops. You should discuss similarities and differences in the degradation of the chemical in the light of the residues that may be present in food commodities for human consumption.

These instructions describe the aims and scope of the required studies, but do not give details of individual study protocols. You should submit kinetics data that are obtained during toxicity studies as part of the toxicology submission in your application.

2. Outline of data requirements and application layout

This section gives a checklist of the data that are required for the metabolism and kinetics studies of an application for agricultural chemical products, and the sections in which the data should be arranged:

- Metabolism studies in target plants
- Metabolism and toxicokinetic studies in laboratory animals
- Metabolism and pharmacokinetic studies in target animals
- Metabolism database.

2.1. Metabolism studies in target plants

The amount of active constituent used in plant metabolism and compound distribution trials should be chosen according to the proposed practical application rates and methods (for example, foliar application, seed treatment or soil treatment), or at exaggerated rates if that is necessary to obtain sufficient quantifiable residues.

Plant metabolism studies are usually carried out on crops typical of those to which the compound will be applied. If the metabolism is the same, or similar, in crops from three crop groups, no further studies are required. The exception is that product use on sugarcane will require a sugarcane or sugar beet study. Crops can be considered under the following groups:

- grasses (such as cereals, sugarcane, pastures)
- leafy crops (such as vegetables, lucerne, clovers)
- pulses and oilseeds
- root vegetables
- fruits.

You should consult us on the applicability of the studies for the proposed registration if the studies have not been conducted on crops similar to the major target crops.

The aims of plant metabolism studies are:

- to provide an estimate of the total terminal residues in the edible parts (food and feedstuff) of treated crops according to the proposed use pattern
- to identify the major components of the total terminal residue (for example, parent compound and metabolites)
- to indicate the distribution of residues within the various crop fractions, including whether the compound is absorbed through the roots and/or foliage or is entirely surface deposited and whether the residues are translocated
- to show the efficiency of extraction procedures for various components of the residue
- to provide guidance on the possible fate of residues during subsequent food processing (for example, if the residue is entirely a surface residue on fruit it may be substantially removed by washing or peeling)
- to assist in determining residue definitions for enforcement and risk assessment.

Further information can be found at the OECD Publications on Pesticide Residues website and the Food and Agriculture Organization's AGP–JMPR Guidance and related documents website.

2.2. Metabolism and toxicokinetic studies in laboratory animals

Studies are required on the fate of the active constituent in experimental animals. We would normally expect the following information on the active constituent from you:

- the degree and rate of absorption after oral administration in at least one mammalian species (an investigation of the extent of absorption after dermal application is desirable; the vehicle chosen for the dermal study should closely resemble that proposed for the product)
- the extent and rate of distribution and storage in the tissue of animals, or any bioaccumulation that may occur
- biotransformation in animals, including the rate and degree of such biotransformation, together with a description of any metabolites produced
- the mode and extent of excretion or elimination of the parent compound and/or its degradation products in animals, including the rate at which such excretion occurs.

2.3. Metabolism and pharmacokinetic studies in target animals

You should conduct metabolism studies using a radiolabelled active substance with, optionally, a pharmacokinetic component, on animal species representative of those likely to come into contact with the material, such as animals directly treated or grazing or fed treated crops or crop commodities. Studies are usually conducted using goats or cows (to represent the ruminants) and chickens. A monogastric animal (for example, a pig) study is not normally required because data are available from studies with rats. However, if metabolism in the rat is different from that in the ruminant and chicken, a pig study will be required.

The aims of livestock animal metabolism studies are:

- to provide an estimate of the total terminal residues in the edible animal commodity
- to identify the major components of the total terminal residues
- to indicate the distribution and nature of residues in muscle, fat, milk, eggs, liver and kidney, to identify target tissues and determine whether the residues are fat-soluble
- to show the efficiency of extraction procedures for various components of the residues
- to identify bound residues
- to assist in determining residue definitions for enforcement and risk assessment.

Measuring the mode and extent of excretion or elimination of the parent compound and/or its degradation products in livestock to identify any potential for bioaccumulation is optional.

If that aspect is included, animal feeding studies might not be required if the study is designed to show that residue levels have reached a plateau and that those in the tissues are less than 0.1 milligram per kilogram. If you are contemplating this approach, you should consult us before electing not to conduct animal feeding studies. Also, you are reminded that a validated non-radiolabel method of residue determination is still required for maximum residue limit establishment and enforcement purposes.

Further information is available at the OECD Publications on Pesticide Residues website and the Food and Agriculture Organization's JMPR Guidance and related documents website.

2.4. Metabolism database

You should also include a metabolism database that is similar in format to the toxicological database described in the toxicology section of the regulatory guidelines.

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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.