

**Ministry of Agriculture and Forestry
Post Office Box 2526
WELLINGTON, NEW ZEALAND
November 2000**

**GUIDELINES FOR
RISK ASSESSMENT AND
HAZARD ANALYSIS
UNDER THE AGRICULTURAL
COMPOUNDS AND VETERINARY
MEDICINES ACT 1997**

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GUIDELINES FOR RISK ASSESSMENT AND HAZARD ANALYSIS UNDER THE AGRICULTURAL COMPOUNDS AND VETERINARY MEDICINES ACT 1997

1 INTRODUCTION

While these guidelines relate to the ACVM Act 1997, the principles described are applicable under the Animal Remedies and Pesticides Acts as well. Users should note that, if the guidelines are used before the commencement of the ACVM Act, public health, environment and consumer protection are also relevant risk areas.

These guidelines have been prepared to encourage a consistent approach to the management of risks posed by the importation, manufacture, sale or use of agricultural compounds, i.e. veterinary medicines and plant compounds. They should be followed by all parties interested in, or affected by, the impact of agricultural compounds. This includes:

- proprietors of trade name products;
- applicants for registration of trade name products;
- registration consultants and independent risk assessors;
- the public; and
- the Agricultural Compounds and Veterinary Medicines (ACVM) Group of the MAF Food Assurance Authority.

The common goals are to facilitate the approval of trade name products to maintain and improve agricultural productivity, and to meet the health needs of livestock and companion animals. To achieve this goal and to minimise the risks posed by agricultural compounds, all parties should understand and apply the common best practices for risk management. The responsibilities of each party are set out in section 3.2

The ACVM Group has prepared these guidelines and ACVM registration standards to help affected parties carry out adequate hazard analyses and risk assessments so that risk management can be undertaken.

The important principles to keep in mind when reading and applying these guidelines are:

- The person who is responsible for a trade name product has a moral and statutory obligation to address potential negative consequences, inherent and acquired hazards, and to provide a technically sound assessment of all the relevant risks.
- Before approving the use of a trade name product, regulators must have confidence that the risks posed by the product are, or can be, adequately managed.

- Registration standards and information requirements will never be so comprehensive that they cover all types of trade name products and all circumstances.

Adhering to the following guidelines should assist in understanding what is expected before an agricultural compound trade name product will be approved for use in New Zealand. It must be noted, however, that while the standards and guidelines for registration provide the general expectations, they do not cover in detail all products under all circumstances. The information requirements and testing specifications are what the ACVM Group specifies as best practice. However, it will consider technically sound cases for equivalence. It will also consider legitimate references to relevant information that it already has, or that is in the public domain.

1.1 Scope

These guidelines specifically address the risk areas specified in the Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997, which are risks to:

- trade in primary produce;
- animal welfare; and
- agricultural security.

The risks to trade in primary produce are specifically concerned with exported primary produce. The ACVM Act also manages the risks associated with breaches in the domestic food residue standards to ensure that the use of agricultural compounds do not exceed the maximum residue limits set for specific substances.

This document does not address all risks posed by agricultural compounds. Environmental and public health risks are addressed elsewhere, in the context of the Hazardous Substances and New Organisms (HSNO) Act 1996. These guidelines also do not address either occupational risks or risks to the consumers from ineffective or misrepresented agricultural compound products. These risks are addressed in other legislation. Even though these guidelines do not specifically address all the other risk areas, the rationale described here is equally valid for analysing hazards in those areas.

These guidelines do not go into detailed explanation of risk management. The reader is advised to be familiar with the Australian/New Zealand Standard for Risk Management (AS/NZS 4360:1999). These guidelines focus on hazard analysis and explain the expected relationship between the analysis of hazards (inherent and acquired) in agricultural compound trade name products and the management of the associated risks.

1.2 Definitions and abbreviations

ACVM Group

The Agricultural Compounds and Veterinary Medicines Group, in the Food Assurance Authority of the Ministry of Agriculture and Forestry, responsible for the administration of the Agricultural Compounds and Veterinary Medicines Act 1997.

Agricultural compound

Any substance, mixture of substances, or biological compound, used or intended for use in the direct management of plants and animals, or to be applied to the land, place, or water on or in which plants and animals are managed, for the purposes of:

- a) managing or eradicating pests, including vertebrate pests; or
- b) maintaining, promoting, or regulating plant or animal productivity and performance or reproduction; or
- c) fulfilling special nutritional requirements; or
- d) the manipulation, capture or immobilisation of animals; or
- e) diagnosing the condition of animals; or
- f) preventing or treating conditions of animals; or
- g) enhancing the effectiveness of an agricultural compound used for the treatment of plants and animals; or
- h) marking animals; and

includes any veterinary medicine, any substance, mixture of substances, or biological compound used for post-harvest pest control or disinfection of raw primary produce, and any substance, mixture of substances, or biological compound declared to be an agricultural compound for the purposes of (the ACVM Act) by Order in Council.

Endpoint

The point in a measurement or testing process that is designated as critical to the definition of an outcome. The tolerable endpoint is the measure of a negative consequence beyond which the negative consequence becomes unacceptable.

Hazard

A source of potential harm or a situation with potential to cause harm. Harm is referred to as a negative consequence.

Negative consequence

The outcome of an event expressed qualitatively or quantitatively, being a harm, loss, injury or disadvantage. There may be a range of possible outcomes associated with an event.

Pathway (hazard/negative consequence)

The circumstances that lead to the

- presence of a hazard;
- opportunity for the hazard to cause a negative consequence; and
- severity of the negative consequence.

Preferred tests

The methodologies for measuring the likelihood and severity of the components of hazard/negative consequence pathways that are accepted by the ACVM Group as common best practice.

Probability

The likelihood of a specific event or outcome, measured by the ratio of specific events or outcomes to the total number of possible events or outcomes. Probability is expressed as a number between 0 and 1, with 0 indicating an impossible event or outcome and 1 indicating an event or outcome that is certain. The term **likelihood** is used as a qualitative description of probability.

Plant compound

Any substance, mixture of substances, or biological compound used or intended for use in the direct management of plants in an agricultural context.

Risk

The chance of something happening that will have an impact upon objectives. It is measured in terms of severity of negative consequences and likelihood.

Risk area

The scope of relevant risks.

Veterinary medicine

Any substance, mixture of substances, or biological compound used or intended for use in the direct management of an animal.

1.3 References

- ACVM registration standards, guidelines, information requirements and policies (available at <http://www.maf.govt.nz/ACVM/>)
- Australian/New Zealand Standard for Risk Management (AS/NZS 4360:1999)
- *Regulatory Control Methodology under the Agricultural Compounds and Veterinary Medicines Act 1997*, December 1999 ISBN 0-478-07575-8

2 STATUTORY BASIS FOR THE ASSESSMENT OF AGRICULTURAL COMPOUNDS

The ACVM Act provides the statutory basis for regulatory control of agricultural compounds. The Act defines an **agricultural compound** (see definitions). It also defines the sub-group used to manage animals as **veterinary medicines**. It does not define the subgroup used to manage plants. For the purposes of these guidelines agricultural compound used to manage plants are referred to as plant compounds.

2.1 Relevant risk areas

According to section 19 of the ACVM Act, the only risks relevant to a decision are:

- risks to trade and market access for primary produce containing any substance, mixture of substances, or biological compound that forms a part of the trade name product;
- risks to agricultural security;
- risks to the welfare of animals, which result from treatment with or exposure to any substance, mixture of substances, or biological compound that forms a part of the trade name product; or
- risks to domestic food residue standards.

(These risk areas are further expanded in section 5 in relation to hazard analysis and risk assessment.)

Section 19 also specifies relevant benefits. These are:

- benefits of the trade name product; and
- likely consequences of the public not having access, or having restricted access, to the trade name product, including consideration of whether alternative means of achieving the stated purpose of the trade name product are available.

2.2 Risk to benefit assessment

Under section 21 of the ACVM Act, MAF must consider any application for registration and must identify the risks and benefits likely to result from the manufacture and use of the trade name product, and any known practicable alternative methods of managing those risks. It must evaluate the likely risks and benefits of each alternative method identified and decline the application if, in its opinion:

- the risks likely to result from the use of that product cannot be sufficiently reduced by imposing conditions on the registration of the trade name product; or
- insufficient information is available to assess the risks likely to result from the use of the trade name product; or

in every other case, MAF must register the trade name product without conditions, or with the conditions imposed in accordance with section 23 that MAF, after taking into account the costs of those conditions, considers will:

- a) manage the risks from the use of the product; and
- b) impose the least cost on the public.

3 RISK ASSESSMENT AND HAZARD ANALYSIS OF AGRICULTURAL COMPOUNDS

3.1 Risk assessment and hazard analysis

Identifying, analysing, evaluating, treating and monitoring risks and informing and consulting with affected parties is the discipline of risk management. These guidelines focus specifically on identifying, analysing and evaluating risks, i.e. hazard analysis and risk assessment associated with agricultural compounds.

Risk assessment involves assessing the nature, magnitude and probability of negative consequences caused by specific hazards. The concept of assessing the risks associated with agricultural compounds is based on the following questions:

- What is the trade name product and what is its intended use?
- What are the **negative consequences** that might occur as a result of use of a particular agricultural compound trade name product?
- What are the **hazards** posed by the trade name product?
- For each hazard/consequence pathway, what is the likely severity (i.e. **magnitude**) of the effect?
- For each hazard/consequence pathway, what is the likelihood (i.e. **probability**) that the consequence will occur?

Hazard analysis is the practice of identifying and evaluating all the causes of negative consequences. It is an essential step in the assessment of risks. A sound and consistent hazard analysis rationale should be applied across the continuum from product development to evaluation of applications for registration, with different responsibilities for applicants, independent assessors and regulators (see section 3.2). However, the outcome should be the same, i.e. a thorough assessment of all hazards (inherent or acquired) associated with a product to ensure that the risks posed by those hazards are sufficiently defined to guide regulatory decision on control to manage the risks.

For convenience, the term negative consequence is explained next. However, hazards and negative consequences are so closely linked that in an analysis, negative consequences and hazards must be considered together.

3.1.1 Negative consequences

Negative consequences are outcomes of harm, loss or disadvantage that are undesirable and unacceptable. Since there is a wide range of possible consequences, the relevant ones have been limited to those that could have an impact in the risk areas specified in the ACVM Act (see section 2.1).

For example, in the area of risks to animal welfare, the negative consequences are characterised by unnecessary pain or distress. A particular negative consequence might be acute toxicity in the treated or exposed animal. In the area of risks to trade in primary produce, the downstream negative consequence might be rejection of a shipment of New Zealand meat or horticulture export produce. However, the immediate negative consequence of concern would be the finding that would prompt such action (e.g. identification of primary produce that exceeds the maximum residue limit (MRL) specified by an importing country). Further discussion of negative consequences can be found in section 5, which deals with each risk area.

3.1.2 Hazards

Hazards are characteristics of trade name products or situations involving trade name products that could cause negative consequences. The hazards are likely to be specific for each trade name product and result in specific negative consequences. Hazards have specific characteristics that will influence both the likelihood and the severity of a negative consequence. Analysis of these characteristics and the negative consequences provides the information needed to assess the risks.

3.1.3 Opportunity

There must be an opportunity for a hazard to have an effect and a negative consequence to be observed (e.g. in an animal treated, or in tested produce, or in situations that do not comply with regulatory requirements). Therefore, hazard analysis has to consider not only the characteristics of the hazards and the negative consequences but also the opportunity for a hazard to have an effect.

3.1.4 Preferred tests and tolerable endpoints

Analyses of hazard/negative consequence pathways should be based on specified tests that are common best practices accepted by the ACVM Group (refer to ACVM registration standards). The results should be compared with tolerable endpoints. Where acceptability is dependent on the benefits exceeding harms, as is the case in regard to risks to animal welfare, there must also be a benefit analysis.

The ACVM registration standards specify the preferred tests and information (and its quality) that must be provided. For example, the preferred tests for residue hazards are specified in the *ACVM - Registration Standard and Guidelines for Residue Data*. The tolerable endpoints are specified as maximum residue limits (specified by importing countries or in the domestic food residue standards for produce marketed in New Zealand). These are absolute tolerable endpoints and do not have to be considered relative to other factors, such as potential benefits. There are other absolute endpoints specified in the registration standards. However, there are also endpoints that are relative to factors such as acceptability of degrees of negative effects, or potential benefits that would offset negative effects.

The need to measure particular components of a hazard/negative consequence pathway is dependent on:

- its relevancy to the specified risk areas; and
- the degree of uncertainty associated with the information available about those components.

For example, information on the efficacy of a trade name product is only needed under certain circumstances. For veterinary medicines, efficacy information is needed when there are animal welfare concerns (see section 5.2). Otherwise, effectiveness is a consumer protection issue. When plant compounds are being considered, efficacy assessment will not be required by the ACVM Group because efficacy is a consumer protection issue and animal welfare is irrelevant.

It must be noted that, while the ACVM Group may not be interested, some other regulatory agency may require particular information. For example, efficacy assessment is likely to be required by the Food Safety Co-ordination Group of the MAF Food Assurance Authority to support a recommended use as good agricultural practice (GAP) for the purpose of establishing an appropriate maximum residue limit, if setting such a limit is necessary.

3.1.5 Relationship between risk management, hazards analysis and risk assessment

While the ACVM Act is expressed in terms of risks, the focus of assessment must be on the potential for, and significance of, particular hazards posed by agricultural compounds, either by a group or by individual trade name products. The hazard analysis model in section 4 describes the ACVM Group's expectations in regard to the hazard analysis/assessment process. If followed, the rationale should identify for any product or agricultural compound group:

- where hazards may cause a particular negative consequence;
- where the hazards occur or are introduced; and
- how significant the hazards are (in terms of probability and magnitude).

The information provided in an assessment should be what is necessary and sufficient to provide confidence in the reliability of the risk assessment. These guidelines provide a generic view of hazard analysis. The ACVM Group is not able to specify the line of enquiry for every kind of product. The rationale must be adapted to specific circumstances and specific products to ensure that the full range of hazards and negative consequences are addressed. The registration standards that have been prepared, and that should be used in conjunction with these guidelines, should be considered an expression of common and acceptable best practices. Any deviation from the standard must be identified and justified technically. In addition, the ACVM Group reserves the right to ask for additional information when adherence to common best practices does not, under the particular circumstances, provide sufficient information to assess a hazard/negative consequence pathways.

3.2 Areas of responsibility

While the shared outcome of regulatory control of agricultural compounds is to ensure that products are available to help maintain agricultural productivity or to meet the health needs of livestock and companion animals, different parties have different responsibilities in achieving that outcome. These guidelines are relevant to all parties but the stage at which they are used varies depending on the stage of the assessment process. The process is a continuum from preparing an assessment, reviewing the assessment and preparing an independent report, evaluating an application and assessment report, and applying risk management conditions through to registering the trade name product in question.

3.2.1 Applicant's responsibility

Applicants for registration of trade name products are responsible for modelling the hazard profile of their products when used as recommended. There may be hazards associated with:

- each constituent (active ingredients, excipients, contaminants and metabolites/breakdown substances);
- product formulation and interaction of formulants;
- manufacturing, including packaging and labelling;
- marketing; and
- use.

Examples of negative consequences that hazards might cause are:

- toxicity from both primary and secondary exposure;
- undesirable side effects;
- residues; and
- pain or suffering resulting from inefficacy of the product.

Applicants must:

- identify potential hazards and the negative consequences they might cause;
- use preferred tests and parameters to characterise hazards or justify the use of equivalent tests and parameters;
- analyse results;
- compare results to specified absolute tolerable endpoints or, where tolerable endpoints are relative to benefits to be achieved, assess the balance of harm to benefits; and
- document the analyses in accordance with relevant ACVM registration standards.

It must be noted that applicants can contract consultants to do this work, but those consultants may not be used as independent assessors for the same work.

3.2.2 Independent assessor's responsibility

Independent assessment reports must be prepared. Assessors must review the hazard analyses carried out by an applicant to confirm:

- that the hazards have been thoroughly identified, characterised and analysed;
- analyses comply with ACVM registration standards;
- appropriate tests were used to characterise the risks;

- results were compared to specified tolerable endpoints or, where tolerable endpoints are relative to benefits to be achieved, assessment of the balance of harm to benefit has been made; and
- any parallels drawn or extrapolations made are reasonable and technically justifiable.

Assessors should apply the same hazard analysis principles and endpoints as used by the applicant and the regulators when assessing applications and the data supporting those applications.

3.2.3 ACVM Group responsibility

The ACVM Group provides the registration standards and sets the tolerable endpoints where possible. These must be reviewed regularly and adjusted when necessary.

The ACVM Group is responsible for reviewing and evaluating applications to register or vary the registration of trade name products. Reviews will focus on assessment reports from independent assessors, but the ACVM Group reserves the right to review the hazard analyses carried out by the applicant if appropriate.

The ACVM Group is also responsible for agricultural compound groups considered to be candidates for exemption from registration under section 75(a) of the ACVM Act, according to its regulatory control principles. In this case, the ACVM Group, rather than applicants, is responsible for assessing available information on the hazards posed by an agricultural compound group. Agricultural compound groups will be exempt from registration via the ACVM Regulations when they are promulgated.

4 RISK ASSESSMENT AND THE HAZARD ANALYSIS MODEL

4.1 Hazard analysis model

While management of specific risk areas is the purpose of the ACVM Act, regulatory control focuses on the management of hazards (see *Regulatory Control Methodology under the Agricultural Compounds and Veterinary Medicines Act 1997*, December 1999 ISBN 0-478-07575-8). Making decisions on regulatory control will be based on hazard analysis and critical control point assessment. The generic model is shown in appendix 1. It is divided into the following five steps.

Step 1: Is the product relevant to the ACVM Act?

The first consideration is the nature and intended purpose of the trade name product. Only products that fit the definition in the ACVM Act are considered to be agricultural compounds. If the product is used to manage animals, it is considered to be a veterinary medicine. This includes products that are used on companion animals (e.g. dogs, cats, horses) as well as livestock (cattle, sheep, horses, etc.) and interest is not limited to an agricultural context. Products used on plants are considered to be plant compounds and interest is limited to the use of those compounds in an agricultural context. For example, a home garden product will not be of interest under the ACVM Act, but the same product packaged and sold for use on crops that may ultimately be offered for sale is of interest. If a trade name product is not an agricultural compound the following steps are irrelevant.

Step 2: Is the trade name product exempt from the requirement for registration?

A number of groups of agricultural compounds are exempt from the requirement for registration. Some exempt groups are given that status provided that certain conditions are met. MAF has already carried out a hazards analysis for each group. The ACVM Regulations should be consulted to ascertain whether the trade name product in question falls into any of those groups. If it is exempt from registration the following steps are irrelevant.

If there is any doubt whether a particular trade name product would be included in an exempt group, this can be confirmed by requesting a class determination on the trade name product from the ACVM Group. This is a discretionary service and there is no regulatory obligation to get a class determination from the Group.

Step 3: Are any of the risk thresholds relevant?

Once it has been confirmed that the trade name product in question is relevant to the ACVM Act and is not exempt from the requirement to be registered, the possibility that any of the risk thresholds might be exceeded must be considered. The general lines of enquiry to be followed for veterinary medicines and plant compounds are

shown in appendix 2 and appendix 3, respectively. Thresholds and criteria are expanded in section 5.

Where thresholds could be exceeded, analyses are required to estimate the probability that hazards posing risks will cause negative consequences and the magnitude of the consequences. Where a risk area is irrelevant or no thresholds are exceeded, there is no need to carry out any assessment. For example, animal welfare is a risk area that is irrelevant to the use of plant compounds. It may be of concern in regard to the environment and effects on non-target animals, but such a risk is managed under the HSNO Act, not the ACVM Act. Similarly, there would not be ACVM Group interest in residues from trade name products used in non-food producing animals or in non-food crops.

Step 4: Undertake and document the hazards analysis and risk assessment

This step begins with identifying the possible negative consequences and matching them with the hazards (inherent or acquired) that could cause those consequences. Focus must be on the hazards when the trade name product is used as intended. The ACVM Group does not expect an applicant to address hazards associated with unintended uses.

The level of analysis of hazards should be commensurate with the level of uncertainty of the probability and magnitude of the negative consequences. That is, the more uncertain the probability or magnitude the more detailed the investigation of the hazard/negative consequence pathway must be.

Unsupported assumptions are of dubious value and should be discounted in the assessment of a trade name product. The applicant must address all the relevant hazard/negative consequence pathways. Assessors must evaluate the information to determine if they have been investigated adequately.

The hazards must be identified, characterised and analysed in regard to both the **probability** (of being present and having a negative effect) and the **magnitude** of that negative consequence. The hazards could be inherent in individual ingredients (see appendix 5) or result from interactions between ingredients in the final formulation (see appendix 6). Other hazards may be introduced in the manufacturing process. A product not complying with its specifications, including packaging and labelling, may contain hazards that have not been assessed.

It must be noted that the ongoing relevance of a risk assessment of an agricultural compound trade name product depends on the product and its use complying with the original specification used in the risk assessment. Details of the chemistry and manufacturing for the product are the foundation of the assessment. Any changes may make the risk assessment undertaken for the original trade name product irrelevant to the altered trade name product. Adequate information must be provided and reviewed to confirm:

- what the product is;
- how it is intended to be used; and
- that it will continually comply with the specification provided for assessment.

Other hazards may be associated with the improper use of a product, e.g. an intravenous product may cause significant tissue damage if it is not administered properly. Not all species react to drugs in the same way, so a trade name product may be safe for use in some species, and quite dangerous in others.

Some negative consequences and hazards are based on external direction, such as importing country requirements or ministerial direction. The ACVM Group will provide a mechanism to keep all parties up-to-date on these matters. Current information should be used and, when in doubt in regard to risk assessment in the areas of trade in primary produce, or ministerial directions on animal welfare, or agricultural security, contact the ACVM Group.

Step 4 must be carefully documented as part of an application to register a trade name product. This documentation will be the subject of the independent assessment reports.

Step 5: Apply conditions

The ACVM Group is responsible for carrying out this step. This is the stage at which conditions will be applied to either:

- decrease the probability of a hazard being present;
- decrease the likelihood of causing negative consequences; or
- reduce the magnitude of the consequences.

The conditions applied should be only what are necessary and sufficient to manage the hazards. Guidance on this step is not provided in this document. A number of the policies governing this step are available on the ACVM Group website (<http://www.maf.govt.nz>).

4.2 Refinement of risks

There are circumstances in which certain substances or types products and hazard/negative consequence pathways are so well documented that assumptions can be made with considerable confidence. In these circumstances no formal assessment may be necessary, or only a superficial assessment to confirm that the outcome is what would be expected. This is especially true when the risks are known to be low. These circumstances are characterised by a high level of certainty in regard to the assumptions being made. Extrapolations can be made confidently without providing additional information. The ACVM Group has published a standard for low risk products which significantly reduces the amount of information needed to assess the risks of such products.

At the other extreme, where there is little or no experience or information available, or outcomes are dependent on fluctuating variables, there is almost no certainty or predictability. Therefore, sufficient information should be provided or expected to engender confidence in the conclusions drawn in the assessment.

The level and detail of the information required is commensurate with the level of uncertainty in regard to the assumption made and the conclusion drawn. Risk

assessment should be refined until the remaining level of uncertainty about the relationship of hazards to negative consequences is tolerable.

The ACVM Group will ask for more detailed information if what is provided does not engender sufficient confidence in regard to conclusions that are drawn about any particular hazard/negative consequence pathway. It is recommended that the applicant, when doing the initial assessment, should take special note of the degree of uncertainty about assumptions and conclusions, and investigate hazard/negative consequences pathways in sufficient detail.

4.3 Information waivers

It is the responsibility of an applicant to provide all the information to support the risk assessment at the time an application to register or vary a trade name product is lodged with the ACVM Group. However, information waivers can be obtained prior to lodging an application when there is technical justification for less or different information; or deviation from the standard methodology for generating particular information.

Some information required may already be in the public domain or held by the ACVM Group. Cross-referencing such information is acceptable, however, it must be noted that the ACVM Group can not use referenced information that is under data protection. If the information is protected, the actual information must be provided in an application. Reference to protected information is unacceptable.

There will be occasions on which certain information specified in the registration standards is not relevant in a particular assessment. There must be a technically supported case presented to explain why the information is not necessary. If the ACVM Group accepts the explanation, it will issue an information waiver.

The registration standards provided by the ACVM Group apply to the average situation. Deviation from the standard, using tests, test protocols, parameters or endpoints that are not accepted by the ACVM Group as common best practice is possible, but must be justified beforehand. When reviewing a risk assessment, independent assessors must note any deviation from the registration standards, the justification for the deviation, and the impact the deviation has on the adequacy of the assessment. The assessor should include this information in his or her report. The assessor does not have the power to issue an information waiver, and should be careful not to assume or advise that the ACVM Group will accept an application that does not comply with the registration standards.

Information waivers must be obtained before an application is lodged with the ACVM Group. In fact, they should be obtained before the risk assessment is reviewed by an independent assessor. Otherwise, that assessor must report that the assessment is incomplete.

Unusual circumstances may require other unspecified information to be provided. Application of the rationale in these guidelines should allow a person to recognise when the average information specified in the standard is not going to be sufficient. The ACVM Group reserves the right to require additional information if it does not

consider the relevant hazard/negative consequence pathways have been adequately addressed.

5 HAZARD ANALYSIS BY RISK AREA

As stated above, to do an adequate risk assessment the relevant negative consequences in each risk area must be identified. Every hazard/negative consequence pathway must be addressed in sufficient detail to engender confidence in the conclusions drawn. Each of the risk areas specified in the ACVM Act is considered separately in this section. The thresholds and criteria agreed to by Government are listed, as is a brief discussion of relevant negative consequences, hazards and preferred tests and tolerable endpoints. The ACVM Group will advise interested parties of any changes in the thresholds and criteria. Any change in standards or ministerial directions will also be advised. Negative consequences and hazards in technical areas are so specific to a trade name products that any guide provided by the ACVM Group must not be considered a comprehensive list of all the relevant consequences and hazards. It is up to the person preparing the assessment to be comprehensive.

Under the ACVM Act, the ACVM Group is primarily interested in effects on the target organisms, while non-target organism effects are considered environmental effects which are the responsibility of the Environmental Risk Management Authority (ERMA) under the Hazardous Substances and New Organisms Act 1996. Appendix 4 graphically shows the pathways for direct and indirect effects. While environmental effects are the responsibility of ERMA, the ACVM Group will be interested in negative consequences on non-target organisms when the consequences are related to any of the risk areas specified in the ACVM Act. For example, the ACVM Group would want the applicant to address the risks of residues in animals grazed under treated orchard trees, or the toxic effects in animals grazed on treated plants.

The ACVM Registration standards describe the accepted common best practice for preferred tests to investigate hazards. They also specify where possible the tolerable end points. The chemistry and manufacturing standard differs in that it states what is expected in describing the trade name product and how it is manufactured. Preferred tests and tolerable endpoints are not relevant to chemistry and manufacturing. Compliance to the chemistry and manufacturing standard is a prerequisite to a hazard analysis because it confirm that the product conforms with and will continue to conform with the product's specifications. Compliance to the manufacturing component is achieved through accreditation for good manufacturing practices (GMP) and is separate from assessment of applications for registration.

5.1 Risks to trade in primary produce

The first risk area listed in section 4 of the ACVM Act is risk to trade in primary produce. This is considered to relate to export trade rather than to domestic trade. It is also considered to relate to official government action (market access) against New Zealand primary produce, not the reduced interest in New Zealand produce (market preferences).

Thresholds:

- i. Non-conformance with international standards for trade in primary produce or bilateral import requirements, for example, maximum residue limits as defined

by Codex Alimentarius Commission or EU residue requirements for imports into the Union; or

- ii. Non-conformance with an agreed New Zealand national requirement, based on regulatory requirements in a significant portion of the international market (this includes assurances on residue limits, regulatory controls on importation, manufacture, sale and use, and efficacy of pest control programmes); or
- iii. Non-conformance with conditions imposed to give effect to a written ministerial direction.

Criteria:

- i. Whether the use of the compound could result in non-conformance with international standards or agreed national requirements;
- ii. Whether the use of the compound could result in non-compliance with bilateral import requirements for primary produce;
- iii. Whether the use of the compound could result in residues that exceed limits prescribed under the Meat Act 1981, and subsequent Acts;
- iv. Whether the formulation or presentation of the compound could encourage misuse or abuse leading to non-conformance with international standards or agreed national requirements;
- v. Whether the production of the compound may need to comply with commonly accepted good management practices in manufacturing, testing or use;
- vi. Whether there are international or competent authority expectations that the compound or ingredients in the compound should be subject to regulatory control;
- vii. Whether any countries have imposed technically supportable restrictions on the use of the compound or its ingredients.

5.1.1 Negative consequences

The down-stream negative consequences could be any official government action taken against New Zealand export primary produce. However, the immediate consequences of concern are findings that would lead to such action. For example, the most common actions are delays or even rejections of shipments because violative residues are found.

Residues are not the only relevant negative consequence. There are other actions, such as restrictions, delays or rejections due to a failure to comply with any other international standard, bilateral import requirement, control programme or restriction/prohibition on the use of certain substances or types of trade name products. The ACVM Group will attempt to maintain up-to-date information on requirements. However, the requirements will vary from time to time and the ACVM

Group cannot provide any assurances that its information is comprehensive and current.

5.1.2 Hazards

The hazards that could prompt a negative consequence are very specific to the consequence. They could be inherent in the product, associated with the use of the product or related to the timing or manner of slaughter/harvesting or storage of the primary produce. It is suggested that a Hazard Analysis Critical Control Point (HACCP) assessment would be the best approach to take to match negative consequences to specific hazards. Such an assessment should highlight the circumstances under which the use of a trade name product is likely to cause non-compliance.

5.1.3 Preferred tests and tolerable endpoints

The most common hazard that could result in risk to trade in primary produce is residues. The *ACVM - Residue Standard and Guidelines for Residue Data* should be referred to in regard to preferred tests. The endpoints are specified by Codex or the importing country.

Descriptions of quality systems based on a HACCP approach may be necessary to provide evidence of compliance in regard to other requirements.

5.2 Risks to animal welfare

Risks to animal welfare include both risk from the use of the product and, in certain cases, risk of failure of products to be effective, resulting in unnecessary pain or distress.

Thresholds:

- i. The use of a compound could result in unacceptable pain or distress in the target animal; or
- ii. The failure to achieve compound claims to prevent, treat or cure conditions that are characterised by unacceptable pain or distress in the target animal.

Criteria:

- i. Whether the use of the compound could produce demonstrable evidence of unnecessary pain or distress; and
- ii. Whether the use of a compound could result in demonstrable evidence of the failure to achieve product claims resulting in unnecessary pain or distress in the target animal.

A target animal is defined as the animal purposefully treated with the compound. It is considered that adverse effects include chronic pain or distress or delayed development of signs or abnormalities in the animal treated, as well as immediate

pain or distress. In the case of a pregnant animal, consequential effects on the offspring are also relevant.

Pain and distress are the parameters for welfare and “unnecessary” has become the measure of those parameters. This takes into consideration the fact that some pain or distress may be necessary to achieve a benefit. This is one of the few cases in which a benefit analysis must be provided as well.

5.2.1 Negative consequences

The negative consequences can be divided into two kinds. The first kind relates to threshold (i) and includes types of pain or distress to the animal due to treatment with, or exposure to, the trade name product. The negative consequences could take the form of death, toxicity, infection, abnormal physiological responses or functions, undesirable pharmacological effects, carcinogenicity, teratogenicity, or any other abnormality that can be related to treatment or exposure to a trade name product. The second kind of consequence relates to threshold (ii) and includes pain or distress caused by failure of the product to achieve the claimed effects. Consequently, the animal suffers the pain or distress that the trade name product was intended to prevent or alleviate.

The negative consequences are all observable signs in the animal so it may be best to chronologically review the time period that the product is in contact or is having an effect on the target animal and relating the consequences to the hazards that may have caused them.

5.2.2 Hazards

The hazards could be any aspect of the product or its use that causes any of the negative consequences. They can be either inherent in the trade name product (e.g. active or excipient ingredients, formulation or formulation type) or acquired during manufacturing, storage, sale or use. It is not the role of the ACVM Group to specify the hazards or even the negative consequences. The product and all aspects of its manufacture, sale and use should be reviewed to pinpoint what the hazards are, where they occur, and the risks associated with the hazard/negative consequence pathways.

As mentioned earlier hazards and consequences are very closely linked and should be considered simultaneously.

5.2.3 Preferred tests and tolerable endpoints

Effects should be measured in the most practical and reliable manner possible.

In regard to toxicity studies, the preferred tests and tolerable endpoints are specified in the *ACVM – Registration Standard for Toxicology*.

In the area of target animal safety the preferred test is administration and observation as specified in the *ACVM - Registration Standard for Target Animal Safety*. Most of

the endpoints are unspecified and are relative to the benefits to be achieved. Absolute tolerable endpoints will never be set in regard to a subjective threshold such as unnecessary pain or distress. Therefore, effects must be measured and a reasonable case must be presented that the benefits are sufficient to offset whatever pain or distress associated with treatment was observed, and that the animal is better off as a result of treatment.

In regard to failure to achieve claims, efficacy testing must be in accordance with the *ACVM - Research Standard* and in accordance with the relevant efficacy standard, where one has been published. Where an efficacy standard has not been published, efficacy testing must be done in a manner that can provide a technically justifiable expression of the effectiveness relative to the claims made about the trade name product. When veterinary medicines are being assessed, efficacy testing will be required for all products intended for use in regard to a disease or abnormality of welfare concern as listed below. As stated, some products do not pose any hazards to animal welfare. In these cases efficacy information does not have to be assessed.

5.2.4 The need for efficacy studies

When considering animal welfare risks from inefficacy of a trade name product, clinical signs of pain or distress must be at least moderate to prompt welfare concern. Conditions for which the clinical signs are no more than mild pain or distress and for which there are alternative products available would not prompt animal welfare concerns, since judgements can be made or advice taken about the appropriateness of a particular product for a particular animal. Therefore, welfare concern is partially based on the ability of persons to observe clinical signs and take action to alleviate pain or distress, and partially on the ability to take the time to choose between products or take advice on products, without compromising the welfare of the animal. However, when determining regulatory control, the determinant factor will be the severity of the pain or distress that the product is intended to prevent or alleviate. The following definitions should be used.

Mild pain or distress is insufficient to alter normal behaviour except in a very transient way. The animals are easily distracted from the pain or distress.

Moderate pain or distress does not prevent normal behaviour but the animal remains aware of the pain or distress and is not easily distracted.

Severe pain or distress debilitates the animal and prevents normal behaviour.

Trade name products that are promoted or sold to prevent, treat or cure any condition that is commonly characterised by at least moderate pain or distress, especially if clinical signs can develop rapidly, must be efficacious. Therefore, efficacy information must be considered when assessing such products for registration. Where specific tolerable endpoints for efficacy have been specified in ACVM efficacy standards, data must confirm that those endpoints will be achieved. Where tolerable endpoints for efficacy are not specified, data must show that a treated animal is better off (either alleviating clinical signs, or preventing, treating or curing the condition), having taken into consideration the pain or distress caused by the treatment.

Where efficacy information is not provided to support the claims to prevent, treat or cure a condition of welfare concern, a trade name product will not be registered.

Adequate efficacy information must be provided at the time an application is lodged or the application will not be processed.

The ACVM Group recognises that there are other conditions that are usually characterised by only mild pain or distress and there is time to choose between alternative products to achieve the most relief for the treated animal(s). There are also products that are used on animals to achieve an effect (e.g. oestrus control) that has nothing to do with treating conditions of animal welfare concern or alleviating clinical signs of pain or distress. Therefore, products marketed to treat such conditions are not of animal welfare concern in regard to their efficacy, and efficacy information will not be required. It must be noted that even though efficacy would not be relevant to registration under the ACVM Act, failure to support claims of efficacy for such products may result in breaches of the Fair Trading Act 1986.

Conditions of welfare concern

As examples of conditions of welfare concern, the following can be characterised by at least moderate pain or distress and commonly by severe clinical signs. Clinical signs can also develop very quickly, providing no opportunity to make judgements about alternative products. MAF considers that efficacy information would be required in all cases for registration of products marketed for use to prevent treat or cure any of these conditions.

- a) Any infectious diseases;
- b) Any parasitic (internal or external) infestation characterised by at least moderate pain or distress and which can escalate to more severe clinical signs and shock;
- c) Any gastro-intestinal disorders characterised by any of the following: abdominal pain, distension, tympani, vomiting, diarrhoea, unusual peristalsis or physiological dysfunction;
- d) Any urogenital disorders characterised by any of the following: pain, distension, anuria, obstruction or physiological dysfunction;
- e) Any *in utero* condition that causes post-natal pain or distress in the offspring;
- f) Any respiratory disorders characterised by any of the following: pain, compromised respiration, coughing, compromised oxygen/carbon dioxide exchange or physiological dysfunction;
- g) Any musculoskeletal disorders characterised by pain or compromised movement;
- h) Any cardiovascular disorders characterised by any of the following: pain, compromised oxygen/carbon dioxide exchange (either general or localised), compromised blood flow (either general or localised), or physiological dysfunction;
- i) Any central nervous system disorders characterised by any of the following: pain, irritation (either general or localised), compromised senses (either general or localised), disorientation or motor dysfunction;

- j) Any neoplasia characterised by any of the following: pain, compromised physiological functions or homeostasis, compromised immunity or resistance to secondary infections (either systemic or localised);
- k) Any immune system disorders characterised by any of the following: pain, compromised immunity or resistance to secondary infections (either general or localised), irritation (either general or localised), or auto-immune reactions;
- l) Any disorders of the eye or conjunctiva characterised by any of the following: pain, spasms, intra-ocular pressure, or unusual lacrimation;
- m) Any disorder of the middle or inner ear characterised by pain or loss of hearing or balance;
- n) Shock;
- o) Any trace element or nutrient deficiency requiring parenteral administration of the deficient element, nutrient or precursor to alleviate pain or distress;
- p) Trauma characterised by at least moderate pain or distress;
- q) Any behavioural condition resulting in hypersensitivity, marked irritability or anxiety, or self-mutilation;
- r) Any skin abnormality characterised by pain or distress or which compromises the integrity of the skin as a barrier to disease.

5.3 Risks to agricultural security

This risk area primarily relates to the impact unwanted organisms could have on New Zealand's environment and agricultural productivity. However, it is also about:

- protecting the effectiveness of control programmes; and
- maintaining national agricultural productivity.

Thresholds:

- i. Interference with the exclusion, eradication or effective management of pests or unwanted organisms pursuant to the Biosecurity Act 1993; or
- ii. Diminished agricultural productivity as a result of interference with pest eradication or management; or
- iii. Failure to achieve product claims against pests that could result in decreased productivity in the national herd/crop; or
- iv. Non-conformance with conditions imposed to give effect to a written ministerial direction.

Criteria:

- i. Whether the use of the compound could hinder the exclusion, eradication or effective management of pests or unwanted organisms;

- ii. Whether the use of the compound could have a significant negative effect on productivity in the national herd/crop as a result of interference with pest eradication and management;
- iii. Whether the use of the compound could result in demonstrable evidence of the failure to achieve product claims to eradicate or effectively manage pests of significance to productivity in the national herd/crop;
- iv. Whether there is demonstrable evidence that the use of the compound would not conform to conditions imposed to give effect to a written ministerial direction.

5.3.1 Negative consequences

The most obvious negative consequence would be the inadvertent introduction of an unwanted organism into New Zealand. This is most likely associated with contamination of trade name products of plant or animal origin or products that contain organisms. However, there is also the possibility of reducing the effectiveness of pest or disease control programmes, possibly by interfering with diagnostic tests or the efficacy of treatments. At this stage, the ACVM Group has not been advised of any specific circumstances that relate to reduced effectiveness of pest or disease control programmes, except in regard to *Mycobacterium* PPD.

Negative effects on national productivity may be difficult to identify and relate to a specific trade name product. It is also difficult to draw a boundary between a local reduction in productivity and the effects on national productivity. Negative consequences in regard to national productivity will require considerable consultation and ministerial agreement before they should be used as relevant to the risk assessment of agricultural compound trade name products. Currently, the only negative consequence that is being considered is anthelmintic resistance because of the impact it could have on national productivity. The ACVM Group will advise interested parties of any change or additional negative consequences that should be taken into consideration.

5.3.2 Hazards

Given the present state of consultation on agricultural security matters, the primary hazard in this risk area is biological contamination with exotic or new organisms.

Inefficacy and uninformed use of anthelmintics are other hazards that must be considered. The ACVM Group will advise interested parties of any changes.

5.3.3 Preferred tests and tolerable endpoints

The preferred testing relates to confirming that products are not contaminated and describing quality systems based on HACCP principles that ensure that contamination will not occur.

The *ACVM – Registration Standard and Guideline for Efficacy of Anthelmintics in Cattle, Sheep, Goats and Deer* should be referred to for preferred tests and tolerable endpoints when measuring efficacy of ruminant anthelmintics.

5.4 Breaches in the domestic food residue standards

Public health is not an area of risk to be managed under the ACVM Act. It is the responsibility of the Ministry of Health and the Environmental Risk Management Authority. However, the ACVM Act does provide power to regulate the use of agricultural compounds to ensure that domestic food residue standards are not breached. This means that, in placing conditions on the manufacture, sale and use of agricultural compounds for trade reasons, regulators must ensure that the same conditions will be sufficient to ensure that the domestic food standards will not be breached. The threshold and criteria relate to domestic sale of primary produce that contains residues that exceed the limits set in the domestic food residue standards.

5.4.1 Negative consequences

The immediate negative consequence is identifying primary produce or food being offered for sale in New Zealand that contains violative residues of agricultural compound substances.

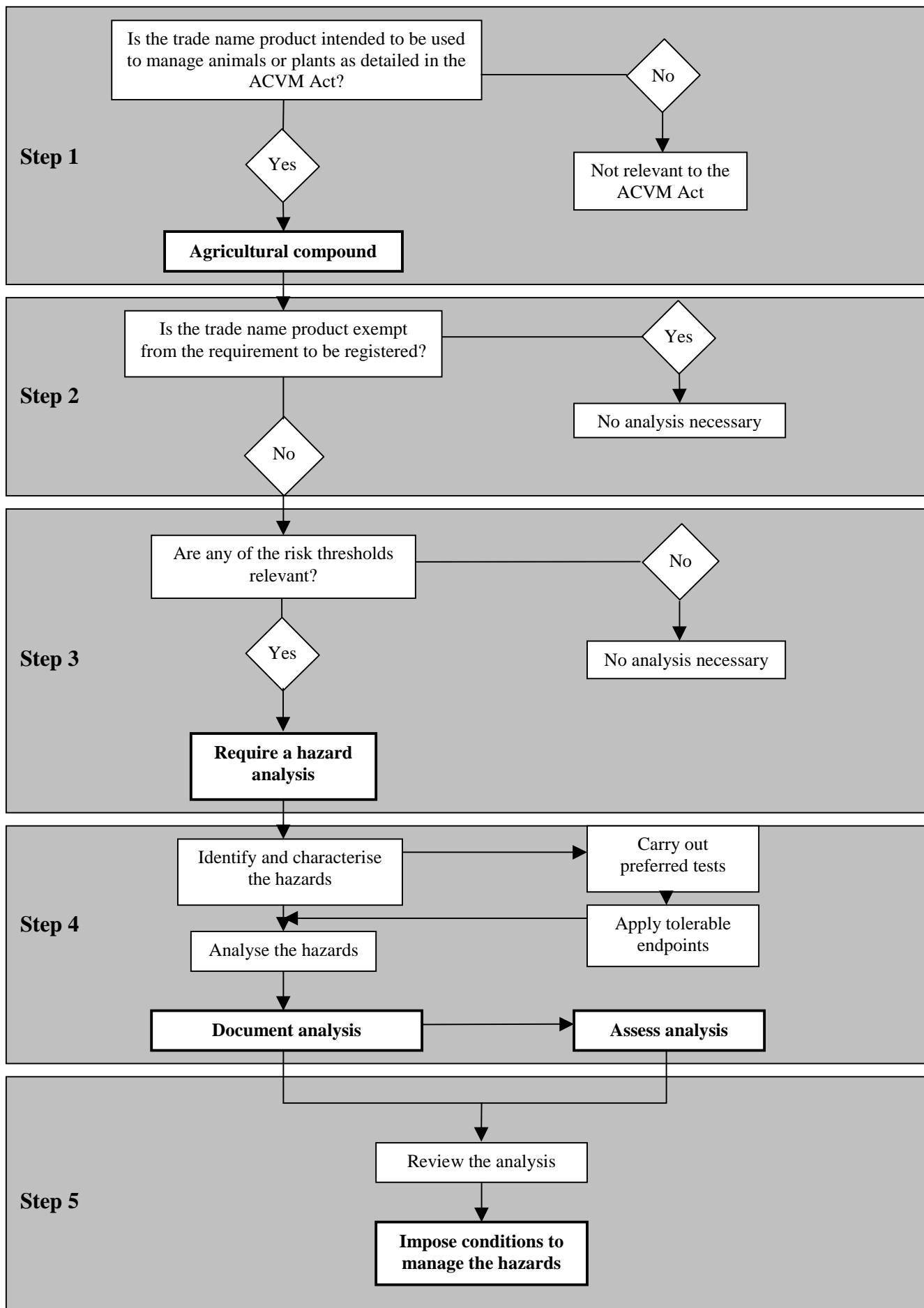
5.4.2 Hazards

The hazards are the substances that are ingredients (actives and excipients) in a trade name product, but there are aspects of the formulation, manufacturing, or use of the trade name product that affect the level of exposure (e.g. sustained release veterinary medicines or the interaction of different spray tank adjuvants). These aspects become hazards in their own right, and should be addressed as hazard/negative consequence pathways.

5.4.3 Preferred tests and tolerable endpoints

The tolerable endpoint is the maximum residue limit specified in the domestic food residue standards. The *ACVM - Registration Standard and Guidelines for Residue Data* should be used as the guide for preferred tests.

APPENDIX 1: GENERIC ASSESSMENT MODEL



APPENDIX 2: RISK AREA ENQUIRY FOR VETERINARY MEDICINES

Does it pose any hazards that could have an impact on animal welfare?

Can it be toxic (including physical damage)?

Can it cause undesirable pharmacological side effects?

Can it fail to prevent, treat or cure as claimed?

Causing unnecessary pain or distress

Does it pose any hazards that could have an impact on agricultural security?

Can it be the source of exotic unwanted organisms?

Can it facilitate the spread of pests or diseases?

Can it interfere with pest management strategies or disease control programmes?

Can it interfere with the effectiveness of compounds to control pests or diseases?

Can it reduce national productivity?

As specified in a written policy direction.

Does it pose any hazards that could have an impact on trade in primary produce?

Are there substances or breakdown substances that could cause default trade MRLs to be exceeded?

Is it tested or manufactured in a manner that would jeopardise trade in primary produce?

Is it sold or intended to be used in a manner that would jeopardise trade in primary produce?

Can it cause quality defects in primary produce?

As specified in a written policy direction.

Does it pose any hazards that could cause a breach in domestic food residue standards?

Are there substances or breakdown substances that could cause domestic MRLs to be exceeded?

APPENDIX 3: RISK AREA ENQUIRY FOR PLANT COMPOUNDS

Does it pose any hazards that could have an impact on animal welfare causing unnecessary pain or distress in a target animal?

Plant compounds are not used on animals so there are no direct effects on animal welfare. Indirect effects are of interest to the ACVM Group but they are primarily environmental hazards of interest to ERMA.

Does it pose any hazards that could have an impact on agricultural security?

Can it be the source of exotic unwanted organisms?

Can it facilitate the spread of pests, weeds or diseases?

Can it interfere with pest management strategies or disease control programmes?

Can it interfere with the effectiveness of compounds to control pests or diseases?

Can it reduce national productivity?

As specified in a written policy direction.

Does it pose any hazards that could have an impact on trade in primary produce?

Are there substances or breakdown substances that could cause default trade MRLs to be exceeded in treated plants or exposed food-producing animals?

Is it tested or manufactured in a manner that would jeopardise trade in primary produce?

Is it sold or intended to be used in a manner that would jeopardise trade in primary produce?

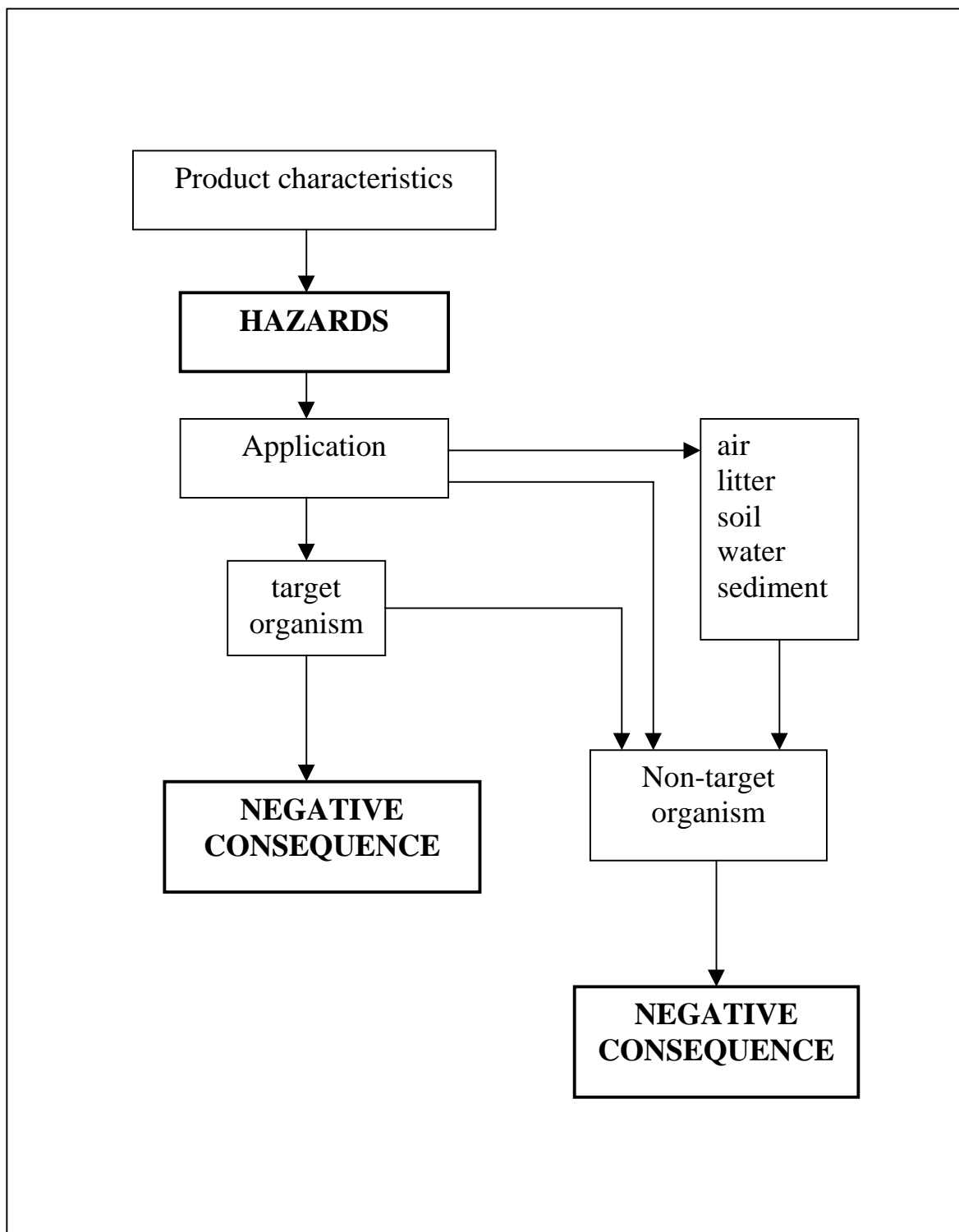
Can it cause quality defects in primary produce?

As specified in a written policy direction.

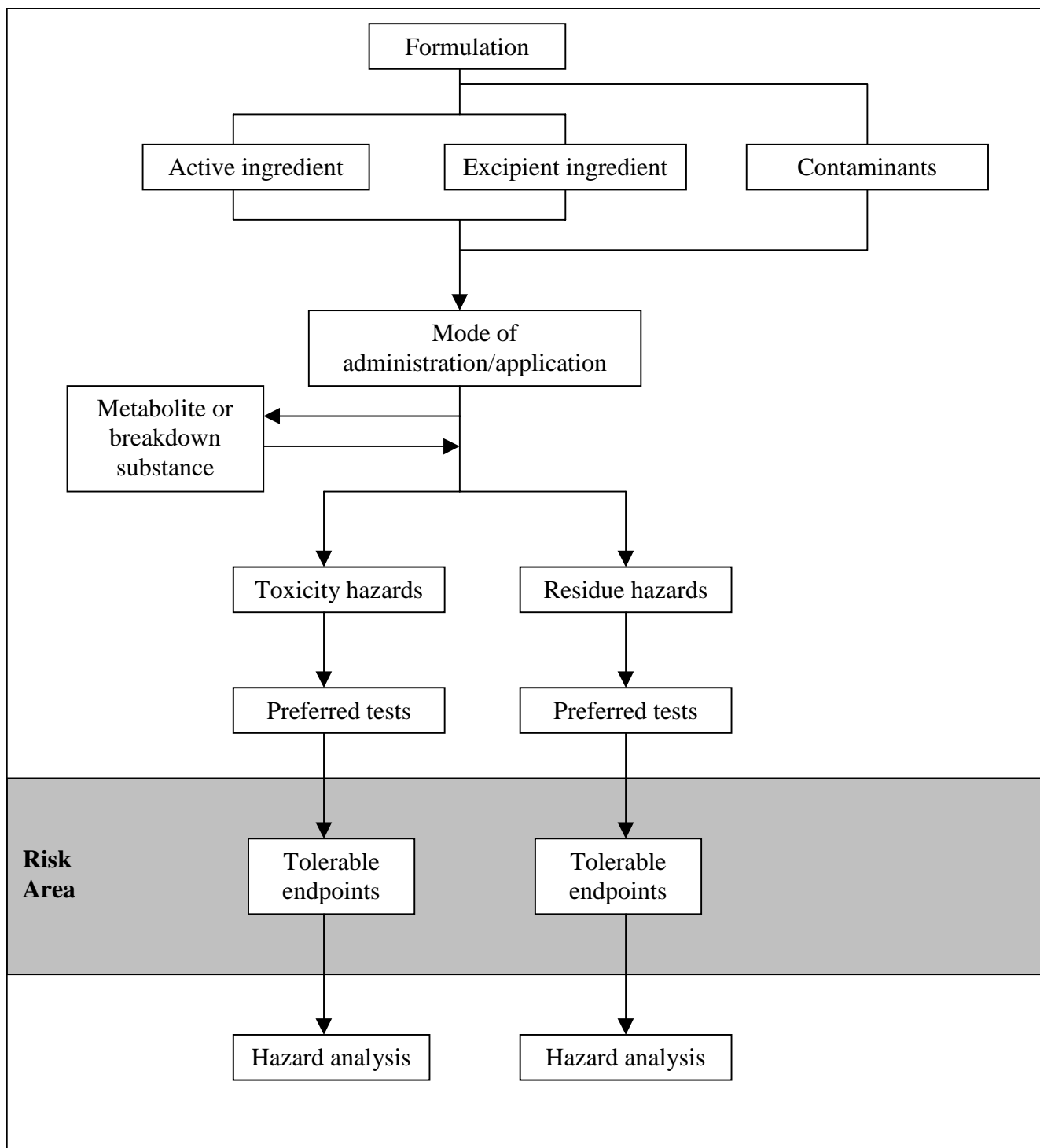
Does it pose any hazards that could cause a breach in domestic food residue standards?

Are there substances or breakdown substances that could cause domestic MRLs to be exceeded in treated plants or exposed food-producing animals?

APPENDIX 4: PATHWAY FOR DIRECT AND INDIRECT EFFECTS



APPENDIX 5: INGREDIENT HAZARDS ANALYSIS



APPENDIX 6: TRADE NAME PRODUCT HAZARDS ANALYSIS

