Ministry of Agriculture and Forestry
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ACVM - REGISTRATION STANDARD FOR TOXICOLOGY AND ENVIRONMENTAL TOXICOLOGY

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Endorsement:
Date:

CONTENTS

ACVM - REGISTRATION STANDARD FOR TOXICOLOGY AND ENVIRONMENTAL TOXICOLOGY

1 INTRODUCTION

This document specifies the minimum requirements for toxicology and environmental toxicology studies submitted in support of an application to register a trade name product, or to vary the conditions on a registered trade name product. Every product that has a new or innovative active substance, a change in formulation or a new use will be required to undergo toxicological assessment.

This standard is compulsory in all cases where toxicology and environmental toxicology information is required to be provided for registration of a trade name product, unless a waiver has been granted by MAF.

Waivers may be granted to reduce the number of studies or type of information that an applicant must submit (e.g. by permitting cross-referencing to existing information held by MAF). *These waivers must be granted by MAF prior to the applicant submitting an application.* This standard will be reviewed periodically, and waivers incorporated if appropriate.

Applicants should note that they are responsible for providing all information required by the ACVM Group of MAF to make a decision on the application. Applications that do not contain the required information will not be assessed. If further advice is required, applicants are advised to contract the services of an appropriate consultant prior to submitting their application.

1.1 Scope

The standard must be followed by:

- all persons applying to register a trade name product or vary the conditions on a registered trade name product where toxicology and environmental toxicology information is required;
- all persons accredited under the Agricultural Compounds and Veterinary Medicines Act 1997 to undertake a risk assessment of applications made to register a trade name product or vary the conditions on a registered trade name product.

The standard provides specifications for:

- general requirements;
- full mammalian toxicology package;
- limited information package;
- environmental toxicology package;
- limited environmental information package.

1.2 Definitions and abbreviations

LD_{50} (Median lethal dose)
A statistically derived single dose of a substance that can be expected to cause death, during exposure or within a fixed time after exposure, in 50% of animals when administered by the oral or dermal route.

NOEL (No observed effect level)
The greatest concentration or amount of an agent, found by study or observation, that causes no detectable, usually adverse, alteration of morphology, functional capacity, growth, development or lifespan of the target.

1.3 References

Licensing Requirements for Animal Remedies in New Zealand
Registration Requirements for Pesticides in New Zealand

OECD's Guidelines for Testing of Chemicals
(refer to the OECD website: http://www.oecd.org/ehs/test/testlist.htm)

OECD Guidance for Country Data Review Reports on Plant Protection Products and their Active Substances
(refer to the OECD website: http://www.oecd.org/ehs/pesticid.htm)

United States Environmental Protection Agency (US EPA) Office of Prevention, Pesticides and Toxic Substances guidelines
(refer to the US EPA website - http://www.epa.gov/epahome/publications.htm)

European Commission Guidelines (Directive 81/852/EEC)

2 GENERAL REQUIREMENTS

2.1 Each application to register a trade name product must supply the information required to enable the toxicological and ecological risks from exposure to the substance to be assessed. The required information must be provided on all active substances in the formulated trade name product and, where possible, information on the acute hazard of the formulated trade name product.

2.2 All studies should be GLP compliant and conducted to either:
- OECD Test Guidelines Methodologies;
- US EPA Office of Prevention, Pesticides and Toxic Substances Guidelines; or
- European Commission Guidelines (Directives).

2.3 Older studies (prior to 1981) and/or non-GLP compliant studies may still be assessed; however, any divergence from the current methodologies must be noted.

3 INFORMATION REQUIREMENTS

Each application for registration of a trade name product or variation of the conditions on a registered trade name product must contain a comprehensive supporting data package. The supporting data package must be compiled under the headings and contain the data to address the outcomes specified below. Table 1 summarises the information requirements for each type of application. (Refer to the documents *Licensing Requirements for Animal Remedies in New Zealand* and/or *Registration Requirements for Pesticides in New Zealand* for definitions of application types.)

3.1 Full mammalian toxicology package

This section details the full list of toxicological studies that are required for a new or innovative active substance.

3.1.1 Introductory information
- table of contents;
- reference to the appropriate section(s) of the chemistry data package covering the identity and properties of each active substance and scheduled substance in the trade name product;
- proposed use pattern, and application rates/dosage of the trade name product;
- summary and conclusion.

3.1.2 Acute studies

These studies should be on the active ingredient or technical concentrate and formulation studies:

- acute oral;
- acute dermal;
- acute inhalation;
- skin irritation/corrosion;
- eye irritation/corrosion;
- skin sensitisation.

3.1.3 Subchronic toxicity studies (less than 12 months and including range-finding studies).

3.1.4 Reproduction studies.

3.1.5 Developmental studies.

3.1.6 Genotoxicity studies.

3.1.7 Long-term toxicity studies (12 months or longer).

3.1.8 Metabolism/toxicokinetic studies.

3.1.9 Other target organ studies (e.g. neurotoxicity or immune effect studies).

3.1.10 Occupational exposure – general information on exposure, extrapolated or measured exposure.

3.1.11 Human toxicological data (if available).

3.1.12 No observed effect level (NOEL).

3.1.13 Proposed measures to control occupational exposure – prior to and during end use, re-entry or rehandling.

3.1.14 Information and training for workers, first aid and safety directions – label, material safety data sheet (MSDS), special training.

3.1.15 Miscellaneous requirements for certain products or uses.

3.1.16 Bibliography.

3.2 Limited information package

This section details a limited package giving information on the formulation, occupational health and safety issues, and to establish toxicological equivalence to an already registered product not under data protection. The assessment will generally involve a review of the existing information, combined with an assessment of the additional studies (or the rationale why these additional studies are not required).

All studies listed below refer to the formulation.

3.2.1 Acute studies

- acute oral;
- acute dermal;
- acute inhalation;
- skin irritation/corrosion;
- eye irritation/corrosion;
- skin sensitisation.

3.2.2 Occupational exposure – general information on exposure, extrapolated or measured exposure.

3.2.3 Human toxicological data (if available).

3.2.4 Suggested label requirements.

3.3 Environmental toxicology package

This section details the complete list of environmental toxicology studies that are required for assessment of a new or innovative active.

3.3.1 Introductory information

- table of contents;
- summary of environmental fate and hazard assessments;
- proposed environmental protection statement(s);
- proposed directions for storage and disposal.

Relevant studies to be addressed from the following list

3.3.2 Physico-chemical degradation

- hydrolysis;
- photo-degradation (aqueous, soil).

3.3.3 Biodegradation

- soils (aerobic and anaerobic);
- water.

3.3.4 Mobility
- potential for transport;
- volatility;
- adsorption/desorption;
- leaching potential.

3.3.5 Field dissipation
- soils;
- water;
- plants.

3.3.6 Accumulation/Metabolism
- bioaccumulation in fish and aquatic organisms;
- accumulation potential in soils;
- others (e.g. birds, earthworms).

3.3.7 Modelling studies.

3.3.8 Aquatic organisms (freshwater and marine)
- acute;
- short-term;
- special studies (chronic, early life-stage, simulated or field testing, etc.).

3.3.9 Birds, mammals and other vertebrates (wild)
- acute;
- short-term;
- special studies (chronic, reproduction, simulated or field testing, etc.).

3.3.10 Non-target invertebrates (terrestrial)
- predators;
- parasites;
- bees;
- earthworms;
- soil micro-organisms;
- others where relevant.

3.3.11 Non-target vegetation (pesticides only)
- results from laboratory tests;
- observations from field studies or efficacy tests.

3.4 Limited environmental information package

This section details a limited environmental package that may be required for a revised formulation or new excipients. The assessment will generally involve a review of the existing information, combined with an assessment of the additional studies (or the rationale why these additional studies are not required).

The information requirements for limited environmental studies are grouped under the headings "Environmental Chemistry and Fate" and "Environmental Toxicology". It is not possible to specify the exact data required for each change in formulation or use as the environmental conditions are potentially different in each case. As an example, new biodegradation studies are likely to be required where the new use is taking place in a different soil type.

3.4.1 Introductory information

- table of contents;
- summary of environmental exposure and hazard assessments;
- proposed environmental protection statement;
- proposed directions for storage and disposal.

3.4.2 Environmental chemistry and fate

Additional studies relevant to revised formulation or new excipients and additional uses.

3.4.3 Environmental toxicology

Additional studies relevant to revised formulation or new excipients and additional uses.

TABLE 1: INFORMATION REQUIREMENTS

Application Type		Toxicology Data Requirements
Trade name products containing any active ingredient that has never been assessed for toxicology purposes by the ACVM Group under the Pesticides Act 1979 for pesticides, or under the Animal Remedies Act 1967 for animal remedies.	Type A1	Full mammalian toxicology and environmental toxicology information packages are required. These consist of the following: • a toxicology assessor's reports on the information packages; • a summary for each package; • the information packages containing the full reports of the tests referred to in sections 3.1 and 3.3.
Trade name products containing only active ingredients that have been previously assessed under the relevant Act by the ACVM Group.	Type A2[1] Type C1[2] Type C2[2]	Limited mammalian toxicology and environmental toxicology packages are required. These consist of the following: • a toxicology assessor's reports on the toxicology information package; • a summary for each package; • the information packages containing the full reports of the tests referred to in sections 3.2 and 3.4.
	Type B1 Type B2 Type C3 Type C4[3] Type C5 Type C6[3] Type C7[3] Type C8[3] Type C9	No toxicology or environmental toxicology information is required.

1 If a trade name product previously registered for non-food use is being proposed for use in food production, the original toxicology data package may not have been a full package. For example, it may not have included long-term feeding studies. Therefore a "top-up" package (so that the total data held by the Group is a full package) will be required in order to assess the acceptability of residues.

2 A limited toxicology data package will be required if there is a significant toxicological change in the impurity profile of the active ingredient(s), or the toxicity of the formulation.

3 These changes may lead to altered residues in food and, while no new toxicology data would be required, such a change would require a reassessment of the acceptability of the residues.

4 RISK ASSESSOR'S REPORT

An accredited assessor must prepare an assessment report for the trade name product. A list of accredited assessors can be obtained from the ACVM Group.

The risk assessor's report must provide a full hazard assessment of the mammalian toxicology information package and the environmental toxicology information package and include a risk assessment summary of this information. This summary should identify:

- the hazardous substance(s) present and their physical and biological properties, including LD_{50}s and NOELs, metabolism and environmental fate with respect to intended use patterns;
- conformance to ACVM standards and guidelines;
- the use of any risk assessment from another regulatory authority and any differences in the information packages supplied to each jurisdiction;
- any substance that requires scheduling under the Toxic Substances Regulations 1983;
- any substance that may require the setting of an Acceptable Daily Intake value for use in establishing permitted Maximum Residue Limits for various foodstuffs;
- any effects that require specific warning/precautionary statements on the label.

Each risk assessor's report must address each active substance in the formulation and its effects. The format and the content of a risk assessor's report are specified in Appendix A. Cognisance should be taken of *OECD Guidance for Country Data Review Reports on Plant Protection Products and their Active Substances* in the production of this report.

If the risk assessor's report states that the information supplied is insufficient or that further work is required, the information package will fail the ACVM Group review and evaluation.

5 INFORMATION PACKAGE SUMMARY

The applicant must prepare a summary of the supporting information package.

This must comprise a summary of the identity of the trade name product, proposed use pattern, estimated residue levels, and must address the toxicological/environmental properties of each active substance in the formulation.

The format and the content of an information package summary are specified in Appendix B. Clear references must be provided to the appropriate studies or reports in the supporting data package. Where data for currently registered trade name products are cross-referenced, the information package summary must provide full references.

APPENDIX A:
CONTENT OF RISK ASSESSOR'S REPORT

SUMMARY AND CONCLUSIONS

1. Identification

1.1. Applicant

1.2. Trade name of product

1.3. Active ingredient(s) and concentration(s)

1.4. Proposed use pattern, application rates/dosage

1.5. Any other scheduled substance(s) present in the trade name product

1.6. Indicate if the substance has been approved for use in any other country and whether a full risk assessment from that jurisdiction has been supplied.

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2. Supporting information

2.1. Mammalian toxicology information

Provide concise statements on the quality, validity, type of studies and completeness of the supporting information. Advise on the potential hazards of the substance and the likely effects following the recommended use of the trade name product.

2.2. Environmental toxicology information

Provide concise statements on the quality, validity, type of studies and completeness of the supporting information. Advise on the environmental fate (with reference to the physical and chemical properties of the substance/formulation) and the potential hazards of the substance and the likely environmental impact following the recommended use of the trade name product.

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3. Conformance

State whether the supporting data conforms to the *ACVM - Registration Standard for Toxicology and Environmental Toxicology*, guidelines and information waivers. Where information waivers have been granted, comment on their impact.

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4. Risk statements

4.1. Note any mammalian or ecotoxicity effects above international harmonised/ recognised effect levels, for example:

- the acute oral toxicity study in rats resulted in an LD_{50} of 2050 mg/kg bodyweight and, therefore, the active ingredient is required to be scheduled under the Toxic Substances Regulations 1983;
- the honeybee contact study resulted in an LD_{50} of 10 mg/bee and, therefore, a warning of this effect is required on the label, e.g. "Toxic to Bees".

4.2. Note any changes to the label that are required based on the hazard/risk assessment for the substance.

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5. Further work or information required

Identify any work that may reduce the level of uncertainty, assist in the explanation or extrapolation of the data or provide a more complete database.

Assessor's Name:
Signature:
Date:

RISK ASSESSOR'S REPORT FOR (ACTIVE INGREDIENT)

One report to be completed for each active substance in the trade name product.

1. Identification

1.1. Applicant

1.2. Trade name of product

1.3. Active ingredient(s) and concentration(s)

1.4. Common name, chemical name, molecular formula, molecular weight.

1.5. Proposed use pattern, application rates/dosage

1.6. Any other scheduled substance(s) present

Comment on the key properties of the substance that impact on the behaviour of the compound in plants and animal tissues, and the environment. Indicate the potential impact of these properties.

1.7. Indicate if the substance has been approved for use in any other country and whether a full risk assessment from that jurisdiction has been supplied.

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2. Supporting information

2.1. Mammalian toxicology information

Provide concise hazard assessment of all the effects (beneficial and adverse) and NOELs from the mammalian toxicology studies (both active ingredient and formulation studies), occupational exposure and human toxicological data (if available), and comment on the validity and completeness of these studies.

2.2. Environmental toxicology information

Provide a concise hazard assessment of the environmental fate studies and the relevant chemical and physical properties (both substance and formulation studies) with particular reference to the potential for persistence and bioaccumulation. Provide a concise hazard assessment of all the effects (beneficial and adverse) and NOELs from the ecotoxicity studies, and comment on the validity and completeness of these studies.

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3. Conformance

State whether the supporting data conforms to the *ACVM - Registration Standard for Toxicology and Environmental Toxicology*, guidelines and information waivers. Where information waivers have been granted, comment on their impact.

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4. Further work or information required

Identify any work that may reduce the level of uncertainty, assist in the explanation or extrapolation of the data or provide a more complete database.

APPENDIX B:
CONTENT OF MAMMALIAN TOXICOLOGY AND ENVIRONMENTAL TOXICOLOGY INFORMATION PACKAGE SUMMARY

MAMMALIAN TOXICOLOGY AND ENVIRONMENTAL TOXICOLOGY INFORMATION PACKAGE SUMMARY FOR (TRADE NAME PRODUCT)

1. Identity

1.1. Applicant

1.2. Trade name of product

1.3. Active ingredient and impurities

Ensure that the chemistry data package provides:

- a list of all active ingredients and impurities or contaminants present in the technical grade material/manufacturing concentrate at levels above 1.0g/kg (0.1%), indicating their concentration and highlighting those considered to be of significance from a human and environmental toxicological point-of-view;
- a list of all compounds of human and environmental significance (e.g. dioxins, HCBs, nitrosamines) present at levels below 1.0 g/kg (0.1%), indicating their concentration and highlighting those considered to be of significance.

1.4. Product

Ensure that the chemistry data package provides:

- a list of all other ingredients present at levels above 1.0g/kg (0.1%) and their concentration in the trade name product;
- identification of any currently scheduled substances in the trade name product;
- a list of the product properties.

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2. Proposed use pattern

2.1. Use situation

2.2. Condition(s) being treated

2.3. Application/administration method

2.4. Application rate/dosage

Provide the proposed application rates/dosage.

2.5. Number and timing of treatments

Provide the normal, minimum and maximum treatment intervals and the number of treatments.

2.6. Estimated residue levels in food and feed

- Estimate the level of residues of each active substance or scheduled substance within the trade name product and of major metabolites that are likely at harvest, slaughter and/or after storage, following the use of the trade name product in accordance with the proposed use directions.
- Indicate if any of these estimates are based on previous assessments or existing approvals.

MAMMALIAN TOXICOLOGY AND ENVIRONMENTAL TOXICOLOGY INFORMATION PACKAGE SUMMARY FOR (ACTIVE INGREDIENT)

One summary to be completed for each active substance in the trade name product.

1. Identity and properties

1.1. Active ingredient common name and chemical name
Include both the ISO common name and the CAS number

1.2. Concentration in the trade name product

1.3. Chemistry and properties
Provide the references to sections(s) in the chemistry data package that describe the properties of relevance to the assessment of the toxicity profile of the active ingredient for humans and the environment.

1.4. Indicate if the substance has been approved for use in any other country and whether a full risk assessment from that jurisdiction has been supplied.

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2. Supporting information

2.1. Mammalian toxicology information
Provide a summary each of the available mammalian toxicology studies on laboratory animals, field trials, occupational exposure and human toxicological data (if available) identifying the clinical signs and/or symptoms of toxicity and any toxicity effect levels determined.

2.2. Environmental toxicology information
Provide a summary of each of the available environmental fate and ecotoxicity studies in the laboratory, field trials or from use, and identify any clinical signs of toxicity and any ecotoxicity effect levels determined.

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3. Risk assessment

3.1. Provide a risk assessment for the above studies particularly noting any mammalian or ecotoxicity effects above international harmonised/recognised threshold effect levels. State whether these effects are noted on the label or provide a risk assessment as to why this effect does not require identification on the label.

3.2. Where applicable, identify any internationally agreed Acceptable Daily Intake values for the active ingredient (or a calculate one from the supplied information) and whether a Maximum Residue Limit is required for the active ingredient.