

**THE SOUTH AFRICAN NATIONAL PESTICIDE
REGISTRATION AUTHORITY**

Registrar: Act No. 36 of 1947

**GUIDELINES ON EQUIVALENCE OF
AGRICULTURAL REMEDIES
(PESTICIDES)**

NOVEMBER 2000

1. INTRODUCTION

The Registrar Act 36/1947 is tasked with ensuring that good quality crop protection chemicals (pesticide) are supplied to users and that these chemicals do not adversely affect the public interest.

Stringent requirements are in place for the evaluation and registration of new compounds but for older compounds and for compounds produced by a different manufacturing process or by a different manufacturer after a patent has expired requirements had been less clear.

This document is aimed at clearing any ambiguity around the registration of a technical material in itself or incorporated in any formulation and to have clear guidelines on what information is required for registration purposes. It is in line with similar policies of the FAO and registration authorities in the UK, Australia and the USA.

These guidelines should be read in conjunction with the "Agricultural Remedies Registration Procedure Policy Document". Applicants are advised to consult the relevant technical adviser for full details on registration requirements before submitting a registration application.

2. USE OF THE GUIDELINES

- These guidelines are to be used by Technical Advisers of Act 36/1947 as well as by existing registration holders and new applicants for registration.
- It is incumbent on manufacturers who manufacture the technical material to supply the information required under point 4 and to follow the steps for determination of equivalence or to supply whatever information they may have on the chemical composition of the product.
- If a compound can be demonstrated to be exactly equivalent to the original registration and subsequent tests on formulated products show beyond doubt that the products are equivalent, the Registrar may, where applicable, decide not to require any additional efficacy data for the generic product and may grant a registration based only on the equivalence data supplied by the applicant (e.g. pesticides used in structural pest control). Proof of registration in other countries e.g. USA, EU and Australia will have to be submitted.

3. DETERMINATION OF EQUIVALENCE

3.1 Technical materials from different manufacturers or manufacturing processes are deemed to be equivalent if:

3.1.1 The material meet the requirements of the original manufacturer or reference profile (see glossary)in the FAO specifications and

3.1.2 Assessments of the manufacturing process used and the impurity profile (together with assessments of the toxicological/ecotoxicological profiles, if necessary) have been carried out with the result that the profiles meet the requirements of sections 3.3,3.4 and 3.5 of this document.

3.2 Changes in manufacturing process

Where a producer changes the manufacturing process for a technical active ingredient, which has previously been registered, equivalence may be determined on the basis of paragraphs 3.1.1 and 3.1.2.

3.3 Equivalence of the impurity profile of a technical material*

3.3.1 Where the maximum levels of non-relevant impurities are not increased by more than 50% (relative to the maximum level in the reference profile), or the absolute level is not increased by more than 3 g/kg (whichever represents the greater increase), and there are no new relevant impurities (see glossary), the technical materials (see glossary)* will normally be considered sufficiently similar as to be equivalent.

3.3.2 Where these differences in maximum impurity concentration are exceeded, the applicant will be asked to provide a reasoned case, with supporting data as required, as to why these particular impurities remain "non-relevant" and the technical materials* are equivalent. The Technical Advisor Act 36/1947 will evaluate the case to decide whether or not the technical material* is equivalent.

3.3.3 Where new impurities are present at >1 g/kg, the applicant will be asked to provide a reasoned case, with supporting data as required, as to why these impurities are "non-relevant" and the technical material* is equivalent. The Technical Advisor Act 36/1947 will evaluate the case to decide whether or not the technical material* is equivalent.

3.3.4 Where relevant impurities are increased in maximum concentration, and/or where new relevant impurities are present, additional toxicological and/or ecotoxicological data will be required as described in paragraphs, 4.1.9.1, 4.1.9.2, 4.1.9.3 and 4.1.9.4.

3.4 Equivalence of the toxicological profiles of a technical material*

3.4.1 The toxicological profile will be considered equivalent to that of the reference profile, where the data required by point 4 of this document do not differ by more than 20% compared to the reference profile (or by a percentage greater than that of the appropriate dosage increments, if more than 20%).

3.4.2 Where necessary additional toxicological data will be assessed by the criterion applied in paragraph 3.4.1 of this document provided that, where appropriate, the organs affected are the same. The "no observable effect levels" (NOELs) or "no observable adverse effect levels" (NOAELs) should not differ by more than the differences in the dose levels used. There should be no change in the assessment in those studies, which produce either positive or negative results.

3.5 Ecotoxicological profiles for the technical materials

(as appropriate to the intended use of the active ingredient)

Where required (see section 3.1 and 3.2 of this document), the ecotoxicological profile will be considered equivalent to that of the reference profile if the data do not differ by more than 20% compared to the reference profile (or by a percentage more than that of the appropriate dosage increment, if greater than 20%), when determined using the same species.

Note : In case where the technical material (see glossary) is not normally isolated, the data and information requirements marked with an asterisk () may be derived from the technical concentrate (see glossary). However, data submitted for the determination of equivalence are expected to correspond to the same form of the technical active ingredient upon which the original reference specification is based.*

4. DATA REQUIREMENTS FOR THE DETERMINATION OF EQUIVALENCE : MINIMUM DATA PACKAGE

4.1 Data requirements for technical materials (TC)

- 4.1.1 Identity of the active ingredient
 - ISO English common name (and its status)
 - Chemical name (IUPAC and CA)
 - CAS No.
 - CIPAC No.
 - Structural formula
 - Molecular formula
 - Molecular mass
- 4.1.2 Physico-chemical properties of the pure active ingredient
 - Vapour pressure
 - Melting point, boiling point, or temperature of decomposition
 - Solubility in water
 - Octanol: water partition coefficient
 - Hydrolysis / degradation characteristics
- 4.1.3 Outline of the manufacturing process
- 4.1.4 Minimum active ingredient content*
- 4.1.5 Maximum limits for the content of impurities present at or above 1 g/kg*, supported by batch analytical data (5 minimum). Relevant impurities (see glossary) in this category must be identified.

Note to paragraphs 4.1.4 and 4.1.5.: The unidentified fraction of the technical material must not exceed 20 g/kg*

- 4.1.6 Maximum limits for relevant impurities present at < 1 g/kg*
- 4.1.7 Information on relevant impurities, with explanations of the effects observed (for example, toxicological effects, or effects on the stability of the active ingredient). Limits set by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR) and/or other registration authorities should accompany this information, identifying the authority responsible for setting the limit.

Note to paragraph 4.1.6 and 4.1.7: Relevant impurities must be included in the data supplied but other impurities (including isomers, etc., of low activity) must not be included.

4.1.8 Nominal content (g/kg) of compounds intentionally added to the technical material* (e.g. stabilizers).

4.1.9 Toxicological summaries (if required see Paragraph 3.3.4)

4.1.9.1 Toxicological profile of the technical material* based on acute oral, dermal and inhalation toxicity, skin and eye irritation, skin sensitization.

4.1.9.2 Toxicological profile of the technical material* based on repeated administration (from subacute to chronic) and studies such as reproductive and development toxicity, genotoxicity, carcinogenicity, etc.

4.1.9.3 Ecotoxicological profile of the technical material* based on toxicity to aquatic and terrestrial organisms (e.g. fish, Daphnia, algae, birds, bees), as appropriate to the intended use.

4.1.9.4 Environmental fate profile of the technical material based on exposure to the environment (e.g. biodegradation in water, abiotic degradation, bioaccumulation in aquatic and terrestrial environment and behaviour in soil and sediments).

4.2 Data requirements for formulations

4.2.1 Main formulation types available

4.2.2 Main countries where these formulations are registered and sold

4.2.3 Physico-chemical properties, as required.

4.3 Methods for analysis and testing*

4.3.1 Methods for identity testing

4.3.2 Methods for determination of active ingredient content

4.3.3 Methods of analysis for impurities in the technical materials*

4.3.4 Test methods for physico-chemical properties.

Note to Section 4.3:

(i) *The methods used to generate data submitted in fulfillment of the requirements for registration must be identified.*

(ii) *Methods for determination of non-relevant impurities may be given in outline but, in cases of doubt, additional information may be required to support the validity of a method. Methods required to assess equivalence must be independently validated and must be published or otherwise made publicly available.*

4.4 Comparative analyses and tests

- 4.4.1 When a new or different manufacturing process is used by the original manufacturer or when a new manufacturer is involved the information as required must be supplied for the product from the new manufacturing process in a comparative tabulated format.
- 4.4.2 All comparative analyses and tests must be done by a laboratory accredited by a recognised GLP authority. Results of analyses done by the manufacturer will be used as corroborative information but is not sufficient on its own.
- 4.4.3 Toxicological summaries required under 4.1.9 must also include information on all relevant impurities

5. STEPS TO BE FOLLOWED TO DETERMINE EQUIVALENCE

- 5.1 The applicant supplies all the applicable information listed under point 4 to the Registrar Act 36/1947
- 5.2 The Technical Adviser Act 36/1947 determines whether all the information is supplied and then decide on equivalence using the following criteria:
- 5.2.1 All the data required were supplied and the comparative analyses and tests show that the product of the applicant is equivalent in all respects to the original or the FAO specification.
- Recommend registration.
- 5.2.2 All the data required was supplied but the comparative analyses and tests show that the product of the applicant is not equivalent due to:
- (a) New or higher relevant impurities in the product but full toxicological summaries were presented on the relevant impurities.
- Refer to a recognised toxicologist in the Dept of Health for an opinion or phytotoxicologist in the ARC where necessary.
 - Recommend registration or not based on the findings of the Dept of Health with or without efficacy tests.
- (b) New or higher relevant impurities in the product but full toxicological summaries were not presented.
- Refer back to applicant to supply additional information
- 5.2.3 All the data were supplied but the comparative analyses and tests were done by a laboratory not recognised by a GLP authority.
- Refer back to applicant for new tests. Applicant can apply to SANAS for evaluation of the test laboratory and the findings of SANAS must be supplied with the comparative test results to Act 36/1947.
 - Refuse the application based on the principle of "non-tested compliance".
- 5.2.4 Insufficient or incomplete data is supplied as stipulated in this document.
- Refer back to the applicant
 - Refuse application outright based on the "not in the public interest" principle.

6. GLOSSARY OF TERMS

6.1 Reference Specification

The current published FAO specification for a pesticide, where this has been developed according to the evaluation procedure of the FAO or the specification submitted by the original registration holder. The reference specification is used to determine the equivalence of a technical material and/or formulation of a parallel or subsequent manufacturer.

6.2 Reference Profile

The composition of the technical material (or technical concentrate where appropriate) upon which the reference specification is based, including active ingredient content (range and specified minimum), impurity profile and impurities identified as relevant (with maximum limits), together with the corresponding toxicological and ecotoxicological profiles. Reference profiles are confidential to Act 36/1947. Where appropriate, a reference profile may incorporate data submitted by more than one applicant or registration holder.

6.3 Relevant Impurities

Those by-products of the manufacture or storage of a pesticide which, compared with the active ingredient, are toxicologically significant to health or the environment, are phytotoxic to treated plants, cause taint in food crops, affect the stability of the pesticide, or cause any other adverse effect.

6.4 Technical material (TC)

A material resulting from a manufacturing process comprising the active ingredient, together with associated impurities. This may contain small amounts of necessary additives.

6.5 Technical concentrate (TK)

A material resulting from a manufacturing process comprising the active ingredient, together with associated impurities. This contain small amounts of necessary additives and appropriate diluents. For use only in the preparation of formulations.