COMMISSION DIRECTIVE 96/46/EC

of 16 July 1996

amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market [1], as last amended by Commission Directive 96/12/EC [2], and in particular Article 18 (2) thereof,

Whereas Annexes II and III to Directive 91/414/EEC set out the requirements for the dossier to be submitted by applicants respectively for the inclusion of an active substance in Annex I and for the authorization of a plant protection product;

Whereas it is necessary to indicate, in Annexes II and III, to the applicants, as precisely as possible, any details on the required information, such as the circumstances, conditions and technical protocols under which certain data have to be generated; whereas these provisions should be introduced as soon as available in order to permit applicants to use them in the preparation of their files;

Whereas it is now possible to introduce more details with regard to the data requirements concerning analytical methods for the active substance provided for in Section 4 of Part A of Annex II;

Whereas it is also now possible to introduce more details with regard to the data requirements concerning analytical methods for the plant protection product provided for in Section 5 of Part A of Annex III;

Whereas the measures provided for in this Directive are in accordance with the opinion of the Standing Committee on Plant Health,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Directive 91/414/EEC is amended as follows:

1. in Part A of Annex II the section headed '4. Analytical methods' is replaced by Annex I hereto;
2. in Part A of Annex III the section headed '5. Analytical methods' is replaced by Annex II hereto.

Article 2

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 30 April 1997. They shall immediately inform the Commission thereof.

When Member States adopt these measures, these shall contain a reference to this Directive or shall be accompanied by such reference at the time of their official publication. The procedure for such reference shall be adopted by the Member States.

Article 3

This Directive shall enter into force on 1 May 1996.

Article 4

This Directive is addressed to the Member States.

Done at Brussels, 16 July 1996.

For the Commission

Franz FISCHLER

Member of the Commission

---

[1] OJ No L 230, 19. 8. 1991, p. 1.
[2] OJ No L 65, 15. 3. 1996, p. 20.

ANNEX I

'4. **ANALYTICAL METHODS**

Introduction

The provisions of this section only cover analytical methods required for post-registration control and monitoring purposes.

For analytical methods used for generation of data as required in this Directive or for other purposes the applicant has to provide a justification for the method used; where necessary separate guidance will be developed for such methods on the basis of the same requirements as defined for methods for post-registration control and monitoring purposes.

Descriptions of methods must be provided and include details of equipment, materials and conditions used.

As far as practicable these methods must employ the simplest approach, involve the minimum cost, and require commonly available equipment.

For this section the following applies:

Impurities	Any component other than the pure active substance which is present in the active substance as manufactured (including non-active isomers) originating from the manufacturing process or from degradation during storage,
Relevant impurities	Impurities of toxicological and/or ecotoxicological or environmental concern,
Significant impurities	Impurities with a content of $\geq$ 1 g/kg in the active substance as manufactured,
Metabolites	Metabolites include products resulting from degradation or reaction of the active substance,
Relevant metabolites	Metabolites of toxicological and/or ecotoxicological or environmental concern.

On request the following samples must be provided:

(i) analytical standards of the pure active substance;

(ii) samples of the active substance as manufactured;

(iii) analytical standards of relevant metabolites and all other components included in the residue definition;

(iv) if available, samples of reference substances for the relevant impurities.

4.1. **Methods for the analysis of the active substance as manufactured**

For this point the following definitions apply:

(i) *Specificity*

Specificity is the ability of a method to distinguish between the analyte being measured and other substances.

(ii) *Linearity*

Linearity is defined as the ability of the method, within a given range, to obtain an acceptable linear correlation between the results and the concentration of analyte in samples.

(iii) *Accuracy*

The accuracy of a method is defined as the degree to which the determined value of analyte in a sample corresponds to the accepted reference value (for example ISO 5725).

(iv) *Precision*

Precision is defined as the closeness of agreement between independent test results obtained under prescribed conditions.

Repeatability: Precision under repeatability conditions, i.e. conditions where independent test results are obtained with the same method on identical test material in the same laboratory by the same operator using the same equipment within short intervals of time.

The reproducibility is not required for the active substance as manufactured (for definition of reproducibility see ISO 5725).

4.1.1. Methods, which must be described in full, must be provided for the determination of pure active substance in the active substance as manufactured as specified in the dossier submitted in support of inclusion in Annex I to Directive 91/414/EEC. The applicability of existing Cipac methods must be reported.

4.1.2. Methods must also be provided for the determination of significant and/or relevant impurities and additives (e.g. stabilizers) in the active substance as manufactured.

4.1.3. Specificity, linearity, accuracy and repeatability

4.1.3.1. Specificity of methods submitted, must be demonstrated and reported. In addition the extent of interference by other substances present in the active substance as manufactured (e.g. isomers, impurities or additives), must be determined.

While interferences due to other components may be identified as systematic errors in the assessment of the accuracy of methods proposed for the determination of pure active substance in the active substance as manufactured, an explanation must be provided for any interference occurring which contributes more than ± 3 % to the total quantity determined. The degree of interference for methods for the determination of impurities must also be demonstrated.

4.1.3.2. The linearity of proposed methods over an appropriate range must be determined and reported. For the determination of pure active substance, the calibration range must extend (by at least 20 %) the highest and lowest nominal content of the analyte in relevant analytical solutions. Duplicate calibration determinations must be made at three or more concentrations. Alternatively, five concentrations, each as single measurements, are acceptable. Reports submitted must include the equation of the calibration line and the correlation coefficient and representative and properly labelled documentation from the analysis, e.g. chromatograms.

4.1.3.3. Accuracy is required for methods for the determination of pure active substance and significant and/or relevant impurities in the active substance as manufactured.

4.1.3.4. For the repeatability in the determination of the pure active substance in principle a minimum of five determinations must be made. The relative standard deviation (% RSD) must be reported. Outliers identified through an appropriate method (e.g. Dixons or Grubbs test), may be discarded. Where outliers have been discarded, that fact must be clearly indicated. An explanation as to the reason for the occurrence of individual outliers, must be attempted.

4.2. Methods for the determination of residues

The methods must be capable of determining the active substance and/or relevant metabolites. For each method and for each relevant representative matrix, the specificity, precision, recovery, and limit of determination must be experimentally determined and reported.

In principle, residue methods proposed should be multi-residue methods; a standard multi-residue method must be assessed and reported as to its suitability for residue determination. Where residue methods proposed are not multi-residue methods, or are not compatible with such methods, an alternative method must be proposed. Where this requirement results in an excessive number of methods for individual compounds, a "common moiety method" may be acceptable.

For this section the following definitions apply:

(i) *Specificity*

Specificity is the ability of a method to distinguish between the analyte being measured and other substances.