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

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[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.

(ii) *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.

Reproducibility: As the definition of reproducibility in relevant publications (for example, in ISO 5725) is in general not practicable for residue analytical methods, reproducibility in the context of this Directive is defined as a validation of repeatability of recovery, from representative matrices and at representative levels, by at least one laboratory which is independent from that which initially validated the study (this independent laboratory may be within the same company) (independent laboratory validation).

(iii) *Recovery*

The percentage of the amount of active substance or relevant metabolite originally added to a sample of the appropriate matrix which contains no detectable level of the analyte.

(iv) *Limit of determination*

The limit of determination (often referred to as limit of quantification) is defined as the lowest concentration tested, at which an acceptable mean recovery is obtained (normally 70 to 110 % with a relative standard deviation of preferably $\leq$ 20 %; in certain justified cases lower or higher mean recovery rates as well as higher relative standard deviations may be acceptable).

4.2.1. Residues in and/or on plants, plant products, foodstuffs (of plant and animal origin), feedingstuffs

Methods submitted must be suitable for the determination of all components included in the residue definition as submitted according to the provisions of section 6, points 6.1 and 6.2 in order to enable Member States to determine compliance with established MRL's or to determine dislodgeable residues.

The specificity of the methods must enable all components included in the residue definition to be determined, using an additional confirmatory method if appropriate.

The repeatability must be determined and reported. The replicate analytical portions for test can be prepared from a common field treated sample, containing incurred residues. Alternatively the replicate analytical portions for test can be prepared from a common untreated sample with aliquots fortified at the required level(s).

The results from an independent laboratory validation must be reported.

The limit of determination including the individual and mean recovery must be determined and reported. The overall relative standard deviation, as well as the relative standard deviation for each fortification level must be experimentally determined and reported.

4.2.2. Residues in soil

Methods for analysis of soil for parent compound and/or relevant metabolites must be submitted.

The specificity of the methods must enable the parent compound and/or relevant metabolites to be determined, using an additional confirmatory method if appropriate.

The repeatability, recovery and the limit of determination including the individual and mean recovery must be determined and reported. The overall relative standard deviation, as well as the relative standard deviation for each fortification level must be experimentally determined and reported.

The proposed limit of determination must not exceed a concentration which is of concern with regard to exposure of non-target organisms or because of phytotoxic effects. Normally the proposed limit of determination should not exceed 0,05 mg/kg.

4.2.3. Residues in water (including drinking water, ground water and surface water)

Methods for analysis in water for parent compound and/or relevant metabolites must be submitted.

The specificity of the methods must enable the parent compound and/or relevant metabolites to be determined, using an additional confirmatory method if appropriate.

The repeatability, recovery and the limit of determination including the individual and mean recovvery must be determined and reported. The overall relative standard deviation, as well as the relative standard deviation for each fortification level must be experimentally determined and reported.

For drinking water the proposed limit of determination must not exceed 0,1 µg/l. For surface water the proposed limit of determination must not exceed a concentration which has an impact on non-target organisms deemed to be unacceptable according to the requirements of Annex VI.

4.2.4. Residues in air

Methods for the analysis in air of the active substance and/or relevant metabolites formed during or shortly after application must be submitted unless it can be justified that exposure of operators, workers or bystanders is not likely to occur.

The specificity of the methods must enable the parent compound and/or relevant metabolites to be determined, using an additional confirmatory method if appropriate.

The repeatability, recovery and the limit of determination including the individual and mean recovery must be determined and reported. The overall relative standard deviation, as well as the relative standard deviation for each fortification level must be experimentally determined and reported.

The proposed limit of determination must take into account relevant health based limit values or relevant exposure levels.

4.2.5. Residues in body fluids and tissues

Where an active substance is classified as toxic or highly toxic appropriate analytical methods must be submitted.

The specificity of the methods must enable the parent compound and/or relevant metabolites to be determined, using an additional confirmatory method if appropriate.

The repeatability; recovery and the limit of determination including the individual and mean recovery must be determined and reported. The overall relative standard deviation, as well as the relative standard deviation for each fortification level must be experimentally determined and reported.'

ANNEX II

'5. **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
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) samples of the preparation;

(ii) analytical standards of the pure active substance;

(iii) samples of the active substance as manufactured;

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

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

For definitions see Annex II, Section 4, points 4.1 and 4.2.

5.1. **Methods for the analysis of the preparation**

5.1.1. Methods, which must be described in full, must be provided for the determination of the active substance in the preparation. In the case of a preparation containing more than one active substance a method capable of determining each, in the presence of the other, should be provided. If a combined method is not submitted, the technical reasons must be stated. The applicability of existing Cipac methods must be reported.

5.1.2. Methods must also be provided for the determination in the preparation of relevant impurities, if the composition of the preparation is such that — on the basis of theoretical consideration — such impurities may be formed by its manufacturing process or from degradation during storage.

If required, methods for the determination of formulants or constituents of formulants in the preparation must be submitted.

5.1.3. Specificity, linearity, accuracy and repeatability

5.1.3.1. Specificity of methods submitted, must be demonstrated and reported. In addition the extent of interference by other substances present in the preparation must be determined.

While interferences due to other components may be identified as systematic errors in the assessment of the accuracy of methods proposed, an explanation must be provided for any interference occurring which contribute more than ± 3 % to the total quantity determined.

5.1.3.2. The linearity of proposed methods over an appropriate range, must be determined and reported. The calibration range must extend (by at least 20 %) the highest and lowest nominal content of the analyte in relevant analytical solutions of the preparation. 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.

5.1.3.3. Accuracy will normally only be required for methods for the determination of pure active substance and relevant impurities in the preparation.

5.1.3.4. For the repeatability 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.

5.2. **Analytical methods for the determination of residues**

Analytical methods for the determination of residues must be submitted unless it is justified that the methods already submitted according to the requirements of Annex II, Section 4, point 4.2 can be applied.

The same provisions as provided in Annex II, Section 4, point 4.2 apply.'