COMMISSION DIRECTIVE 94/40/EC

of 22 July 1994

amending Council Directive 87/153/EEC fixing guidelines for the assessment of additives in animal nutrition

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Directive 70/524/EEC of 23 November 1970 concerning additives in feedingstuffs [1], as last amended by Commission Directive 94/17/EC [2], and in particular Article 9 (2) thereof,

Whereas Council Directive 70/524/EEC provides for guidelines for the assessment of additives in animal nutrition subsequently adopted by Council Directive 87/153/EEC [3] and any amendment thereto in the light of advances in scientific and technical knowledge;

Whereas those guidelines should be supplemented by the establishment of criteria for examining requests for the authorization of enzymes and microorganisms for use as feed additives;

Whereas pursuant to the provisions of Council Directive 93/114/EC [4] it is necessary to include in the Community procedure for the authorization of additives the requirements of Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms [5], as amended by Commission Directive 94/15/EC [6] for a specific environmental-risk evaluation, in order that they may be applicable to all additives containing or consisting of genetically modified organisms; whereas as a consequence, it is appropriate to amend Directive 87/153/EEC in order to comply with the requirements of Directive 90/220/EEC;

Whereas, since numerous amendments have been made, it appears useful to provide a consolidation of the guidelines in the Annex to this Directive;

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

HAS ADOPTED THIS DIRECTIVE:

Article 1

The Annex to Directive 87/153/EEC is hereby replaced by the Annex to this Directive.

Article 2

Member States shall bring into force the laws, regulations or administrative provisions necessary to comply with this Directive by 1 October 1994 at the latest. They shall immediately inform the Commission thereof.

When Member States adopt these provisions, 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 Member States.

Article 3

This Directive shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Communities.*

Done at Brussels, 22 July 1994.

For the Commission

René STEICHEN

Member of the Commission

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(1) OJ No L 270, 14. 12. 1970, p. 1.
(2) OJ No L 105, 26. 4. 1994, p. 19.
(3) OJ No L 64, 7. 3. 1987, p. 19.
(4) OJ No L 334, 31. 12. 1993, p. 24.
(5) OJ No L 117, 8. 5. 1990, p. 15.
(6) OJ No L 103, 22. 4. 1994, p. 20.

ANNEX

GUIDELINES FOR THE ASSESSMENT OF ADDITIVES IN FEEDINGSTUFFS

GENERAL ASPECTS

These guidelines are intended as a guide for establishing dossiers on substances and preparations being submitted for authorization as additives in feedingstuffs. These dossiers must enable an assessment to be made of the additives based on the present state of knowledge and make it possible to ensure their compliance with the fundamental principles laid down for their admission, which are the subject of the provisions of Article 7 (2) of Directive 70/524/EEC.

All the studies outlined in these guidelines may be required and, if necessary, additional information will be requested. As a general rule, studies to establish the identity, conditions of use, physico-chemical properties, methods of determination and efficacy of the additive, and also its metabolism, biological and toxicological effects on target species must be provided. When the additive is intended for a category of animals belonging to a defined species, these studies must be performed on this target category. The studies necessary for the evaluation of risks to human health or the environment will depend essentially on the nature of the additive and the circumstances of its use. In this respect, no strict rule is applicable.

It may not always be necessary to subject additives intended exclusively for pet food to as exhaustive a program of chronic toxicity, mutagenicity and carcinogenicity testing as that required for additives intended for feeding to livestock from which products for human consumption are derived. To determine chronic toxicity, studies on two target species or on one target species and rats for a period of one year will generally suffice. Mutagenesis and carcinogenesis studies can generally be dispensed with if the chemical composition, practical experience, or other considerations do not indicate the likelihood of changes. It is possible to dispense with the analysis of residues in pet animals.

Knowledge of the metabolism of the additive in productive livestock and of the residues and their bioavailability is essential. In particular it must enable the extent of the toxicological studies to be performed on laboratory animals in order to assess the risks, if any, to the consumer to be determined. This evaluation cannot be based solely on data confined to determining the direct effects of the additives on laboratory animals. The latter does not provide specific information on the actual effects of residues resulting from the metabolism in the species for which the additive is intended.

Any application for authorization of an additive or a new usage for an additive shall be supported by a dossier which should include detailed reports presented in the order and with the numbering proposed in these guidelines. Reasons must be given for the omission from the dossier of any data prescribed in these guidelines. Publications to which reference is made must be attached to it the reports of experiments must include the plan, the reference number, the date of the beginning and the end of the experiment, detailed description of the tests, results and their analysis and also the name, address and signature of the person responsible for the study. Each batch of the feedingstuffs used in the experimental studies on animals must be analysed for the concentration of the relevant active substances using an appropriate method and a report of the analytical results must be provided. The report must also mention the individual doses determined in each experimental study, the corresponding dates, the name, address and signature of the person responsible for the controls. Furthermore, a certificate drawn up by the laboratory or laboratories where the experiments were conducted to the effect that the tests were carried out in accordance with the principles of good laboratory practices pursuant to Council Directive 87/18/EEC, on the harmonization of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances [1], must be attached to the report.

The determination of physico-chemical, toxicological and ecotoxicological properties shall be performed in accordance with the methods established by Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances [2], as last amended by Commission Directive 93/105/EC [3], or with methods internationally recognized by scientific bodies. The use of other methods should be justified.

[1] OJ No L 15, 17. 1. 1987, p. 29.
[2] OJ No L 196, 16. 8. 1967, p. 1.
[3] OJ No L 294, 30. 11. 1993, p. 21.

Each dossier shall contain an adequate summary. The dossiers relating to antibiotics, coccidiostats and other medicinal substances, growth promoters, microorganisms and/or enzyme preparations, must be accompanied by a monograph, conforming with the model provided in Section V, enabling the additive concerned to be identified and characterized in accordance with Article 8 (1) of Directive 70/524/EEC.

The term 'additive', as used in these guidelines, refers to the active substances or the preparations containing active substances in the state in which they will be incorporated in premixtures and feedingstuffs. An active substance may be a chemically specified substance, a microorganism or an enzyme preparation.

In these guidelines the expression 'Chemically specified substances', means chemical substances for which a chemical name is agreed according to IUPAC nomenclature.

The Commission must be notified within a reasonable time by the Member State which forwarded the dossier to it of any modification to the manufacturing process or the composition of an additive, its field of application or its conditions of use. This could necessitate the submission of documentation suitable for a new assessment. These requirements will be especially necessary for products derived from microorganisms, the genetic characteristics of which have been modified or which arise as natural mutants.

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SECTION II: Identity, characterization and conditions of use of the additive
Methods of control

SECTION III: Studies concerning the efficacy of the additive

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2. Studies concerning the effects of additives on animal production
3. Studies concerning the quality of animal produce

SECTION IV: Studies concerning the safety of use of the additive

1. Studies on target species
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1.2. Microbiological studies of the additive
1.3. Study of the metabolism and residues
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3. Studies on laboratory animals

SECTION V: Form of monograph

SECTION I

SUMMARY OF THE DATA IN THE DOSSIER

SECTION II

IDENTITY, CHARACTERIZATION AND CONDITIONS OF USE OF THE ADDITIVE METHODS OF CONTROL

1. Identity of the additive

1.1. Proposed proprietary name(s)

1.2. Type of additive according to its main function

1.3. Qualitative and quantitative composition (active substance, other components, impurities)

1.4. Physical state, particle size

1.5. Manufacturing process including any specific processing procedures

N.B.: If the active substance is a mixture of active components, each of which is clearly definable, the main components must be described separately and the proportions in the mixture given.

2. Specifications concerning the active substance

2.1. For chemically specified substances: generic name, chemical name according to Iupac nomenclature, other generic international names and abbreviations. Chemical Abstracts Service Number (CAS).

For microorganisms: name and taxonomic description according to the internatinal Codes of Nomenclature. Other internationally recognized manuals of classification can also be used [1].

For enzyme preparations: name according to main enzymatic activities as described by IUB/Iupac. Einecs and CAS Number.

2.2. Formula, empirical and structural, and molecular weight. Qualitative and quantitative composition of the main components, if the active substance is a fermentation product.

For microorganisms: name and place of culture collection, if possible one in an EC collection, where the strain is deposited and depositing number, genetic modification and all relevant properties for its identification. In addition, origin, appropriate morphological and physiological characteristics, developmental stages, relevant factors that may be involved in its biological activity (as an additive) and other genetic data for identification. Number of colony forming units (CFU) per gram.

For enzyme preparations: biological origin (in case of microbial origin: name and place of culture collection, if possible one in an EC collection, where the strain is deposited and depositing number, genetic modification and all relevant properties for its identification including genetic data), the activities towards relevant chemically pure model substrates and other physico-chemical characteristics.

2.3. *Degree of purity*

Qualitative and quantitative composition of the impurities.

For microorganisms: genetic stability and purity of strains cultivated.

For enzyme preparations:

— purity, by checking the level of contaminating microorganisms, heavy metals, absence of toxins derived from the source organism (e.g. mycotoxins), as shown by a suitable method;

— absence of antimicrobial activity at feed concentration level as determined by a suitable method;

— composition of the non-enzymatic components (particularly Total Organic Solids TOS [2]).

2.4. *Relevant properties*

For chemically specified substances: Electrostatic properties, melting point, boiling point, decomposition temperature, density, vapour pressure, solubility in water and organic solvents, mass and absorption spectra and any other appropriate physical properties.

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[1] Such as *Bergey's Manual of Systematic Bacteriology, The Yeasts, a taxonomic study* by Lodder and Kreger van Rij, *Ainsworth and Bisby's Dictionary of the Fungi* by Hawksworth, Sutton and Ainsworth or *The Genus Aspergillus* by Raper and Fennell.

[2] TOS (%) = 100 − (% ash + water + % diluents and/or additives and ingredients).

For microorganisms : properties relevant to identification and proposed use (e.g. vegetative or sporulated form, CFU per g)

For enzyme preparations : optimal PH (value(s), optimal temperature(s) and other appropriate properties).

2.5. *Manufacturing, purification processes and media used*

Variation in the composition of the batches in the course of production.

3. Physico-chemical, technological and biological properties of the additive

3.1. Stability (for microorganisms : loss of biological activity, e.g. viability) on exposure to environmental conditions such as light, temperature, pH, moisture and oxygen. Shelf life.

3.2. Stability (for microorganisms : loss of biological activity, e.g. viability) during the preparation of premixtures and feedingstuffs, in particular stability to heat, pressure and moisture. Possible decomposition products.

3.3. Stability (for microorganisms : loss of biological activity, e.g. viability) during the storage of premixtures and feedingstuffs under defined conditions. Shelf life.

For enzyme preparations : Details of the presence of unexpected reaction products formed by either enzymatic or chemical reactions of the enzyme preparation with feed constituents or by degradation of the enzyme preparation during storage of the feedingstuff.

3.4. Other appropriate physico-chemical, technological or biological properties such as ability to obtain homogeneous mixtures in premixtures and feedingstuffs, dust-forming properties, and for microorganisms and/or enzyme preparations, assessment of resistance to degradation or loss of biological activity in the digestive tract or by systems of simulation in vitro.

3.5. Physico-chemical or biological incompatibilities or interactions (e.g. with feedingstuffs, other approved additives or with medicinal products).

4. Conditions of use of the additive

4.1. Proposed use in animal nutrition (e.g. species and category of animal, type of feedingstuff, period of administration and withdrawal period).

4.2. *Contra-indications*

4.3. Proposed dosing in premixtures and feedingstuffs expressed as :

— a percentage of the active substance by weight for premixtures and as mg/kg for feedingstuffs, in case of chemically specified substances,

— appropriate units of biological activity such as CFU per gram of product for microorganisms or relevant activity units for enzyme preparations.

4.4. Other known uses of the active substance or the preparation (e.g. in foodstuffs, human or veterinary medicine, agriculture and industry). For each use give the proprietary names, indications and contra-indications.

4.5. If necessary, measures for the prevention of risks and means of protection during manufacture and handling.

5. Control methods

5.1. Description of the methods used for the determination of the criteria listed under items 1.3., 2.3., 2.4., 2.5., 3.1., 3.2., 3.3., 3.4. and 4.3.

5.2. Description of the qualitative and quantitative analytical methods for routine control of the additive in premixtures and feedingstuffs.

5.3. Description of the qualitative and quantitative analytical methods for determining residues of additives in animal produce.

N.B. The methods specified and the results should be accompanied by information as to percentage recovery, specificity, sensitivity, limits of detection, possible interferences, reproducibility and to the sampling method used. Reference standards of the preparation and of the active substance must be available.

In the case of microorganisms state methods of detection, enumeration, identification and relevant markets.