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(Acts whose publication is obligatory)

COMMISSION DIRECTIVE 2001/36/EC

of 16 May 2001

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 2001/28/EC ([2]), and in particular Article 18(2) thereof,

Whereas:

(1) Annexes IIB and IIIB to Directive 91/414/EEC set out the requirements for the dossier to be submitted by an applicant respectively for the inclusion of an active substance consisting of micro-organisms or viruses in Annex I to that Directive and for the authorisation of a plant protection product based on preparations of micro-organisms or viruses.

(2) It is necessary to indicate, in Annexes IIB and IIIB to 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; these provisions should be introduced as soon as available in order to permit applicants to use them in preparation of their dossiers.

(3) It is appropriate to differentiate data requirements for chemical substances and micro-organisms in some respects, as several requirements, e.g. on some issues concerning fate and behaviour in the environment and residues, are specific to chemicals while others, such as those on infectiveness, are specific to micro-organisms.

(4) It is now possible to introduce more precision with regard to the data requirements as experience was gained during the evaluation of several new active substances consisting of micro-organisms. In particular the areas of occupational health, consumer exposure, environmental risk have been subject to major changes.

(5) The Scientific Committee on Plants provided an opinion which dealt with the principles associated with the use of micro-organisms as plant protection products and the Committee provided comments on an early draft of the data requirements. The recommendations made by the Committee in the opinion ([3]), including the proposed amendments to the text of the draft data requirements were taken into account by the Commission.

(6) 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

Annex II to Directive 91/414/EEC shall be amended as set out in Annex I to this Directive.

Article 2

Annex III to Directive 91/414/EEC shall be amended as set out in Annex II to this Directive.

Article 3

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 1 May 2002 at the latest. They shall forthwith inform the Commission thereof.

([1]) OJ L 230, 19.8.1991, p. 1.
([2]) OJ L 113, 24.4.2001, p. 5.
([3]) Scientific Committee on Plants SCP/MICR/006 final.

When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

Article 4

This Directive shall enter into force on the 20th day following its publication in the *Official Journal of the European Communities*.

Article 5

This Directive is addressed to the Member States.

Done at Brussels, 16 May 2001.

For the Commission

David BYRNE

Member of the Commission

ANNEX I

Annex II to Directive 91/414/EEC is amended as follows:

(1) The following point 2.4 is added to the introduction:

'2.4. By way of derogation from point 2.1, for active substances consisting of micro-organisms or viruses, tests and analyses done to obtain data on the properties and/or safety with respect to other aspects than human health, may have been conducted by official or officially recognised testing facilities or organisations which satisfy at least the requirements under points 2.2 and 2.3 of the introduction of Annex III.'

(2) Part B is replaced by the following:

'**PART B**

Introduction

(i) Active substances are defined in Article 2(4) and include chemical substances and micro-organisms including viruses.

This Part provides data requirements for active substances consisting of micro-organisms, including viruses.

For the purposes of Annex II, Part B, the term "micro-organism" is used and is defined as follows:

"A microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material".

The definition applies to, but is not limited to, bacteria, fungi, protozoa, viruses and viroids.

(ii) For all micro-organisms that are subject to application all available relevant knowledge and information in literature should be provided.

The most important and informative information is obtained by the characterisation and identification of a micro-organism. Such information is found in sections 1 to 3 (identity, biological properties and further information) which form the basis for an assessment of human health and environmental effects.

Newly generated data from conventional toxicological and/or pathological experiments on laboratory animals are normally required unless the applicant can justify, on the basis of the previous information, that the use of the micro-organism, under the proposed conditions of use, does not have any harmful effects on human and animal health or on groundwater or any unacceptable influence on the environment.

(iii) Pending the acceptance of specific guidelines at international level, the information required shall be generated using available test guidelines accepted by the competent authority (e.g. USEPA guideline ([1])); where appropriate test guidelines as described in Annex II, Part A, should be adapted in such a way that they are appropriate for micro-organisms. Testing should include viable and, if appropriate, non-viable micro-organisms, and a blank control.

(iv) Where testing is done, a detailed description (specification) of the material used and its impurities, according to the provisions of section 1, point 1.4, must be provided. The material used should be of that specification that will be used in the manufacture of preparations to be authorised.

Where studies are conducted using micro-organisms produced in the laboratory or in a pilot plant production system, the studies must be repeated using micro-organisms as manufactured, unless it can be demonstrated that the test material used is essentially the same for the purposes of the testing and assessment.

([1]) USEPA Microbial Pesticide Test Guidelines, OPPTS Series 885, February 1996 (http://www.epa.gov/oppbppd1/biopesticides/guidelines/series885.htm).

(v) Where the micro-organism has been genetically modified, as defined in Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms ([2]), a copy of the evaluation of the data concerning the assessment of risk to the environment, as stated in Article 1(3) of Directive 91/414/EEC, has to be submitted.

(vi) Where relevant, data should be analysed using appropriate statistical methods. Full details of the statistical analysis should be reported (e.g. all point estimates should be given with confidence intervals, exact p-values should be given rather than stating significant/non significant).

(vii) In the case of studies in which dosing extends over a period, dosing should preferably be done using a single batch of the micro-organism, if stability permits.

If the studies are not performed using a single batch of the micro-organism, the similarity of the different batches has to be stated.

Whenever a study implies the use of different doses, the relationship between dose and adverse effect must be reported.

(viii) If the plant protection action is known to be due to the residual effect of a toxin/metabolite or if significant residues of toxins/metabolites are to be expected not related to the effect of the active substance, a dossier for the toxin/metabolite has to be submitted in accordance with the requirements of Annex II, Part A.

1. IDENTITY OF THE MICRO-ORGANISM

The identification together with the characterisation of the micro-organism provides the most important information and is a key point for decision-making.

1.1. **Applicant**

The name and address of the applicant (permanent community address) must be provided, as must the name, position, telephone and fax number of the appropriate person to contact.

Where, in addition, the applicant has an office, agent or representative in the Member State to which the application for inclusion in Annex I is submitted, and if different, in the rapporteur Member State appointed by the Commission, the name and address of the local office, agent or representative must be provided, as must the name, position, telephone and fax number of the appropriate person to contact.

1.2. **Producer**

The name and address of the producer or producers of the micro-organism must be provided as must the name and address of each plant in which the micro-organism is produced. A contact point (preferably a central contact point, to include name, telephone and fax number) must be provided, with a view to providing updating information and responding to queries arising, regarding production technology, processes and the quality of product (including where relevant, individual batches). Where, following inclusion of the micro-organism in Annex I, there are changes in the location or number of producers, the information required must again be notified to the Commission and the Member States.

1.3. **Name and species description, strain characterisation**

(i) The micro-organism should be deposited at an internationally recognised culture collection and given an accession number and these details must be submitted.

(ii) Each micro-organism that is subject to the application should be identified and named at the species level. The scientific name and taxonomic grouping, i.e. family, genus, species, strain, serotype, pathovar or any other denomination relevant to the micro-organism, must be stated.

It must be indicated whether the micro-organism:

— is indigenous or non-indigenous at the species level to the intended area of application,

— is a wild type,

([2]) OJ L 117, 8.5.1990, p. 15.

— is a spontaneous or induced mutant,

— has been modified, using techniques described in Annex IA, Part 2, and Annex IB to Directive 90/220/EEC.

In the latter two cases, all known differences between the modified micro-organism and the parent wild strain must be provided.

iii) Best available technology should be used to identify and characterise the micro-organism at the strain level. The appropriate test procedures and criteria used for identification (e.g. morphology, biochemistry, serology, molecular identification) must be provided.

iv) Common name or alternative and superseded names and code names used during the development, if any, must be provided.

(v) Relationships to known pathogens should be indicated.

1.4. **Specification of the material used for manufacturing of formulated products**

1.4.1. *Content of the micro-organism*

The minimum and maximum content of the micro-organism in the material used for manufacturing of formulated products, must be reported. The content should be expressed in appropriate terms, such as number of active units per volume or weight or any other manner that is relevant to the micro-organism.

Where the information provided relates to a pilot plant production system, the information required must again be provided to the Commission and the Member States once industrial scale production methods and procedures have stabilised, if production changes result in a changed specification of purity.

1.4.2. *Identity and content of impurities, additives, contaminating micro-organisms*

It is desirable to have a plant protection product without contaminants (including contaminating micro-organisms), if possible. The level and nature of acceptable contaminants should be judged from a risk assessment point of view, by the competent authority.

If possible and appropriate, the identity and maximum content of all contaminating micro-organisms, expressed in the appropriate unit, must be reported. The information on identity must be provided where possible as outlined in Annex II, Part B, section1, point 1.3.

Relevant metabolites (i.e. if expected to be of concern to human health and/or the environment) known to be formed by the micro-organism should be identified and characterised at different states or growth stages of the micro-organism (see Annex IIB, Introduction, (viii)).

Where relevant detailed information on all components such as condensates, culture medium, etc. must be provided.

In the case of chemical impurities that are relevant for human health and/or the environment, the identity and maximum content, expressed in appropriate terms, must be provided.

In the case of additives, the identity and content in g/kg must be provided.

The information on identity of chemical substances such as additives must be provided as outlined in Annex II, Part A, section 1, point 1.10.

1.4.3. *Analytical profile of batches*

Where relevant, the same data as outlined in Annex II, Part A, section 1, point 1.11, have to be reported, using the appropriate units.

2. BIOLOGICAL PROPERTIES OF THE MICRO-ORGANISM

2.1. **History of the micro-organism and its uses. Natural occurrence and geographical distribution**

Familiarity, interpreted as the availability of relevant knowledge of the micro-organism, should be presented.

2.1.1. *Historical background*

The historical background of the micro-organism and its use (tests/research projects or commercial use) must be provided.

2.1.2. *Origin and natural occurrence*

The geographical region and the place in the ecosystem (e.g. host plant, host animal, or soil from which the micro-organism was isolated) must be stated. The method of isolation of the micro-organism should be reported. The natural occurrence of the micro-organism in the relevant environment shall be given if possible at strain level.

In the case of a mutant, or a genetically modified micro-organism (as defined in Annex IA, Part 2, and Annex IB to Directive 90/220/EEC), detailed information should be provided on its production and isolation and on the means by which it can be clearly distinguished from the parent wild strain.

2.2. **Information on target organism(s)**

2.2.1. *Description of the target organism(s)*

Where relevant, details of harmful organisms against which protection is afforded, must be provided.

2.2.2. *Mode of action*

The principal mode of action should be indicated. In connection with the mode of action it should also be stated if the micro-organism produces a toxin with a residual effect on the target organism. In that case, the mode of action of this toxin should be described.

If relevant, information on the site of infection and mode of entry into the target organism and its susceptible stages should be given. The results of any experimental studies must be reported.

It should be stated by which way an uptake of the micro-organism, or its metabolites (especially toxins) may occur (e.g. contact, stomach, inhalation). It must also be stated whether or not the micro-organism or its metabolites are translocated in plants and, where relevant, how this translocation takes place.

In case of pathogenic effect on the target organism, infective dose (the dose needed to cause infection with the intended effect on a target species) and transmissibility (possibility of spread of the micro-organism in the target population, but also from one target species to another (target) species) after application under the proposed condition of use shall be indicated.

2.3. **Host specificity range and effects on species other than the target harmful organism**

Any available information on the effects on non-target organisms within the area to which the micro-organism may spread shall be given. The occurrence of non-target organisms being either closely related to the target species or being especially exposed shall be indicated.

Any experience of the toxic effect of the active substance or its metabolic products on humans or animals, of whether the organism is capable of colonising or invading humans or animals (including immunosuppressed individuals) and whether it is pathogenic shall be stated. Any experience of whether the active substance or its products may irritate skin, eyes or respiratory organs of humans or animals and whether it is allergenic in contact with skin or when inhaled shall be stated.

2.4. **Development stages/life cycle of the micro-organism**

Information on the life cycle of the micro-organism, described symbiosis, parasitism, competitors, predators, etc., including host organisms, as well as vectors for viruses, must be presented.

The generation time and the type of reproduction of the micro-organism must be stated.

Information on the occurrence of resting stages and their survival time, their virulence and infection potential must be provided.

The potential of the micro-organism to produce metabolites, including toxins that are of concern for human health and/or the environment, in its different development stages after the release, must be indicated.

2.5. **Infectiveness, dispersal and colonisation ability**

The persistence of the micro-organism and information on its life cycle under the typical environmental conditions of use must be indicated. In addition, any particular sensitivity of the micro-organism to certain compartments of the environment (e.g. UV light, soil, water) must be stated.

The environmental requirements (temperature, pH, humidity, nutrition requirements, etc.) for survival, reproduction, colonisation, damage (including human tissues) and effectiveness of the micro-organism must be stated. The presence of specific virulence factors should be indicated.

The temperature range at which the micro-organism grows must be determined, including minimum, maximum and optimum temperatures. This information is of particular value as a trigger for studies of effects on human health (section 5).

The possible effect of factors such as temperature, UV light, pH, and the presence of certain substances on the stability of relevant toxins must also be stated.

Information on possible dispersal routes of the micro-organism (via air as dust particles or aerosols, with host organisms as vectors, etc.), under typical environmental conditions relevant to the use, must be provided.

2.6. **Relationships to known plant or animal or human pathogens**

The possible existence of one or more species of the genus of the active and/or, where relevant, contaminating micro-organisms known to be pathogenic to humans, animals, crops or other non-target species and the type of disease caused by them shall be indicated. It shall be stated whether it is possible, and if so, by which means to clearly distinguish the active micro-organism from the pathogenic species.

2.7. **Genetic stability and factors affecting it**

Where appropriate, information on genetic stability (e.g. mutation rate of traits related to the mode of action or uptake of exogenous genetic material) under the environmental conditions of proposed use must be provided.

Information must also be provided on the micro-organism's capacity to transfer genetic material to other organisms as well as its capacity to being pathogenic for plants, animals or man. If the micro-organism carries relevant additional genetic elements, the stability of the encoded traits should be indicated.

2.8. **Information on the production of metabolites (especially toxins)**

If other strains belonging to the same microbial species as the strain subject to the application are known to produce metabolites (especially toxins) with unacceptable effects on human health and/or the environment during or after application, the nature and structure of this substance, its presence inside or outside the cell and its stability, its mode of action (including external and internal factors of the micro-organism necessary to action) as well as its effect on humans, animals or other non-target species shall be provided.

The conditions under which the micro-organism produces the metabolite(s) (especially toxin(s)) must be described.

Any available information on the mechanism by which the micro-organisms regulate the production of the(se) metabolite(s) should be provided.

Any available information on the influence of the produced metabolites on the micro-organism's mode of action should be provided.

2.9. **Antibiotics and other anti-microbial agents**

Many micro-organisms produce some antibiotic substances. Interference with the use of antibiotics in human or veterinary medicine must be avoided at any stage of the development of a microbial plant protection product.

Information on the micro-organism's resistance or sensitivity to antibiotics or other anti-microbial agents must be provided, in particular the stability of the genes coding for antibiotic resistance, unless it can be justified that the micro-organism has no harmful effects on human or animal health, or that it can not transfer its resistance to antibiotics or other anti-microbial agents.

3. FURTHER INFORMATION ON THE MICRO-ORGANISM

Introduction

(i) The information provided must describe the intended purposes for which preparations containing the micro-organism are used, or are to be used and the dose and manner of their use or proposed use.

(ii) The information provided must specify the normal methods and precautions to be followed in the handling, storage and transport of the micro-organism.

(iii) The studies, data and information submitted, must demonstrate the suitability of measures proposed for use in emergency situations.

(iv) The information and data referred to are required for each micro-organism, except where otherwise specified.

3.1. **Function**

The biological function must be specified from among the following:

— control of bacteria,

— control of fungi,

— control of insects,

— control of mites,

— control of molluscs,

— control of nematodes,

— control of weeds,

— other (must be specified).

3.2. **Field of use envisaged**

The field(s) of use, existing and proposed, for preparations containing the micro-organism must be specified from among the following:

— field use, such as agriculture, horticulture, forestry, and viticulture,

— protected crops (e.g. in greenhouses),

— amenity,

— weed control on non-cultivated areas,

— home gardening,

— house plants,

— stored products,

— other (specify).

3.3. **Crops or products protected or treated**

Details of existing and intended use in terms of crops, groups of crops, plants, or plant products protected, must be provided.

3.4. **Method of production and quality control**

Full information on how the micro-organism is produced in bulk must be provided.

Both production method/process and product must be subject to a continuous quality control by the applicant. In particular, the occurrence of spontaneous changing of major characteristics of the micro-organism and of the absence/presence of significant contaminants should be monitored. The quality assurance criteria for the production should be submitted.

The techniques used to ensure a uniform product, and the assay methods for its standardisation, maintenance and purity of the micro-organism must be described and specified (e.g. HACCP).

3.5. **Information on the occurrence or possible occurrence of the development of resistance of the target organism(s)**

Available information on the possible occurrence of the development of resistance or cross-resistance of the target organism(s) must be provided. Where possible, appropriate management strategies should be described.

3.6. **Methods to prevent loss of virulence of seed stock of the micro-organism**

Methods to prevent loss of virulence of starting cultures are to be provided.

In addition, any method, if available, that could prevent the micro-organism from losing its effects on the target species must be described.

3.7. **Recommended methods and precautions concerning handling, storage, transport or fire**

A safety data sheet similar to that required for chemical active substances in Article 27 of Directive 67/548/EEC ([3]) must be provided for each micro-organism.

3.8. **Procedures for destruction or decontamination**

In many cases the preferred or sole means of safe disposal of micro-organisms, contaminated materials, or contaminated packaging, is through controlled incineration in a licensed incinerator.

Methods to dispose safely of the micro-organism or, where necessary, to kill it prior to disposal, and methods to dispose of contaminated packaging and contaminated materials, must be fully described. Data must be provided for such methods to establish their effectiveness and safety.

3.9. **Measures in case of an accident**

Information on procedures for rendering the micro-organism harmless in the environment (e.g. water or soil) in case of an accident must be provided.

4. ANALYTICAL METHODS

Introduction

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

([3]) See doc. 6853/VI/98, Concise outline report of the first peer review meeting on micro-organisms.

Post-approval monitoring might be considered for all areas of risk assessment. This is particularly the case when (strains of) micro-organisms that are non-indigenous to the intended area of application are considered for approval. 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. The applicability of any internationally recognised method must be reported.

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

Data on specifity, linearity, accuracy and repeatability, as defined in Annex II, Part A, points 4.1 and 4.2, are also required for methods used to analyse micro-organisms and their residues.

For this section the following applies:

Impurities	Any component (including contaminating micro-organisms and/or chemical substances) other than the specified micro-organism, originating from the manufacturing process or from degradation during storage
Relevant impurities	Impurities, as defined above, that are of concern for human or animal health and/or the environment
Metabolites	Metabolites include products resulting from degradative and biosynthetic reactions taking place within the micro-organism or other organisms used to produce the micro-organism of interest
Relevant metabolites	Metabolites that are of concern for human or animal health and/or the environment
Residues	Viable micro-organisms and substances produced in significant quantities by these micro-organisms which persist after the disappearance of the micro-organisms and are of concern for human or animal health and/or the environment.

On request the following samples must be provided:

(i) samples of the micro-organism as manufactured;

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

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

4.1. **Methods for the analysis of the micro-organism as manufactured**

— Methods for the identification of the micro-organism.

— Methods for providing information on possible variability of seed stock/active micro-organism.

— Methods to differentiate a mutant of the micro-organism from the parent wild strain.

— Methods for the establishment of purity of seed stock from which batches are produced and methods to control that purity.

— Methods to determine the content of the micro-organism in the manufactured material used for the production of formulated products and methods to show that contaminating micro-organisms are controlled to an acceptable level.

— Methods for the determination of relevant impurities in the manufactured material.

— Methods to control the absence and to quantify (with appropriate limits of determination) the possible presence of any human and mammalian pathogens.

— Methods to determine storage stability, shelf-life of the micro-organism, if appropriate.

4.2. **Methods to determine and quantify residues (viable or non-viable)**

of:

— the active micro-organism(s),

— relevant metabolites (especially toxins),

on and/or in crop, in foodstuffs and feeding stuffs, in animal and human body tissues and fluids, in soil, in water (including drinking water, ground water and surface water) and in air where relevant.

Analytical methods for amount or activity of proteinaceous products should also be included, e.g. by testing exponential cultures and culture supernatants in an animal cell bioassay.

5. EFFECTS ON HUMAN HEALTH

Introduction

(i) Available information based on the properties of the micro-organism and corresponding organisms (sections 1 to 3), including health and medical reports may be sufficient for a decision whether the micro-organism would cause health effects (infectious/pathogenic/toxic) in humans or not.

(ii) The information provided, taken together with that provided for one or more preparations containing the micro-organism, must be sufficient to permit an evaluation to be made as to the risks for man, directly and/or indirectly associated with the handling and use of plant protection products containing the micro-organism, and the risk for man handling treated products, and the risk for man arising from residual traces or contaminants remaining in food and water. In addition, the information provided must be sufficient to:

— permit a decision to be made as to whether, or not, the micro-organism can be included in Annex I,

— specify appropriate conditions or restrictions to be associated with any inclusion in Annex I,

— specify risk and safety phrases (once introduced) for the protection of man, animals and the environment to be included on packaging (containers),

— identify relevant first aid measures as well as appropriate diagnostic and therapeutic measures to be followed in the event of infection or another adverse effect in man.

(iii) All effects found during investigations should be reported. Investigations which may be necessary in order to evaluate the probable mechanism involved, and to assess the significance of these effects, must also be performed.

(iv) For all studies actual achieved dose in colony forming units per kg body weight (cfu/kg), as well as in other appropriate units, must be reported.

(v) Evaluation of the micro-organism should be carried out in a tier-wise manner.

The first tier (Tier I) includes available basic information and basic studies, which have to be performed for all micro-organisms. Expert judgment will be necessary to decide about the appropriate test programme on a case-by-case basis. Newly generated data from conventional toxicological and/or pathological experiments on laboratory animals are normally required unless the applicant can justify, on the basis of the previous information, that the use of the micro-organism, under the proposed conditions of use, does not have any harmful effects on human and animal health. Pending the acceptance of specific guidelines at international level, the information required shall be generated using available test guidelines (e.g. USEPA OPPTS Guidelines).

Tier II studies must be conducted if tests under Tier I have shown adverse health effects. The type of study to be performed depends on the effects observed in the Tier I studies. Before performing such studies, the applicant shall seek agreement of the competent authorities on the type of study to be performed.

TIER I

5.1. **Basic information**

Basic information is required about the micro-organism's potential to cause adverse effects such as ability to colonise, to cause damage and to produce toxins and other relevant metabolites.

5.1.1. *Medical data*

Where available, and without prejudice to the provisions of Article 5 of Council Directive 80/1107/EEC of 27 November 1980 on the protection of workers from the risks related to chemical, physical and biological agents at work ([4]) and Articles 5 to 17 of Council Directive 90/679/EEC of 26 November 1990 on the protection of workers from the risks related to biological agents at work ([5]), practical data and information relevant to the recognition of the symptoms of infection or pathogenicity and on the effectiveness of first aid and therapeutic measures have to be submitted. Where relevant, the effectiveness of potential antagonists, should be investigated and reported. Where relevant, methods to kill or render the micro-organism uninfective must be indicated (see section 3, point 3.8).

Data and information relevant to the effects of human exposure, where available and of the necessary quality, are of particular value, in confirming the validity of extrapolations made and conclusions reached with respect to target organs, virulence, and the reversibility of adverse effects. Such data can be generated following accidental or occupational exposure.

5.1.2. *Medical surveillance on manufacturing plant personnel*

Available reports of occupational health surveillance programmes, supported with detailed information on the design of the programme and on exposure to the micro-organism must be submitted. Such reports should, where feasible, include data relevant to the mechanism of action of the micro-organism. These reports shall, where available, include data from persons exposed in manufacturing plants or after application of the micro-organism (e.g. in efficacy trials).

Special attention should be devoted to those whose susceptibility may be affected, e.g. pre-existing disease, medication, compromised immunity, pregnancy or breast feeding.

5.1.3. *Sensitisation/allergenicity observations, if appropriate*

Available information on the sensitisation and allergenic response of workers, including workers in manufacturing plants, agricultural and research workers and others exposed to the micro-organism must be provided, and include, where relevant, details of any incidences of hypersensitivity and chronic sensitisation. The information provided should include details of frequency, level and duration of exposure, symptoms observed and other relevant clinical observation. Information should be given about whether workers have been subjected to any allergy tests or interviewed about allergenic symptoms.

5.1.4. *Direct observation, e.g. clinical cases*

Available reports from the open literature on the micro-organism or closely related members of the taxonomic group (relating to clinical cases), where they are from reference journals or official reports, must be submitted together with reports of any follow-up studies undertaken. Such reports are of particular value and should contain complete descriptions of the nature, level and duration of exposure, as well as the clinical symptoms observed, first aid and therapeutic measures applied and measurements and observations made. Summary and abstract information is of limited value.

If there are animal studies performed, reports relating to clinical cases can be of particular value in confirming the validity of interpretations from animal data to man and in identifying unexpected adverse effects which are specific to humans.

5.2. *Basic studies*

In order to make it possible to correctly interpret the obtained results, it is of greatest importance that the suggested test methods are relevant regarding species sensitivity, administration route, etc., and relevant from a biological and toxicological point of view. The way of administration of the test micro-organism depends on the main exposure routes to humans.

To evaluate medium- and long-term effects after acute, sub-acute or semi-chronic exposure to micro-organisms, it is necessary to use the options provided in most of the OECD guidelines, to extend the studies concerned with a recovery period (after which full macroscopic and microscopic pathology is to be

([4]) OJ L 327, 3.12.1980, p. 8.
([5]) OJ L 374, 31.12.1990, p. 1.

performed, including an exploration for micro-organisms in the tissues and organs). This facilitates the interpretation of certain effects and provides the possibility to recognise infectiveness and/or pathogenicity, which in turn helps taking decisions on other issues such as the necessity to perform long-term studies (carcinogenicity etc., see point 5.3), and whether or not to perform residue studies (see point 6.2).

5.2.1. *Sensitisation* ([6])

Aim of the test

The test will provide sufficient information to assess the potential of the micro-organism to provoke sensitisation reactions by inhalation as well as with dermal exposure. A maximised test has to be performed.

Circumstances in which required ([7])

Information on sensitisation must be reported.

5.2.2. *Acute toxicity, pathogenicity and infectiveness*

The studies, data and information to be provided and evaluated must be sufficient to permit the identification of effects following a single exposure to the micro-organism, and in particular to establish, or indicate:

— the toxicity, pathogenicity and infectiveness of the micro-organism,

— the time course and characteristics of the effects with full details of behavioural changes and possible gross pathological findings at post-mortem,

— where possible mode of toxic action,

— the relative hazards associated with the different routes of exposure, and

— blood analyses throughout the studies in order to evaluate the clearance of the micro-organism.

Acute toxic/pathogenic effects may be accompanied by infectiveness and/or more long-term effects which cannot be observed immediately. With a view to health evaluation, it is therefore necessary to carry out studies on the ability to infect in connection with oral intake, inhalation and intraperitoneal/subcutaneous injection by test mammals.

During the acute toxicity, pathogenicity and infectiveness studies, an estimation of the micro-organism and/or the active toxin clearance in the organs deemed to be relevant for microbial examination (e.g. liver, kidneys, spleen, lungs, brain, blood and site of administration) must be performed.

The observations to be made should reflect expert scientific judgement and may include the micro-organism numeration in all the tissues likely to be affected (e.g. showing lesions) and in the main organs: kidneys, brain, liver, lungs, spleen, bladder, blood, lymphatic ganglia, gastrointestinal tract, thymus gland and lesions at the inoculation site in the dead or moribund animals and at interim and final sacrifice.

The information generated through acute toxicity, pathogenicity and infectiveness testing is of particular value in assessing hazards likely to arise in accident situations and consumer risks due to exposure to possible residues.

([6]) The available methods for testing dermal sensitisation are not suitable for testing micro-organisms. Sensitisation by inhalation is most probably a greater problem compared with dermal exposure to micro-organisms but so far, there are no validated test methods. Development of these kinds of methods is therefore of great importance. Until then, all micro-organisms should be regarded as potential sensitisers. This approach also takes into consideration immuno-compromised or other sensitive individuals in the population (e.g. pregnant women, new-born children or elderly).

([7]) As a consequence of the absence of proper test methods all micro-organisms will be labelled as potential sensitisers, unless the applicant wants to demonstrate the non-sensitising potential by submitting data. Therefore, this data requirement should be regarded as not obligatory but optional, on a provisional base.

5.2.2.1. Acute oral toxicity, pathogenicity and infectiveness

Circumstances in which required

The acute oral toxicity, pathogenicity and infectiveness of the micro-organism must be reported.

5.2.2.2. Acute inhalation toxicity, pathogenicity and infectiveness

Circumstances in which required

The inhalation toxicity ([8]), pathogenicity and infectiveness of the micro-organism must be reported.

5.2.2.3. Intraperitoneal/subcutaneous single dose

The intraperitoneal/subcutaneous test is considered a highly sensitive assay to elicit in particular infectiveness.

Circumstances in which required

The intraperitoneal injection is always required for all micro-organisms, however, expert judgement may be exercised to evaluate whether subcutaneous injection is preferred instead of intraperitoneal injection if the maximum temperature for growth and multiplication is lower than 37 °C.

5.2.3. *Genotoxicity testing*

Circumstances in which required

If the micro-organism produces exotoxins according to point 2.8, then these toxins and any other relevant metabolites in the culture medium must also be tested for genotoxicity. Such tests on toxins and metabolites should be performed using the purified chemical if possible.

If basic studies do not indicate that toxic metabolites are formed, studies on the micro-organism itself should be considered depending on expert judgement on the relevance and validity of the basic data. In the case of a virus the risk of insertional mutagenesis in mammal cells or the risk of carcinogenicity has to be discussed.

Aim of the test

These studies are of value in:

— the prediction of genotoxic potential,

— the early identification of genotoxic carcinogens,

— the elucidation of the mechanism of action of some carcinogens.

It is important that a flexible approach is adopted, with selection of further tests being dependent upon interpretation of results at each stage.

Test conditions ([9])

Genotoxicity of cellular micro-organisms will be studied after breaking of the cells, wherever possible. Justification should be provided on the method of sample preparation used.

Genotoxicity of viruses should be studied on infectious isolates.

5.2.3.1. *In vitro* studies

Circumstances in which required

Results of *in vitro* mutagenicity tests (bacterial assay for gene mutation, test for clastogenicity in mammalian cells and test for gene mutation in mammalian cells) must be provided.

([8]) An inhalation study may be replaced by an intratracheal study.

([9]) As the present test methods are designed to be performed on soluble chemicals, it is necessary that the methods are developed so as to become relevant for micro-organisms.

5.2.4. *Cell culture study*

This information must be reported for intracellular replicating micro-organisms, such as viruses, viroids or specific bacteria and protozoa, unless the information from sections 1 to 3 clearly demonstrates that the micro-organism does not replicate in warm-blooded organisms. A cell culture study should be performed in human cell or tissue cultures of different organs. Selection can be based on expected target organs after infection. If human cell or tissue cultures of specific organs are not available, other mammal cell and tissue cultures can be used. For viruses, the ability to interact with the human genome is a key consideration.

5.2.5. *Information on short-term toxicity and pathogenicity*

Aim of the test

Short-term toxicity studies must be designed to provide information as to the amount of the micro-organism that can be tolerated without toxic effects under the conditions of the study. Such studies provide useful data on the risks for those handling and using preparations containing the micro-organism. In particular, short-term studies provide an essential insight into possible cumulative actions of the micro-organism, and the risks to workers who may be intensively exposed. In addition short-term studies provide information useful in the design of chronic toxicity studies.

The studies, data and information to be provided and evaluated, must be sufficient to permit the identification of effects following repeated exposure to the micro-organism, and in particular to further establish, or indicate:

— the relationship between dose and adverse effects,

— toxicity of the micro-organism including where necessary the NOAEL for toxins,

— target organs, where relevant,

— the time course and characteristics of the effects with full details of behavioural changes and possible gross pathological findings at post-mortem,

— specific toxic effects and pathological changes produced,

— where relevant the persistence and reversibility of certain toxic effects observed, following discontinuation of dosing,

— where possible, the mode of toxic action, and

— the relative hazard associated with the different routes of exposure.

During the short-term toxicity study, an estimation of the micro-organism clearance in the main organs must be performed.

Investigations should be included for pathogenicity and infectiveness end points.

Circumstances in which required

The short-term toxicity (minimum 28 days) of the micro-organism must be reported.

The choice of test species has to be justified. The choice of study length depends on acute toxicity and clearance data.

Expert judgement is required to decide what route of administration is preferable.

5.2.5.1. Health effects after repeated inhalatory exposure

Information on the health effects after repeated inhalatory exposure is considered necessary, particularly for the risk assessment of the occupational setting. Repeated exposure might influence the clearance capacity (e.g. resistance) of the host (human). Furthermore, for proper risk assessment the toxicity after repeated exposure to contaminants, growth medium, co-formulants and the micro-organism needs to be addressed. It should be kept in mind that the formulants in the plant protection product can influence the toxicity and infectiveness of a micro-organism.

Circumstances in which required

Information on the short-term infectiveness, pathogenicity and toxicity (respiratory route) of a micro-organism is required, unless the information already provided is sufficient to assess human health effects. This can be the case if it is demonstrated that the test material has no inhalable fraction and/or repeated exposure is not expected.

5.2.6. *Proposed treatment: first aid measures, medical treatment*

The first aid measures to be used in the event of infection and in the event of contamination of eyes must be provided.

Therapeutic regimes for use in the event of ingestion or contamination of eyes and skin must be described in full. Information based on practical experience, where it exists and is available, in other cases on theoretical grounds, as to the effectiveness of alternative treatment regimes, where relevant, must be provided.

Information on resistance to antibiotics must be provided.

(END OF TIER I)

TIER II

5.3. **Specific toxicity, pathogenicity and infectiveness studies**

In certain cases, it can be necessary to carry out supplementary studies to further clarify the adverse human effects.

In particular, if results from earlier studies indicate that the micro-organism may cause long-term health effects, studies on chronic toxicity, pathogenicity and infectiveness, carcinogenicity and reproductive toxicity must be carried out. Furthermore, where a toxin is produced, kinetic studies must be performed.

Studies required must be designed on an individual basis, in the light of the particular parameters to be investigated and the objectives to be achieved. Before performing such studies, the applicant shall seek agreement of the competent authorities on the type of study to be performed.

5.4. ***In vivo* studies in somatic cells**

Circumstances in which required

If all the results of the *in vitro* studies are negative further testing must be done with consideration of other relevant information available. The test can be an *in vivo* study or an *in vitro* study using a different metabolising system from that/those previously used.

If the *in vitro* cytogenetic test is positive, an *in vivo* test using somatic cells (metaphase analysis in rodent bone marrow or micronucleus test in rodents) must be conducted.

If either of the *in vitro* gene mutation tests are positive, an *in vivo* test to investigate unscheduled DNA synthesis or a mouse spot test must be conducted.

5.5. **Genotoxicity — *In vivo* studies in germ cells**

Aim of the test and test conditions

See point 5.4.

Circumstances in which required

When any result of an *in vivo* study in somatic cells is positive, *in vitro* testing for germ cell effects may be justified. The necessity for conducting these tests will have to be considered on a case-by-case basis, taking into account other relevant information available including use and expected exposure. Suitable tests would need to examine interaction with DNA (such as the dominant lethal assay), to look at the potential for inherited effects and possibly make a quantitative assessment of heritable effects. It is recognised that in view of their complexity, the use of quantitative studies would require strong justification.

(END OF TIER II)

5.6. **Summary of mammalian toxicity, pathogenicity and infectiveness and overall evaluation**

A summary of all data and information provided under points 5.1 through 5.5, must be submitted, and include a detailed and critical assessment of those data in the context of relevant evaluative and decision making criteria and guidelines, with particular reference to the risks for man and animals that may or do arise, and the extent, quality and reliability of the data base.

It must be explained whether exposure of animals or humans has any implications for vaccination or serological monitoring.

6. RESIDUES IN OR ON TREATED PRODUCTS, FOOD AND FEED

Introduction

(i) The information provided, taken together with that for one or more preparations containing the micro-organism, must be sufficient to permit an evaluation to be made as to the risk for man and/or animals, arising from exposure to the micro-organism and its residual traces and metabolites (toxins) remaining in or on plants or plant products.

(ii) In addition, the information provided must be sufficient to:

— permit a decision to be made as to whether or not the micro-organism can be included in Annex I to Directive 91/414/EEC,

— specify appropriate conditions or restrictions to be associated with any inclusion in Annex I to Directive 91/414/EEC,

— where relevant, set maximum residue levels, preharvest intervals to protect consumers and waiting periods, to protect workers handling the treated crops and products.

(iii) For the evaluation of risk arising from residues, experimental data on levels of exposure to the residue may not be required where it can be justified, that the micro-organism and its metabolites are not hazardous to humans in the concentrations that could occur as a result of authorised use. This justification can be based on open literature, on practical experience and on information submitted in sections 1 through 3 and section 5.

6.1. **Persistance and likelihood of multiplication in or on crops, feedingstuffs or foodstuffs**

A substantiated estimation of persistance/competitiveness of the micro-organism and relevant secondary metabolites (especially toxins) in or on the crop under the environmental conditions prevailing at and after the intended use, taking into account in particular the information provided in section 2, has to be delivered.

Moreover, the application shall state to which extent and on which basis it is considered that the micro-organism can (or cannot) multiply in or on the plant or plant product or during processing of raw products.

6.2. **Further information required**

Consumers may be exposed to micro-organisms for a considerable time as a result of the consumption of treated food commodities; potential effects on the consumers must, therefore, be derived from chronic or semi-chronic studies, so that a toxicological end point, such as the ADI, can be established for risk management.

6.2.1. *Non-viable residues*

A non viable micro-organism is a micro-organism that is not capable of replication or of transferring genetic material.

If relevant quantities of the micro-organism or of produced metabolites, especially toxins, have been found to be persistant in section 2, points 2.4 and 2.5, full experimental residue data as provided for in Annex II, Part A, section 6, is required, if concentrations of the micro-organism and/or its toxins in or on the treated foodstuffs or feedingstuffs are expected to occur in concentrations higher than under natural conditions or in a different phenotypic state.

In agreement with Directive 91/414/EEC, the conclusion concerning the difference between natural concentrations and an elevated concentration due to treatment with the micro-organism, is to be based on experimentally obtained data, and not on extrapolations or calculations using models.

Before performing such studies, the applicant shall seek agreement of the competent authorities on the type of study to be performed.

6.2.2. *Viable residues*

If the information submitted according to point 6.1 suggests persistance of relevant amounts of the micro-organism in or on treated products, food or feed, possible effects on humans and/or animals must be investigated, unless it can be justified from section 5, that the micro-organism and its metabolites and/or degradation products are not hazardous to humans in the concentrations and of the nature that could occur as a result of authorised use.

In agreement with Directive 91/414/EEC, the conclusion concerning the difference between natural concentrations and an elevated concentration due to treatment with the micro-organism, is to be based on experimentally obtained data, and not on extrapolations or calculations using models.

The persistence of viable residues needs special attention if infectiveness or pathogenicity to mammals have been found in sections 2.3, 2.5 or 5 and/or if any other information suggests a hazard to consumers and/or workers. In this case the competent authorities may require studies similar to those provided for in Part A.

Before performing such studies, the applicant shall seek agreement of the competent authorities on the type of study to be performed.

6.3. **Summary and evaluation of residue behaviour resulting from data submitted under points 6.1 and 6.2**

7. FATE AND BEHAVIOUR IN THE ENVIRONMENT

Introduction

(i) Information on the origin, the properties, and the survival of the micro-organism and its residual metabolites as well as its intended use form the basis for an assessment of environmental fate and behaviour.

Experimental data are normally required unless it can be justified that an assessment of its fate and behaviour in the environment can be performed with the information already available. This justification can be based on open literature, on practical experience and, on information submitted in sections 1 through 6. The function of the micro-organism in environmental processes (as defined in section 2, point 2.1.2) is of particular interest.

(ii) The information provided, taken together with other relevant information, and that for one or more preparations containing the micro-organism, must be sufficient to permit an assessment of its fate and behaviour as well as that of its residual traces and toxins, where they are of significance for human health and/or the environment.

(iii) In particular, the information provided should be sufficient to:

— decide whether, or not, the micro-organism can be included in Annex I,

— specify appropriate conditions or restrictions to be associated with any inclusion in Annex I,

— specify the hazard symbols (once introduced), the indications of danger, and relevant risk and safety phrases for the protection of the environment, which are to be included on packaging (containers),

— predict the distribution, fate, and behaviour in the environment of the micro-organism and its metabolites as well as the time courses involved,

— identify measures necessary to minimise contamination of the environment and impact on non-target species.

(iv) Any relevant metabolites (i.e. of concern for human health and/or the environment) formed by the test organism under any relevant environmental conditions should be characterised. If relevant metabolites are present in or produced by the micro-organism, data as outlined under Annex II, Part A, point 7 may be required, if all of the following conditions are met:

— the relevant metabolite is stable outside the micro-organism, see point 2.8, and

— a toxic effect of the relevant metabolite is independent of the presence of the micro-organism, and

— the relevant metabolite is expected to occur in the environment in concentrations considerably higher than under natural conditions.

(v) Available information on the relationship with naturally occurring wild type relatives should be taken into account.

(vi) Before performing studies as referred to below, the applicant shall seek agreement of the competent authorities on whether studies need to be performed and, if so, the type of study to be conducted. The information from the other sections has, also, to be taken into account.

7.1. **Persistence and multiplication**

Where relevant, appropriate information on the persistence and multiplication of the micro-organism, in all environmental compartments has to be given, unless it can be justified that exposure of the particular environmental compartment to the micro-organism is unlikely to occur. Special attention shall be given to

— competitiveness under the environmental conditions prevailing at and after the intended use, and

— population dynamics in seasonally or regionally extreme climates (particularly hot summer, cold winter and rainfall) and to agricultural practices applied after intended use.

Estimated levels of the specified micro-organism in a time course after use of the product under the proposed conditions of use shall be given.

7.1.1. *Soil*

Information on viability/population dynamics should be reported in several cultivated and uncultivated soils representative of soils typical of the various Community regions where use exists or is anticipated. The provisions on choice of soil and its collection and handling, as referred to in Part A, point 7.1, Introduction, have to be followed. If the test organism is to be used in association with other media, e.g. rockwool, this must be included in the test range.

7.1.2. *Water*

Information should be reported on viability/population dynamics in natural sediment/water systems under both dark and illuminated conditions.

7.1.3. *Air*

In case of particular concerns for operator, worker or bystander exposure, information on the concentrations in air might be necessary.

7.2. **Mobility**

The possible spread of the micro-organism and its degradation products in relevant environmental compartments has to be evaluated, unless it can be justified that exposure of the particular environmental compartments to the micro-organism is unlikely to occur. In this context, the intended use (e.g. field or greenhouse, application to soil or to crops), life cycle stages, including occurrence of vectors, persistence and the ability of the organism to colonise adjacent habitats are of particular interest.

The spread, the persistence and probable transport ranges need special attention if toxicity, infectiveness or pathogenicity have been reported or if any other information suggests possible hazard to humans, animals or to the environment. In this case the competent authorities may require studies similar to those provided for in Part A. Before performing such studies, the applicant shall seek agreement of the competent authorities on the type of study to be performed.

8. EFFECTS ON NON-TARGET ORGANISMS

Introduction

(i) The information on identity, biological properties and further information in sections 1 to 3 and 7 is central to the assessment of impact on non-target species. Additional useful information may be found on fate and behaviour in the environment in section 7 and on residue levels in plants in section 6 which, together with information on the nature of the preparation and its manner of use, defines the nature and extent of potential exposure. The information submitted in accordance with section 5 will provide essential information as to effects to mammals and the mechanisms involved.

Experimental data are normally required, unless it can be justified that an assessment of effects on non-target organisms can be performed with the information already available.

(ii) The choice of the appropriate non-target organisms for testing of environmental effects should be based on the identity of the micro-organism (including the host specificity, mode of action and ecology of the organism). From such knowledge it would be possible to choose the appropriate test-organisms, such as organisms closely related to the target organism.

(iii) The information provided, taken together with that for one or more preparations containing the micro-organism, must be sufficient to permit an assessment of the impact on non-target species (flora and fauna), likely to be at risk from exposure to the micro-organism, where they are of environmental significance. Impact can result from single, prolonged or repeated exposure and can be reversible or irreversible.

(iv) In particular, the information provided for the micro-organism, together with other relevant information, and that provided for one or more preparations containing it, should be sufficient to:

— decide whether, or not, the micro-organism can be included in Annex I,

— specify appropriate conditions or restrictions to be associated with any inclusion in Annex I,

— permit an evaluation of short- and long-term risks for non-target species — populations, communities, and processes — as appropriate,

— classify the micro-organism as to biological hazard,

— specify the precautions necessary for the protection of non-target species, and

— specify the hazard symbols (once introduced), the indications of danger, and relevant risk and safety phrases for the protection of the environment, to be mentioned on packaging (containers).

(v) There is a need to report all potentially adverse effects found during routine investigations on environmental effects, to undertake and report, where required by the competent authorities, such additional studies which may be necessary to investigate the probable mechanisms involved and to assess the significance of these effects. All available biological data and information which is relevant to the assessment of the ecology profile of the micro-organism must be reported.

(vi) For all studies, average achieved dose in cfu/kg body weight as well as in other appropriate units must be reported.

(vii) It may be necessary to conduct separate studies for relevant metabolites (especially toxins), where these products can constitute a relevant risk to non-target organisms and where their effects cannot be evaluated by the available results relating to the micro-organism. Before such studies are performed, the applicant shall seek agreement of the competent authorities on whether such studies need to be performed and, if so, the type of study to be conducted. The information from sections 5, 6 and 7 has to be taken into account.

(viii) In order to facilitate the assessment of the significance of test results obtained, the same strain (or recorded origin) of each relevant species should, where possible, be used in the various tests specified.

(ix) Tests must be performed unless it can be justified that the non-target organism will not be exposed to the micro-organism. If it is justified that the micro-organism does not cause toxic effects or is not pathogenic or infective to vertebrates or plants, only reaction to appropriate non-target organisms must be investigated.

8.1. **Effects on birds**

Aim of the test

Information on toxicity, infectiveness and pathogenicity to birds must be reported.

8.2. **Effects on aquatic organisms**

Aim of the test

Information on toxicity, infectiveness and pathogenicity to aquatic organisms must be reported.

8.2.1. *Effects on fish*

Aim of the test

Information on toxicity, infectiveness and pathogenicity to fish must be reported.

8.2.2. *Effects on freshwater invertebrates*

Aim of the test

Information on toxicity, infectiveness and pathogenicity to freshwater invertebrates must be reported.

8.2.3. *Effects on algae growth*

Aim of the test

Information on effects on algal growth, growth rate and capacity to recover must be reported.

8.2.4. *Effects on plants other than algae*

Aim of the test

Information on effects on plants other than algae must be reported.

8.3. **Effects on bees**

Aim of the test

Information on toxicity, infectiveness and pathogenicity to bees must be reported.

8.4. **Effects on arthropods other than bees**

Aim of the test

Information on toxicity, infectiveness and pathogenicity to arthropods other than bees must be reported. The selection of the test species should be related to the potential use of the plant protection products (e.g. foliar or soil application). Special attention should be given to organisms used for biological control and organisms playing an important role in integrated pest management.

8.5. **Effects on earthworms**

Aim of the test

Information on toxicity, infectiveness and pathogenicity to earthworms must be reported.

8.6. **Effects on non-target soil micro-organisms**

Impact on relevant non-target micro-organisms and on their predators (e.g. protozoa for bacterial inoculants) should be reported. Expert judgement is required to decide whether additional studies are necessary. Such decision will take into consideration the available information in this and other sections, in particular data on the specificity of the micro-organism, and the expected exposure. Useful information may also be available from the observations carried out in efficacy testing. Special attention should be given to organisms used in integrated crop management (ICM).

8.7. **Additional studies**

The additional studies might include further acute studies on additional species or processes (such as sewage systems) or higher tier studies such as chronic, sub-lethal or reproductive studies on selected non-target organisms.

Before performing such studies, the applicant shall seek agreement of the competent authorities on the type of study to be performed.

9. SUMMARY AND EVALUATION OF ENVIRONMENTAL IMPACT

A summary and evaluation of all data relevant to the environmental impact, should be carried out according to the guidance given by the competent authorities of the Member States concerning the format of such summaries and evaluations. It should include a detailed and critical assessment of those data in the context of relevant evaluative and decision making criteria and guidelines, with particular reference to the risks for the environment and non-target species that may or do arise, and the extent, quality and reliability of the data base. In particular the following issues should be addressed:

— distribution and fate in the environment, and the time courses involved,

— identification of non-target species and populations at risk, and the extent of their potential exposure,

— identification of precautions necessary to avoid or minimise contamination of the environment, and for the protection of non-target species.'

ANNEX II

Annex III to Directive 91/414/EEC is amended as follows:

(1) The following point 2.6 is added to the introduction:

'2.6. By way of derogation from point 2.1, for active substances consisting of micro-organisms or viruses, tests and analyses done to obtain data on the properties and/or safety with respect to other aspects than human health, may have been conducted by official or officially recognised testing facilities or organisations which satisfy at least the requirements under points 2.2 and 2.3 of the introduction of Annex III.'

(2) PART B is replaced by the following:

'**PART B**

Introduction

(i) This Part provides data requirements for the authorisation of a plant protection product based on preparations of micro-organisms including viruses.

The term "micro-organism" as defined in the introduction of Annex II, Part B, also applies to Annex III, Part B.

(ii) Where relevant, data should be analysed using appropriate statistical methods. Full details of the statistical analysis should be reported (e.g. all point estimates should be given with confidence intervals, exact p-values should be given rather than stating significant/non significant).

(iii) Pending the acceptance of specific guidelines at international level, the information required shall be generated using test guidelines accepted by the competent authority (e.g. USEPA guideline ([1])); where appropriate test guidelines as described in Annex II, Part A, should be adapted in such a way that they are appropriate for micro-organisms. Testing should include viable and, if appropriate, non-viable micro-organisms, and a blank control.

(iv) Whenever a study implies the use of different doses, the relationship between dose and adverse effect must be reported.

(v) Where testing is done, a detailed description (specification) of the material used and its impurities, according to the provisions of section 1, point 1.4, must be provided.

(vi) In cases where a new preparation is to be dealt with, extrapolation from Annex II, Part B, could be acceptable, provided that all the possible effects of the formulants and other components, especially on pathogenicity and infectiveness, are also evaluated.

1. IDENTITY OF THE PLANT PROTECTION PRODUCT

The information provided, taken together with that provided for the micro-organism(s), must be sufficient to precisely identify and define preparations. The information and data referred to, unless otherwise specified, are required for all plant protection products. This is with the view to identify if any factor could alter the properties of the micro-organism as a plant protection product in comparison to the micro-organism as such, which is treated in Annex II, Part B, to Directive 91/414/EEC.

1.1. **Applicant**

The name and address of the applicant (permanent community address) must be provided as must the name, position, telephone and fax number of the appropriate person to contact.

Where, in addition, the applicant has an office, agent or representative in the Member State in which the authorisation is being sought, the name and address of the local office, agent or representative should be provided, as should the name, position, telephone and fax number of the appropriate person to contact.

([1]) USEPA Microbial Pesticide Test Guidelines, OPPTS Series 885, February 1996 (http://www.epa.gov/oppbppd1/biopesticides/guidelines/series885.htm).

1.2. **Manufacturer of the preparation and the micro-organism(s)**

The name and address of the manufacturer of the preparation and of each micro-organism in the preparation must be provided as must the name and address of each manufacturing plant in which the preparation and micro-organism are manufactured.

A contact point (preferable a central contact point, to include name, telephone and fax numbers) must be provided for each manufacturer.

If the micro-organism originates from a producer from which data according to Annex II, Part B, had not been submitted previously, detailed information on the name and species description, as required in Annex II, Part B, section 1.3, and on impurities, as required in Annex II, Part B, section 1.4, have to be provided.

1.3. **Trade name or proposed trade name, and manufacturer's development code number of the preparation if appropriate**

All former and current trade names and proposed trade names and development code numbers of the preparation referred to in the dossier as well as the current names and numbers must be provided. Full detail of any differences must be provided. (The proposed trade name must not give rise to confusion with the trade name of already authorised plant protection products.)

1.4. **Detailed quantitative and qualitative information on the composition of the preparation**

(i) Each micro-organism that is subject to the application should be identified and named at the species level. The micro-organism should be deposited at a recognised culture collection and given an accession number. The scientific name must be stated, as well as the group assignment (bacteria, virus, etc.) and any other denomination relevant to the micro-organism (e.g. strain, serotype). In addition, the development phase of the micro-organism (e.g. spores, mycelium) in the marketed product shall be stated.

(ii) For preparations the following information must be reported:

— the content of the micro-organism(s) in the plant protection product and the content of the micro-organism in the material used for manufacturing of plant protection products. These must include the maximum, minimum and nominal content of the viable and non-viable material,

— the content of formulants,

— the content of other components (such as by-products, condensates, culture medium, etc.) and contaminating micro-organisms, derived from production process.

The contents should be expressed in terms as provided for in Article 6(2) of Directive 78/631/EEC for chemicals and appropriate terms for micro-organisms (number of active units per volume or weight or any other manner that is relevant to the micro-organism).

(iii) Formulants must where possible, be identified either by their chemical name as given in Annex I to Directive 67/548/EEC, or, if not included in this Directive, in accordance with both IUPAC and CA nomenclature. Their structure or structural formula must be provided. For each component of the formulants the relevant EC (Einecs or Elincs) number and CAS number where they exist, must be provided. Where the information provided does not fully identify a formulant, an appropriate specification must be provided. The trade name of formulants, where they exist, must also be provided.

(iv) For formulants the function must be given:

— adhesive (sticker)
— antifoaming agent
— antifreeze
— binder
— buffer
— carrier
— deodorant
— dispersing agent
— dye
— emetic
— emulsifier
— fertiliser
— odorant
— parfume
— preservative
— propellant
— repellent
— safener
— solvent
— stabiliser
— synergist
— thickener
— wetting agent
— miscellaneous (specify).

(v) Identification of contaminating micro-organisms and other components derived from production process.

Contaminating micro-organisms must be identified as outlined in Annex II, Part B, section 1, point 1.3.

Chemicals (inert components, by-products, etc.) must be identified as outlined in Annex II, Part A, section 1, point 1.10.

Where the information provided does not fully identify a component, such as condensate, culture medium, etc., detailed information on the composition must be provided for each such component.

1.5. **Physical state and nature of the preparation**

The type and code of preparation must be designated according to the "Catalogue of pesticide formulation types and international coding system (GIFAP Technical Monograph No 2, 1989)".

Where a particular preparation is not defined precisely in this publication a full description of the physical nature and state of the preparation must be provided, together with a proposal for a suitable description of the type of preparation and a proposal for its definition.

1.6. **Function**

The biological function must be specified from among the following:

— control of bacteria,

— control of fungi,

— control of insects,

— control of mites,

— control of molluscs,

— control of nematodes,

— control of weeds,

— other (must be specified).

2. PHYSICAL, CHEMICAL AND TECHNICAL PROPERTIES OF THE PLANT PROTECTION PRODUCT

The extent to which plant protection products for which authorisation is sought comply with relevant FAO specifications, as agreed by the Group of Experts on Pesticide Specification of the FAO Panel of Experts on Pesticide Specifications, Registration Requirements and Application Standards, must be stated. Divergences from FAO specifications must be described in detail, and justified.

2.1. **Appearance (colour and odour)**

A description of both the colour and odour, if any, and the physical state of the preparation, must be provided.

2.2. **Storage stability and shelf-life**

2.2.1. *Effects of light, temperature and humidity on technical characteristics of the plant protection product*

(i) The physical and biological stability of the preparation at the recommended storage temperature including information on the growth of contaminating micro-organisms must be determined and reported. The conditions under which the test has been performed must be justified.

(ii) Additionally in the case of liquid preparations, the effect of low temperatures on physical stability, must be determined and reported according to CIPAC ([2]) Methods MT 39, MT 48, MT 51 or MT 54 as appropriate.

(iii) The shelf life of the preparation at the recommended storage temperature must be reported. Where shelf life is less than two years, the shelf life in months, with appropriate temperature specifications, must be reported. Useful information is given in GIFAP ([3]) Monograph No 17.

2.2.2. *Other factors affecting stability*

Effect of exposure to air, packaging, etc., on the product stability must be explored.

2.3. **Explosivity and oxidising properties**

Explosivity and oxidising properties will be determined as defined in Annex III, Part A, section 2, point 2.2, unless it can be justified that it is technically or scientifically not necessary to perform such studies.

2.4. **Flash point and other indications of flammability or spontaneous ignition**

Flash point and flammability must be determined, as defined in Annex III, Part A, section 2, point 2.3, unless it can be justified that it is technically or scientifically not necessary to perform such studies.

2.5. **Acidity, alkalinity and if necessary pH value**

Acidity, alkalinity and pH will be determined as defined in Annex III, Part A, section 2, point 2.4, unless it can be justified that it is technically or scientifically not necessary to perform such studies.

2.6. **Viscosity and surface tension**

Viscosity and surface tension will be determined as defined in Annex III, Part A, section 2, point 2.5, unless it can be justified that it is technically or scientifically not necessary to perform such studies.

2.7. **Technical characteristics of the plant protection product**

The technical characteristics of the preparation must be determined to permit a decision to be made as to its acceptability. If tests have to be performed, they must be done at temperatures compatible with survival of the micro-organism.

2.7.1. *Wettability*

The wettability of solid preparations which are diluted for use (e.g. wettable powders and water dispersible granules), must be determined and reported according to CIPAC Method MT 53.3.

([2]) Collaborative International Pesticides Analytical Council.
([3]) International Group of National Pesticide Manufacturers' Associations.

2.7.2. *Persistent foaming*

The persistence of foaming of preparations to be diluted with water, must be determined and reported according to CIPAC Method MT 47.

2.7.3. *Suspensibility and suspension stability*

— The suspensibility of water dispersible products (e.g. wettable powders, water dispersible granules, suspension concentrates) must be determined and reported according to CIPAC Method MT 15, MT 161 or MT 168 as appropriate.

— The spontaneity of dispersion of water dispersible products (e.g. suspension concentrates and water dispersible granules) must be determined and reported according to CIPAC Methods MT 160 or MT 174 as appropriate.

2.7.4. *Dry sieve test and wet sieve test*

In order to ensure that dustable powders have a suitable particle size distribution for ease of application, a dry sieve test must be conducted and reported according to CIPAC Method MT 59.1.

In the case of water dispersible products, a wet sieve test must be conducted and reported according to CIPAC Method MT 59.3 or MT 167 as appropriate.

2.7.5. *Particle size distribution (dustable and wettable powders, granules), content of dust/fines (granules), attrition and friability (granules)*

(i) The size distribution of particles in the case of powders, must be determined and reported according to OECD Method 110.

The nominal size range of granules for direct application must be determined and reported in accordance with CIPAC MT 58.3, for water dispersible granules in accordance with CIPAC MT 170.

(ii) The dust content of granular preparations, must be determined and reported according to CIPAC Method MT 171. If relevant for operator exposure the particle size of dust must be determined and reported according to OECD Method 110.

(iii) The friability and attrition characteristics of granules, must be determined and reported once internationally agreed methods are available. Where already data are available they must be reported together with the method used.

2.7.6. *Emulsifiability, re-emulsifiability, emulsion stability*

(i) The emulsifiability, emulsion stability and re-emulsifiability of preparations which form emulsions, must be determined and reported according to CIPAC Method MT 36 or MT 173 as appropriate.

(ii) The stability of dilute emulsions and of preparations which are emulsions, must be determined and reported according to CIPAC Method MT 20 or MT 173.

2.7.7. *Flowability, pourability (rinsability) and dustability*

(i) The flowability of granular preparations must be determined and reported according to CIPAC Method MT 172.

(ii) The pourability (including rinsed residue) of suspensions (e.g. suspension concentrates, suspo-emulsions), must be determined and reported according to CIPAC Method MT 148.

(iii) The dustability of dustable powders must be determined and reported according to CIPAC Method MT 34 or another suitable method.

2.8. **Physical, chemical and biological compatibility with other products including plant protection products with which its use is to be authorised**

2.8.1. *Physical compatibility*

The physical compatibility of recommended tank mixes must be determined and reported.

2.8.2. *Chemical compatibility*

The chemical compatibility of recommended tank mixes must be determined and reported except where examination of the individual properties of the preparations would establish beyond reasonable doubt that there is no possibility of reaction taking place. In such cases it is sufficient to provide that information as justification for not practically determining the chemical compatibility.

2.8.3. *Biological compatibility*

The biological compatibility of tank mixes must be determined and reported. Effects (e.g. antagonism, fungicidal effects) on the activity of the micro-organism after mixing with other micro-organisms or chemicals must be described. The possible interaction of the plant protection product with other chemical products to be applied on the crops under the expected condition of use of the preparation should be investigated, based on the efficacy data. Intervals between application of the biological pesticide and chemical pesticides should be specified, if appropriate, in order to avoid loss of efficacy.

2.9. **Adherence and distribution to seeds**

In the case of preparations for seed treatment, both distribution and adhesion must be investigated and reported; in the case of distribution according to CIPAC Method MT 175.

2.10. **Summary and evaluation of data presented under points 2.1 to 2.9**

3. DATA ON APPLICATION

3.1. **Field of use envisaged**

The field(s) of use, existing and proposed, for preparations containing the micro-organism must be specified from among the following:

— field use, such as agriculture, horticulture, forestry and viticulture,

— protected crops (e.g. in glasshouses),

— amenity,

— weed control on non-cultivated areas,

— home gardening,

— house plants,

— stored products,

— other (specify).

3.2. **Mode of action**

The way by which uptake of the product may occur (e.g. contact, stomach, inhalation) or the pest controlling action (fungitoxic, fungistatic action, nutrient competition, etc.) must be stated.

It must also be stated whether or not the product is translocated in plants and, where relevant, if such translocation is apoplastic, symplastic or both.

3.3. **Details of intended use**

Details of the intended use, e.g. types of harmful organisms controlled and/or plants or plant products to be protected, must be provided.

Intervals between the application of the plant protection product containing micro-organisms and chemical pesticides, or a list with active substances of chemical plant protection products not to be used together with the plant protection product containing micro-organisms on the same crop, should also be provided.

3.4. **Application rate**

For each method of application and each use, the rate of application per unit (ha, m^2, m^3) treated, in terms of g or kg or l for the preparation and in terms of appropriate units for the micro-organism, must be provided.

Application rates shall normally be expressed in g or kg/ha or in kg/m^3 and where appropriate in g or kg/tonne; for protected crops and home gardening use rates shall be expressed in g or kg/100 m^2 or g or kg/m^3.

3.5. **Content of micro-organism in material used (e.g. in the diluted spray, baits or treated seed)**

The content of micro-organism shall be reported, as appropriate, in number of active unit/ml or g or any other relevant unit.

3.6. **Method of application**

The method of application proposed must be described fully, indicating the type of equipment to be used, if any, as well as the type and volume of diluent to be used per unit of area or volume.

3.7. **Number and timing of applications and duration of protection**

The maximum number of applications to be used and their timing, must be reported. Where relevant the growth stages of the crop or plants to be protected and the development stages of the harmful organisms, must be indicated. Where possible and necessary the interval between applications, in days, must be stated.

The duration of protection afforded both by each application and by the maximum number of applications to be used, must be indicated.

3.8. **Necessary waiting periods or other precautions to avoid phytopathogenic effects on succeeding crops**

Where relevant, minimum waiting periods between last application and sowing or planting of succeeding crops, which are necessary to avoid phytopathogenic effects on succeeding crops, must be stated, and follow from the data provided under section 6, point 6.6.

Limitations on choice of succeeding crops, if any, must be stated.

3.9. **Proposed instructions for use**

The proposed instructions for use of the preparation, to be printed on labels and leaflets, must be provided.

4. FURTHER INFORMATION ON THE PLANT PROTECTION PRODUCT

4.1. **Packaging and compatibility of the preparation with proposed packaging materials**

(i) Packaging to be used must be fully described and specified in terms of the materials used, manner of construction (e.g. extruded, welded, etc.), size and capacity, size of opening, type of closure and seals. It must be designed in accordance with the criteria and guidelines specified in the FAO "Guidelines for the Packaging of Pesticides".

(ii) The suitability of the packaging, including closures, in terms of its strength, leakproofness and resistance to normal transport and handling, must be determined and reported according to ADR methods 3552, 3553, 3560, 3554, 3555, 3556, 3558, or appropriate ADR Methods for intermediate bulk containers, and, where for the preparation child-resistant closures are required, according to ISO standard 8317.

(iii) The resistance of the packaging material to its contents must be reported according to GIFAP Monograph No 17.

4.2. **Procedures for cleaning application equipment**

Cleaning procedures for both application equipment and protective clothing must be described in detail. The effectiveness of the cleaning procedure must be determined, using e.g. biotests, and reported.

4.3. **Re-entry periods, necessary waiting periods or other precautions to protect man, livestock and the environment**

The information provided must follow from and be supported by the data provided for the micro-organism(s) and that provided under sections 7 and 8.

(i) Where relevant pre-harvest intervals, re-entry periods or withholding periods necessary to minimise the presence of residues in or on crops, plants and plant products, or in treated areas or spaces, with a view to protecting man or livestock, must be specified e.g.:

— pre-harvest interval (in days) for each relevant crop,

— re-entry period (in days) for livestock, to areas to be grazed,

— re-entry period (in hours or days) for man to crops, buildings or spaces treated,

— withholding period (in days) for animal feedingstuffs,

— waiting period (in days), between application and handling treated products.

(ii) Where necessary, in the light of the test results, information on any specific agricultural, plant health or environmental conditions under which the preparation may or may not be used must be provided.

4.4. **Recommended methods and precautions concerning: handling, storage, transport or fire**

The recommended methods and precautions concerning handling procedures (detailed) for the storage, at both warehouse and user level of plant protection products, for their transport and in the event of fire must be provided. Where relevant, information on combustion products must be provided. The risks likely to arise and the methods and procedures to minimise the hazards arising, must be specified. Procedures to preclude or minimise the generation of waste or leftovers must be provided.

Where relevant, assessment has to be done according to ISO TR 9122.

The nature and characteristics of protective clothing and equipment proposed must be provided. The data provided must be sufficient to evaluate the suitability and effectiveness under realistic conditions of use (e.g. field or glasshouse circumstances).

4.5. **Measures in the case of an accident**

Whether arising during transport, storage or use, detailed procedures to be followed in the event of an accident, must be provided and include:

— containment of spillages,

— decontamination of areas, vehicles and buildings,

— disposal of damaged packaging, adsorbents and other materials,

— protection of emergency workers and bystanders,

— first aid measures.

4.6. **Procedures for destruction or decontamination of the plant protection product and its packaging**

Procedures for destruction and decontamination must be developed for both small quantities (user level) and large quantities (warehouse level). The procedures must be consistent with provisions in place relating to the disposal of waste and of toxic waste. The means of disposal proposed should be without unacceptable influence on the environment and be the most cost effective and practical means of disposal feasible.

4.6.1. *Controlled incineration*

In many cases the preferred or sole means to safely dispose of plant protection products and in particular the formulants contained in it, contaminated materials, or contaminated packaging, is through controlled incineration in a licensed incinerator.

The applicant must provide detailed instructions for safe disposal.

4.6.2. *Others*

Other methods to dispose of plant protection products, packaging and contaminated materials, where proposed, must be fully described. Data must be provided for such methods, to establish their effectiveness and safety.

5. ANALYTICAL METHODS

Introduction

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

It is desirable to have a plant protection product without contaminants, if possible. The level of acceptable contaminants should be judged from a risk assessment point of view, by the competent authority.

Both production and product must be subject to a continuous quality control by the applicant. The quality criteria for the product should be submitted.

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. The applicability of existing CIPAC methods must be reported.

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 (including contaminating micro-organisms and/or chemical substances) other than the specified micro-organism, originating from the manufacturing process or from degradation during storage
Relevant impurities	Impurities, as defined above, that are of concern for human or animal health and/or the environment
Metabolites	Metabolites include products resulting from degradative and biosynthetic reactions taking place within the micro-organism or other organisms used to produce the micro-organism of interest
Relevant metabolites	Metabolites that are of concern for human or animal health and/or the environment

Residues	Viable micro-organisms and substances produced in significant quantities by these micro-organisms which persist after the disappearance of the micro-organisms and are of concern for human or animal health and/or the environment.

On request the following samples must be provided:

(i) samples of the preparation;

(ii) samples of the micro-organism as manufactured;

(iii) analytical standards of the pure micro-organism;

(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.

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

— Methods, which must be described in full, must be provided for the identification and the determination of the content of the micro-organism in the preparation. In the case of a preparation containing more than one micro-organism, methods capable of identifying and determining the content of each one should be provided.

— Methods to establish regular control of the final product (preparation) in order to show that it does not contain other organisms than the indicated ones and to establish its uniformity.

— Methods to identify any contaminating micro-organisms of the preparation.

— Methods used to determine the storage stability and shelf life of the preparation must be provided.

5.2. **Methods to determine and quantify residues**

Analytical methods for the determination of residues, as defined in Annex II, Part B, section 4, point 4.2, must be submitted unless it is justified that the information already submitted according to the requirements of Annex II, Part B, section 4, point 4.2, is sufficient.

6. EFFICACY DATA

The provisions for efficacy data have already been adopted under Commission Directive 93/71/EEC ([4]).

7. EFFECTS ON HUMAN HEALTH

For proper evaluation of the toxicity including potential for pathogenicity and infectiveness of preparations sufficient information should be available on acute toxicity, irritation and sensitisation of the micro-organism. If possible, additional information on mode of toxic action, toxicological profile and all other known toxicological aspects of the micro-organism should be submitted. Special attention should be given to co-formulants.

While performing toxicology studies, all signs of infection or pathogenicity should be noted. Toxicology studies should include clearance studies.

In the context of the influence that impurities and other components can have on toxicological behaviour, it is essential that for each study submitted, a detailed description (specification) of the material used, be provided. Tests must be conducted using the plant protection product to be authorised. In particular, it must be clear that the micro-organism used in the preparation, and the conditions of culturing it, are the same for which information and data are submitted in the context of Annex II, Part B.

A tiered testing system will be applied to the study of the plant protection product.

([4]) OJ L 221, 31.8.1993, p. 27.

7.1. **Basic acute toxicity studies**

The studies, data and information to be provided and evaluated, must be sufficient to permit the identification of effects following a single exposure to the plant protection product, and in particular to establish, or indicate:

— the toxicity of the plant protection product,

— toxicity of the plant protection product relative to the micro-organism,

— the time course and characteristics of the effect with full details of behavioural changes and possible gross pathological findings at post-mortem,

— where possible the mode of toxic action, and

— the relative hazard associated with the different routes of exposure.

While the emphasis must be on estimating the toxicity ranges involved, the information generated must also permit the plant protection product to be classified in accordance with Directive 78/631/EEC. The information generated through acute toxicity testing is of particular value in assessing hazards likely to arise in accident situations.

7.1.1. *Acute oral toxicity*

Circumstances in which required

An acute oral test should always be carried out unless the applicant can justify to the satisfaction of the competent authority that Article 3(2) of Directive 78/631/EEC can be invoked.

Test guideline

The test must be carried out in accordance with Method B.1 or B.1 *bis* of Commission Directive 92/69/EEC ([5]).

7.1.2. *Acute inhalation toxicity*

Aim of the test

The test will provide the inhalation toxicity to rats of the plant protection product.

Circumstances in which required

The test must be carried out where the plant protection product:

— is used with fogging equipment,

— is an aerosol,

— is a powder containing a significant proportion of particles of diameter < 50 micrometre (> 1 % on a weight basis),

— is to be applied from aircraft in cases where inhalation exposure is relevant,

— is to be applied in a manner which generates a significant proportion of particles or droplets of diameter < 50 micrometre (> 1 % on a weight basis),

— contains a volatile component at greater than 10 %.

Test guideline

The test must be carried out in accordance with Method B.2 of Directive 92/69/EEC.

([5]) OJ L 383, 29.12.1992, p. 113.

7.1.3. *Acute percutaneous toxicity*

Circumstances in which required

An acute percutaneous test should always be carried out unless the applicant can justify to the satisfaction of the competent authority that Article 3(2) of Directive 78/631/EEC can be invoked.

Test guideline

The test must be carried out in accordance with Method B.3 of Directive 92/69/EEC.

7.2. **Additional acute toxicity studies**

7.2.1. *Skin irritation*

Aim of the test

The test will provide the potential of skin irritancy of the plant protection product including the potential reversibility of the effects observed.

Circumstances in which required

The skin irritancy of the plant protection product must always be determined, except where the formulants are not expected to be skin irritant or the micro-organism is shown not to be skin irritant or where it is likely, as indicated in the test guideline, that severe skin effects can be excluded.

Test guideline

The test must be carried out in accordance with Method B.4 of Directive 92/69/EEC.

7.2.2. *Eye irritation*

Aim of the test

The test will provide the potential for eye irritation of the plant protection product, including the potential reversibility of the effects observed.

Circumstances in which required

The eye irritancy of the plant protection product must be determined, where the formulants are suspected to be eye irritant, except where the micro-organism is eye irritant or where it is likely, as indicated in the test guideline, that severe effects on the eyes may be produced.

Test guideline

The eye irritation must be determined in accordance with Method B.5 of Directive 92/69/EEC.

7.2.3. *Skin sensitisation*

Aim of the test

The test will provide sufficient information to assess the potential of the plant protection product to provoke skin sensitisation reactions.

Circumstances in which required

The test must be carried out where the formulants are suspected to have skin sensitising properties, except where the micro-organism(s) or the formulants are known to have skin sensitising properties.

Test guideline

The tests have to be carried out in accordance with Method B.6 of Directive 92/69/EEC.

7.3. **Data on exposure**

The risks for those in contact with plant protection products (operators, bystanders, workers), depend on the physical, chemical and toxicological properties of the plant protection product as well as the type of the product (undiluted/diluted), formulation type, and on the route, the degree and duration of exposure. Sufficient information and data must be generated and reported to permit an assessment of the extent of exposure to the plant protection product likely to occur under the proposed conditions of use.

In the cases where there is particular concern on the possibility of dermal absorption based on the information for the micro-organism available in Annex II, Part B, section 5, or from the information provided for the preparation in the present section of Annex III, Part B, further dermal absorption data can be necessary.

Results from exposure monitoring during production or use of the product must be submitted.

The abovementioned information and data must provide the basis for the selection of appropriate protective measures including personal protective equipment to be used by operators and workers and to be specified on the label.

7.4. **Available toxicological data relating to non-active substances**

A copy of the notification and the safety data sheet submitted in the context of European Parliament and Council Directive 1999/45/EC ([6]) and Commission Directive 91/155/EEC of 5 March 1991 defining and laying down the detailed arrangements for the system of specific information relating to dangerous preparations in implementation of Article 10 of Directive 88/379/EEC ([7]) must be submitted for each formulant. All other available information should be submitted.

7.5. **Supplementary studies for combinations of plant protection products**

Aim of the test

In certain cases it may be necessary to carry out the studies as referred to under points 7.1 to 7.2.3 for a combination of plant protection products where the product label includes requirements for use of the plant protection product with other plant protection products and/or with adjuvants as a tank mix. Decisions as to the need for supplementary studies must be made on a case-by-case basis, taking into account the results of the acute toxicity studies of the individual plant protection products, the possibility for exposure to the combination of the products concerned and available information or practical experience with the products concerned or similar products.

7.6. **Summary and evaluation of health effects**

A summary of all data and information provided under paragraphs 7.1 through 7.5, must be submitted, and include a detailed and critical assessment of those data in the context of relevant evaluative and decision-making criteria and guidelines, with particular reference to the risks for man and animals that may or do arise, and the extent, quality and reliability of the database.

8. RESIDUES IN OR ON TREATED PRODUCTS, FOOD AND FEED

The same provisions as detailed in Annex II, Part B, section 6, apply; the information required according to this section has to be provided unless it is possible to extrapolate the residue behaviour of the plant protection product on the basis of the data available for the micro-organism. Special attention should be paid towards the influence of formulation substances on the residue behaviour of the micro-organism and its metabolites.

([6]) OJ L 200, 30.7.1999, p. 1.
([7]) OJ L 76, 22.3.1991, p. 35.

9. FATE AND BEHAVIOUR IN THE ENVIRONMENT

The same provisions as detailed in Annex II, Part B, section 7, apply; the information required according to this section has to be provided unless it is possible to extrapolate the fate and behaviour of the plant protection product in the environment on the basis of the data available in Annex II, Part B, section 7.

10. EFFECTS ON NON-TARGET ORGANISMS

Introduction

(i) The information provided, taken together with that for the micro-organism(s), must be sufficient to permit an assessment of the impact on non-target species (flora and fauna), of the plant protection product, when used as proposed. Impact can result from single, prolonged or repeated exposure, and can be reversible, or irreversible.

(ii) The choice of the appropriate non-target organisms for testing of environmental effects should be based on the information on the micro-organism, as required in Annex II, Part B, and on the information on the formulants and other components, as required by sections 1 to 9 of the present Annex. From such knowledge it would be possible to choose the appropriate test organisms, such as organisms closely related to the target organism.

(iii) In particular, the information provided for the plant protection product, together with other relevant information, and that provided for the micro-organism, should be sufficient to:

— specify the hazard symbols, the indications of danger, and relevant risk and safety phrases for the protection of the environment, to be mentioned on packaging (containers),

— permit an evaluation of the short- and long-term risks for non-target species — populations, communities, and processes as appropriate,

— permit an evaluation whether special precautions are necessary for the protection of non-target species.

(iv) There is a need to report all potentially adverse effects found during routine investigations of environmental effects and to undertake and report such additional studies which may be necessary to investigate the mechanisms involved and assess the significance of these effects.

(v) In general, much of the data relating to impact on non-target species, required for authorisation of plant protection products, will have been submitted and evaluated for the inclusion of the micro-organism(s) in Annex I.

(vi) Where exposure data are necessary to decide whether a study has to be performed, the data obtained in accordance with the provisions of Annex III, Part B, section 9, should be used.

For the estimation of exposure of organisms all relevant information on the plant protection product and on the micro-organism must be taken into account. Where relevant the parameters provided for in this section should be used. Where it appears from available data that the plant protection product has a stronger effect than the micro-organism, the data on effects on non target organisms of the plant protection product have to be used for the calculation of relevant effect/exposure ratios.

(vii) In order to facilitate the assessment of the significance of test results obtained, the same strain of each relevant species should where possible be used in the various specified tests for effects on non target organisms.

10.1. **Effects on birds**

The same information as provided in Annex II, Part B, section 8, point 8.1, has to be reported where it is not possible to predict the effects of the plant protection product on the basis of the data available for the micro-organism, unless it can be justified that exposure of birds is unlikely to occur.

10.2. **Effects on aquatic organisms**

The same information as provided in Annex II, Part B, section 8, point 8.2, has to be reported where it is not possible to predict the effects of the plant protection product on the basis of the data available for the micro-organism, unless it can be justified that exposure of aquatic organisms is unlikely to occur.

10.3. **Effects on bees**

The same information as provided in Annex II, Part B, section 8, point 8.3, has to be reported where it is not possible to predict the effects of the plant protection product on the basis of the data available for the micro-organism, unless it can be justified that exposure of bees is unlikely to occur.

10.4. **Effects on arthropods other than bees**

The same information as provided in Annex II, Part B, section 8, point 8.4, has to be reported where it is not possible to predict the effects of the plant protection product on the basis of the data available for the micro-organism, unless it can be justified that exposure of arthropods other than bees is unlikely to occur.

10.5. **Effects on earthworms**

The same information as provided in Annex II, Part B, section 8, point 8.5, has to be reported where it is not possible to predict the effects of the plant protection product on the basis of the data available for the micro-organism, unless it can be justified that exposure of earthworms is unlikely to occur.

10.6. **Effects on soil micro-organisms**

The same information as provided in Annex II, Part B, section 8, point 8.6, has to be reported where it is not possible to predict the effects of the plant protection product on the basis of the data available for the micro-organism, unless it can be justified that exposure of non target soil micro-organisms is unlikely to occur.

10.7. **Additional studies**

Expert judgement is required to decide whether additional studies are necessary. Such decision will take into consideration the available information in this and other sections, in particular data on the specificity of the micro-organism, and the expected exposure. Useful information may also be available from the observations carried out in efficacy testing.

Special attention should be given to possible effects on naturally occurring and deliberately released organisms of importance in IPM. In particular the compatibility of the product with IPM should be taken into consideration.

Additional studies might include further studies on additional species or higher tier studies such as studies on selected non-target organisms.

Before performing such studies, the applicant shall seek agreement of the competent authorities on the type of study to be performed.

11. SUMMARY AND EVALUATION OF ENVIRONMENTAL IMPACT

A summary and evaluation of all data relevant to the environmental impact should be carried out according to the guidance given by the competent authorities of the Member States concerning the format of such summaries and evaluations. It should include a detailed and critical assessment of those data in the context of

relevant evaluative and decision making criteria and guidelines, with particular reference to the risks for the environment and non-target species that may or do arise, and the extent, quality and reliability of the database. In particular the following issues should be addressed:

— prediction of distribution and fate in the environment, and the time courses involved,

— identification of non-target species and populations at risk, and prediction of the extent of potential exposure,

— identification of precautions necessary to avoid or minimise contamination of the environment, and for the protection of non-target species.'