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(Acts whose publication is obligatory)

**COUNCIL DIRECTIVE 2005/25/EC**

**of 14 March 2005**

**amending Annex VI to Directive 91/414/EEC as regards plant protection products containing micro-organisms**

(Text with EEA relevance)

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community,

Having regard to Council Directive 91/414/EC of 15 July 1991 concerning the placing of plant protection products on the market <sup>(1)</sup>, and in particular Article 18(1) thereof,

Having regard to the proposal from the Commission,

Whereas:

- (1) In accordance with Directive 91/414/EEC, Member States have to ensure that plant protection products are not authorised unless they comply with the requirements provided for in that Directive.
- (2) Directive 91/414/EEC provides for the establishment of Uniform Principles pursuant to which the Member States have to carry out the evaluation of plant protection products with a view to their authorisation.
- (3) Uniform Principles have been laid down for Member States to use in the evaluation and authorisation of chemical plant protection products only. However, there are no equivalent principles for Member States to apply in the evaluation and authorisation of plant protection products containing micro-organisms. It is appropriate to lay down additional Uniform Principles for this type of plant protection product.

- (4) Requirements for the dossiers to be submitted by applicants for the authorisation of plant protection products containing micro-organisms having been included in Directive 91/414/EEC by Commission Directive 2001/36/EEC <sup>(2)</sup>, it is now necessary to lay down Uniform Principles for the evaluation of a dossier concerning plant protection products containing micro-organisms based on such data requirements.

- (5) The provisions of this Directive concerning the protection of water, including the provisions related to monitoring, are without prejudice to Member States' obligations under the Directives concerned, and in particular Council Directives 75/440/EEC of 16 June 1975 concerning the quality required of surface water intended for the abstraction of drinking water in the Member States <sup>(3)</sup>, 80/68/EEC of 17 December 1979 on the protection of groundwater against pollution caused by certain dangerous substances <sup>(4)</sup>, 98/83/EC of 3 November 1998 on the quality of water intended for human consumption <sup>(5)</sup> and Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy <sup>(6)</sup>.

<sup>(1)</sup> OJ L 230, 19.8.1991, p. 1. Directive as last amended by Commission Directive 2004/99/EC (OJ L 309, 16.10.2004, p. 6).

<sup>(2)</sup> OJ L 164, 20.6.2001, p. 1.

<sup>(3)</sup> OJ L 194, 25.7.1975, p. 26. Directive to be repealed from 22.12.2007 by Directive 2000/60/EC (OJ L 327, 22.12.2000, p. 1).

<sup>(4)</sup> OJ L 20, 26.1.1980, p. 43. Directive to be repealed from 22.12.2013 by Directive 2000/60/EC.

<sup>(5)</sup> OJ L 330, 5.12.1998, p. 32. Directive as last amended by Regulation (EC) No 1882/2003 of the European Parliament and of the Council (OJ L 284, 31.10.2003, p. 1).

<sup>(6)</sup> OJ L 327, 22.12.2000, p. 1. Directive as amended by Decision No 2455/2001/EC (OJ L 331, 15.12.2001, p. 1).

- (6) The provisions of this Directive concerning genetically modified organisms are without prejudice to Member States' obligations under Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms <sup>(7)</sup>.
- (7) The Scientific Committee on Plants has provided an opinion on this Directive, and this opinion has been taken into account.
- (8) Directive 91/414/EEC should therefore be amended accordingly,

When Member States adopt those measures, they shall contain a reference to this Directive or shall be accompanied by such reference on the occasion of their official publication. The methods of making such reference shall be laid down by Member States.

2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

*Article 3*

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

HAS ADOPTED THIS DIRECTIVE:

*Article 1*

Annex VI to Directive 91/414/EEC is hereby amended in accordance with the Annex to this Directive.

*Article 2*

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 28 May 2006. They shall immediately forward to the Commission the text of those measures together with a correlation table between such measures and this Directive.

*Article 4*

This Directive is addressed to the Member States.

Done at Brussels, 14 March 2005.

*For the Council*  
*The President*  
F. BODEN

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<sup>(7)</sup> OJ L 106, 17.4.2001, p. 1. Directive as last amended by Regulation (EC) No 1830/2003 (OJ L 268, 18.10.2003, p. 24).

## ANNEX

Annex VI is hereby amended as follows:

- (1) The title 'Uniform Principles for evaluation and authorisation of plant protection products' shall be replaced by

'PART I

**UNIFORM PRINCIPLES FOR EVALUATION AND AUTHORISATION OF CHEMICAL PLANT PROTECTION PRODUCTS';**

- (2) The following Part shall be added after Part I

'PART II

**UNIFORM PRINCIPLES FOR EVALUATION AND AUTHORISATION OF PLANT PROTECTION PRODUCTS CONTAINING MICRO-ORGANISMS'**

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## A. **INTRODUCTION**

- 1. The principles developed in Part II of this Annex aim to ensure that evaluations and decisions with regard to authorisation of plant protection products, provided they are microbial plant protection products, result in the implementation of the requirements of Article 4(1)(b), (c), (d) and (e) of this Directive by all Member States at a high level of protection of human and animal health and the environment.
- 2. In evaluating applications for granting authorisations Member States shall:
  - (a) — ensure that dossiers on microbial plant protection products supplied are in accordance with the requirements of Annex IIIB, at the latest at the time of finalisation of the evaluation for the purpose of decision-making, without prejudice, where relevant, to the provisions of Article 13 (1)(a), (4) and (6) of this Directive,
  - ensure that the data submitted are acceptable in terms of quantity, quality, consistency and reliability and sufficient to permit a proper evaluation of the dossier,
  - evaluate, where relevant, justifications submitted by the applicant for not supplying certain data;

- (b) take into account the Annex IIB data concerning the active substance consisting of micro-organisms (including viruses) in the plant protection product, submitted for the purpose of inclusion of the micro-organism concerned in Annex I, and the results of the evaluation of those data, without prejudice, where relevant, to the provisions of Article 13(1)(b), (2), (3) and (6) of this Directive;
  - (c) take into consideration other relevant technical or scientific information they can reasonably possess with regard to the performance of the plant protection product or to the potentially adverse effects of the plant protection product, its components or its metabolites/toxins.
3. Where, in the specific principles on evaluation, reference is made to Annex IIB data, this shall be understood as being the data referred to in point 2(b).
4. Where the data and information provided are sufficient to permit completion of the evaluation for one of the proposed uses, applications must be evaluated and a decision made for the proposed use.

Taking account of justifications provided and with the benefit of any subsequent clarifications, Member States shall reject applications for granting authorisations for which the data gaps are such that it is not possible to finalise the evaluation and to make a reliable decision for at least one of the proposed uses.

5. During the process of evaluation and decision-making, the Member State shall cooperate with the applicants in order to resolve any questions on the dossier quickly or to identify at an early stage any additional studies necessary for a proper evaluation of the dossier, or to amend any proposed conditions for the use of the plant protection product or to modify its nature or its composition in order to ensure full satisfaction of the requirements of this Annex or of this Directive.

Member States shall normally come to a reasoned decision within 12 months of receiving a technically complete dossier. A technically complete dossier is one that satisfies all the requirements of Annex IIIB.

6. The judgements made by the competent authorities of the Member States during the evaluation and decision-making process must be based on scientific principles, preferably recognised at international level, and be made with the benefit of expert advice.
7. A microbial plant protection product may contain viable and non-viable micro-organisms (including viruses) and formulation substances. It may also contain relevant metabolites/toxins produced during growth, residues from the growth medium, and microbial contaminants. The micro-organism, relevant metabolites/toxins and the plant protection product with residual growth medium and microbial contaminants present must all be evaluated.
8. Member States must take into account those guidance documents taken note of in the Standing Committee on the Food Chain and Animal Health (SCFCAH).
9. For genetically modified micro-organisms, Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms <sup>(1)</sup>, must be taken into account. The evaluation completed in the framework of that Directive must be provided and taken into account.
10. Definitions and explanations of microbiological terms

Antibiosis: A relationship between two or more species in which one species is actively harmed (as by the production of toxins by the harming species).

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<sup>(1)</sup> OJ L 106, 17.4.2001, p. 1. Directive as last amended by Regulation (EC) No 1830/2003 (OJ L 268, 18.10.2003, p. 24).

**Antigenic:** Any substance that, as a result of coming in contact with appropriate cells, induces a state of sensitivity and/or immune responsiveness after a latent period (days to weeks) and which reacts in a demonstrable way with antibodies and/or immune cells of the sensitised subject in vivo or in vitro.

**Antimicrobial:** Antimicrobial agents or antimicrobial(s) refer to naturally occurring, semi-synthetic or synthetic substances that exhibit antimicrobial activity (kill or inhibit the growth of micro-organisms).

The term 'Antimicrobial(s)' includes:

- antibiotics, which refer to substances produced by or derived from micro-organisms, and
- anticoccidials, which refer to substances that are active against coccidia, single cell protozoan parasites.

**CFU:** Colony-forming unit; one or more cells that grow to form a single visible colony.

**Colonisation:** Proliferation and persistence of a micro-organism in an environment, such as on external (skin) or internal body surfaces (intestine, lungs). For colonisation, the micro-organism should at least persist for a longer period than expected in a specific organ. The population of micro-organisms may decline but at a slower rate than normal clearance; it may be a steady population or it may be a growing population. Colonisation can be related to harmless and functional micro-organisms as well as to pathogenic micro-organisms. The possible occurrence of effects is not indicated.

**Ecological niche:** Unique environmental position occupied by a particular species, perceived in terms of actual physical space occupied and function performed within the community or ecosystem.

**Host:** An animal (including humans) or plant that harbours or nourishes another organism (parasite).

**Host specificity:** The range of different host-species that can be colonised by a microbial species or strain. A host-specific micro-organism colonises or has adverse effects on one or only a small number of different host-species. A non-host-specific micro-organism might colonise or might have adverse effects on a broad range of different host-species.

**Infection:** The introduction or entry of a pathogenic micro-organism into a susceptible host, whether or not it causes pathological effects or disease. The organism must enter the body of the host, usually the cells, and be able to reproduce to form new infective units. Simply ingesting a pathogen does not imply infection.

**Infective:** Capable of transmitting an infection.

**Infectivity:** The characteristics of a micro-organism that allow it to infect a susceptible host.

**Invasion:** The entry of a micro-organism into the host body (e.g. actual penetration of the integument, gut epithelial cells, etc.). 'Primary invasiveness' is a property of pathogenic micro-organisms.

**Multiplication:** Ability of a micro-organism to reproduce and increase in numbers during an infection.

**Mycotoxin:** A fungal toxin.

**Non-viable micro-organism:** A micro-organism that is not capable of replication or of transferring genetic material.

**Non-viable residue:** A residue that is not capable of replication or of transferring genetic material.

**Pathogenicity:** The ability of a micro-organism to cause disease and/or inflict damage on the host. Many pathogens cause disease by a combination of (i) toxicity and invasiveness or (ii) toxicity and colonising ability. However, some invasive pathogens cause disease that results from an abnormal reaction of the host's defence system.

**Symbiosis:** A type of interaction between organisms where one organism lives in intimate association with another, which is favourable for both organisms.

**Viable micro-organism:** A micro-organism that is capable of replication or of transferring genetic material.

**Viable residue:** A residue that is capable of replication or of transferring genetic material.

**Viroid:** Any of a class of infectious agents consisting of a small strand of RNA not associated with any protein. The RNA does not code for proteins and is not translated; it is replicated by host cell enzymes. Viroids are known to cause several plant diseases.

**Virulence:** Measurement of the degree of disease producing ability of a micro-organism as indicated by the severity of the disease produced. Measure of the dosage (inoculum size) required to cause a specific degree of pathogenicity. It is measured experimentally by the median lethal dose ( $LD_{50}$ ) or median infective dose ( $ID_{50}$ ).

## B. EVALUATION

The objective of an evaluation is to identify and assess, on a scientific basis and until further experience is reached on a case-by-case basis, potential adverse effects on human and animal health and the environment of the use of a microbial plant protection product. The evaluation shall also be carried out in order to identify the need for risk management measures and to identify and recommend suitable measures.

Due to the ability of micro-organisms to replicate, there is a clear difference between chemicals and micro-organisms used as plant protection products. Hazards arising are not necessarily of the same nature as those presented by chemicals, especially in relation to the capacity of micro-organisms to persist and multiply in different environments. Moreover, micro-organisms consist of a wide range of different organisms, all with their own unique characteristics. These differences between micro-organisms should be taken into account in the evaluation.

The micro-organism in the plant protection product should ideally function as a cell factory working directly on the spot where the target organism is harmful. Thus understanding the mode of action is a crucial step in the evaluation process.

Micro-organisms may produce a range of different metabolites (e.g. bacterial toxins or mycotoxins) many of which may have toxicological significance, and one or more of which may be involved in the mode of action of the plant protection product. The characterisation and identification of relevant metabolites should be assessed and the toxicity of these metabolites should be addressed. Information on production and/or relevance of metabolites may be deduced from:

- (a) toxicity studies,
- (b) biological properties of the micro-organism,
- (c) relationship to known plant, animal or human pathogens,
- (d) mode of action,
- (e) analytical methods.

On the basis of this information, metabolites may be considered as possibly being relevant. Therefore potential exposure to these metabolites should be assessed, in order to decide on their relevance.

## 1. General principles

- 1.1. Having regard to current scientific and technical knowledge, Member States shall evaluate the information provided in accordance with the requirements of Annex IIB and IIIB and in particular:
- (a) identify the hazards arising, assess their significance and make a judgement as to the likely risks to humans, animals or the environment; and
  - (b) assess the performance in terms of efficacy and phytotoxicity/pathogenicity of the plant protection product for each use for which authorisation is sought.

- 1.2. The quality/methodology of tests, where there are no standardised test methods, must be evaluated and the following characteristics, when available, of the methods described must be assessed:

relevance; representativeness; sensitivity; specificity; reproducibility; interlaboratory validations; predictiveness.

- 1.3. In interpreting the results of evaluations, Member States shall take into consideration possible elements of uncertainty in the information obtained during the evaluation, in order to ensure that the chances of failing to detect adverse effects or of underestimating their importance are reduced to a minimum. The decision-making process shall be examined to identify critical decision points or items of data for which uncertainties could lead to a false classification of risk.

The first evaluation made shall be based on the best available data or estimates reflecting the realistic conditions of use of the plant protection product. This must be followed by a repeat evaluation, taking account of potential uncertainties in the critical data and of a range of use conditions that are likely to occur and resulting in a realistic worst-case approach, to determine whether it is possible that the initial evaluation could have been significantly different.

- 1.4. Member States shall evaluate each microbial plant protection product for which an application for authorisation is made in that Member State — the information evaluated for the micro-organism can be taken into account. Member States must take into account the fact that any co-formulants might have an impact on the characteristics of the plant protection product compared to the micro-organism.
- 1.5. In evaluating applications and granting authorisations Member States shall consider the proposed practical conditions of use and in particular the purpose of use, the dose, the manner, frequency and timing of applications, and the nature and composition of the plant protection product. Whenever possible Member States shall also take into account the principles of integrated pest control.
- 1.6. In the evaluation, Member States shall consider the agricultural, plant health or environmental (including climatic) conditions in the areas of use.
- 1.7. Where specific principles in Section 2 provide for the use of calculation models in the evaluation of a plant protection product, those models shall:
- (a) make a best possible estimation of all relevant processes involved taking into account realistic parameters and assumptions,
  - (b) be submitted to an evaluation as referred to in point 1.3.,
  - (c) be reliably validated with measurements carried out under circumstances relevant for the use of the model,
  - (d) be relevant to the conditions in the area of use,

- (e) be supported with details indicating how the model calculates estimates provided, and explanations of all the inputs to the model and details of how they have been derived.

- 1.8. The data requirements, specified in Annex IIB and IIIB, contain guidance as to when and how certain information must be submitted and as to procedures that must be followed when preparing and evaluating a dossier. That guidance must be respected.

## 2. **Specific principles**

Member States shall implement the following principles in the evaluation of the data and information submitted in support of applications, without prejudice to the general principles prescribed in Section 1:

### 2.1. *Identity*

#### 2.1.1. Identity of the micro-organism in the plant protection product

The identity of the micro-organism should be clearly established. It must be ensured that the appropriate data are provided to allow for checking the identity of the micro-organism at strain level in the plant protection product.

The identity of the micro-organism shall be evaluated on the strain level. Where the micro-organism is either a mutant or a genetically modified organism <sup>(1)</sup>, the specific differences from other strains within the same species must be recorded. Occurrence of resting stages must be recorded.

The deposition of the strain at an internationally recognised culture collection must be checked.

#### 2.1.2. Identity of the plant protection product

Member States shall evaluate the detailed quantitative and qualitative information provided on the composition of the plant protection product, such as that concerning the micro-organism (see above), relevant metabolites/toxins, residual growth medium, co-formulants and microbial contaminants present.

### 2.2. *Biological, physical, chemical, and technical properties*

#### 2.2.1. Biological properties of the micro-organism in the plant protection product

- 2.2.1.1. The origin of the strain, where relevant, its natural habitat including indications on the natural background level, life cycle and the possibilities for survival, colonisation, reproduction and dispersal must be evaluated. Proliferation of indigenous micro-organisms should after a short growth period level off and continue as for the background micro-organisms.

- 2.2.1.2. The ability of micro-organisms to adapt to the environment must be evaluated. In particular, Member States must take account of the following principles:

- (a) depending on the conditions (e.g. availability of substrates for growth and metabolism) micro-organisms can switch on or off the expression of given phenotypic traits;
- (b) the microbial strains most adapted to the environment can survive and multiply better than the non-adapted strains. Adapted strains have a selective advantage and can form the majority within a population after a number of generations;

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<sup>(1)</sup> See definition of 'genetically modified' in Directive 2001/18/EC.

- (c) the relatively rapid multiplication of micro-organisms leads to a higher frequency of mutations. If a mutation is promoting survival in the environment, the mutant strain can become dominant;
- (d) the properties of viruses, in particular, can change rapidly, including their virulence.

Therefore, where appropriate, information on the genetic stability of the micro-organism under the environmental conditions of proposed use must be evaluated, as well as information on the micro-organism's capacity to transfer genetic material to other organisms and information on the stability of encoded traits.

2.2.1.3. The mode of action of the micro-organism should be evaluated in as much detail as appropriate. The possible role of metabolites/toxins for the mode of action should be evaluated and when identified, the minimal effective concentration for each active metabolite/toxin should be established. Information on mode of action can be a very valuable tool in identifying potential risks. Aspects to be considered in the evaluation, are:

- (a) antibiosis,
- (b) induction of plant resistance,
- (c) interference with the virulence of a pathogenic target organism,
- (d) endophytic growth,
- (e) root colonisation,
- (f) competition of ecological niche (e.g. nutrients, habitats),
- (g) parasitisation,
- (h) invertebrate pathogenicity.

2.2.1.4. In order to evaluate possible effects on non-target organisms, information on the micro-organism's host specificity must be evaluated, taking into account the characteristics and properties described in (a) and (b).

- (a) The ability of a micro-organism to be pathogenic for non-target organisms (humans, animals, and other non-target organisms) must be assessed. Any relationship to known plant, animal or human pathogens that are species of the genus of the active and/or contaminating micro-organisms must be assessed.
- (b) Pathogenicity as well as virulence is strongly related to the host-species (e.g. determined by body temperature, physiological environment) and to the host conditions (e.g. health condition, immune status). For example, multiplication in humans depends upon the ability of the micro-organism to grow at the body temperature of the host. Some micro-organisms can only grow and be metabolically active at temperatures far below or above human body temperature, and therefore can not be pathogenic for humans. However, the route of entry of the micro-organism into the host (oral, inhalation, skin/wound) can also be the critical factor. For example, a microbial species may cause a disease following entry via skin damage, but not via the oral route.

2.2.1.5. Many micro-organisms produce antibiosis substances that cause normal interferences in the microbial community. Resistance to antimicrobial agents of importance for human and veterinary medicine must be assessed. The possibility for transfer of genes that code for resistance to antimicrobial agents must be evaluated.

### 2.2.2. Physical, chemical and technical properties of the plant protection product

2.2.2.1. Depending on the nature of the micro-organism and the formulation type, the technical properties of the plant protection product must be evaluated.

2.2.2.2. Shelf-life and storage stability of the preparation must be evaluated, taking into account possible changes in composition such as growth of the micro-organism or of contaminating micro-organisms, production of metabolites/toxins, etc.

2.2.2.3. Member States shall evaluate the physical and chemical properties of the plant protection product and the retention of these characteristics after storage and take into consideration:

- (a) where a suitable Food and Agriculture Organisation of the United Nations (FAO) specification exists, the physical and chemical properties addressed in that specification,
- (b) where no suitable FAO specification exists, all relevant physical and chemical properties for the formulation referred to in the Manual on the development and use of FAO and World Health Organisation (WHO) specifications for pesticides.

2.2.2.4. Where the proposed label claims include requirements or recommendations for use of the preparation with other plant protection products or adjuvants as a tank mix, and/or where the proposed label includes indications concerning the compatibility of the preparation with other plant protection products as a tank mix, those plant protection products or adjuvants must be physically and chemically compatible in the tank mix. Biological compatibility must also be demonstrated for tank-mixtures, i.e. it must be shown that each plant protection product in the mixture performs as expected and that no antagonism occurs.

### 2.3. Further information

#### 2.3.1. Quality control of the production of the micro-organism in the plant protection product

The quality assurance criteria proposed for production of the micro-organism must be evaluated. In the evaluation criteria relating to process control, good manufacturing practice, operational practices, process flows, cleaning practices, microbial monitoring and hygiene conditions should be taken into account to ensure good quality of the micro-organism. The quality, stability, purity etc., of the micro-organism must be addressed in the quality control system.

#### 2.3.2. Quality control of the plant protection product

The quality assurance criteria proposed must be evaluated. If the plant protection product contains metabolites/toxins produced during growth and residues from the growth medium this should be evaluated. The possibility of the occurrence of contaminating micro-organisms must be evaluated.

### 2.4. Efficacy

2.4.1. Where the proposed use concerns the control of or protection against an organism, Member States shall evaluate the possibility that this organism could be harmful under the agricultural, plant health and environmental (including climatic) conditions in the area of the proposed use.

2.4.2. Member States shall evaluate whether significant damage, loss or inconvenience could occur under the agricultural, plant health and environmental (including climatic) conditions in the area of proposed use if the plant protection product were not used.

2.4.3. Member States shall evaluate the efficacy data provided for in Annex IIIB on the plant protection product having regard to the degree of control or the extent of the effect desired and having regard to relevant experimental conditions such as:

- (a) the choice of the crop or cultivar;

- (b) the agricultural and environmental (including climatic) conditions (if necessary for acceptable efficacy such data/information should also be given for the time before and after application),
- (c) the presence and density of the harmful organism,
- (d) the development stage of crop and organism,
- (e) the amount of the microbial plant protection product used,
- (f) if required on the label, the amount of adjuvant added,
- (g) the frequency and timing of the applications,
- (h) the type of application equipment,
- (i) the need for any special cleaning measures for the application equipment.

2.4.4. Member States shall evaluate the performance of the plant protection product under the range of agricultural, plant health and environmental (including climatic) conditions likely to be encountered in practice in the area of proposed use. The effect on integrated control must be included in the evaluation. In particular, consideration should be paid to:

- (a) the level, consistency and duration of the effect sought in relation to the dose in comparison with a suitable reference product or products, where they exist, and an untreated control;
- (b) where relevant, the effect on yield or reduction of loss in storage, in terms of quantity and/or quality, in comparison with a suitable reference product or products, where they exist, and an untreated control.

Where no suitable reference product exists, Member States shall evaluate the performance of the plant protection product to determine whether there is a consistent and defined benefit under the agricultural, plant health and environmental (including climatic) conditions likely to be encountered in practice in the area of proposed use.

2.4.5. Member States shall evaluate the degree of adverse effects on the treated crop after use of the plant protection product according to the proposed conditions of use in comparison, where relevant, with a suitable reference product or products, where they exist, and/or an untreated control.

- (a) This evaluation will take into consideration the following information:
  - (i) efficacy data;
  - (ii) other relevant information on the plant protection product such as nature of the plant protection product, dose, method of application, number and timing of applications, incompatibility with other crop treatments;
  - (iii) all relevant information on the micro-organism, including biological properties e.g. mode of action, survival, host specificity.
- (b) This evaluation will include:
  - (i) the nature, frequency, level and duration of observed phytotoxic/phytopathogenic effects and the agricultural, plant health and environmental (including climatic) conditions that affect them;
  - (ii) differences between main cultivars with regard to their sensitivity to phytotoxic/phytopathogenic effects;

- (iii) the part of the treated crop or plant products where phytotoxic/phytopathogenic effects are observed;
- (iv) adverse impact on the yield of the treated crop or plant products in terms of quantity and/or quality;
- (v) adverse impact on treated plants or plant products to be used for propagation, in terms of viability, germination, sprouting, rooting and establishment;
- (vi) where micro-organisms are disseminated, the adverse impact on adjacent crops.

2.4.6. Where the plant protection product label includes requirements for use of the plant protection product with other plant protection products and/or with adjuvants as a tank mix, Member States shall make the evaluations referred to in points 2.4.3 to 2.4.5 in relation to the information supplied for the tank mix.

Where the plant protection product label includes recommendations for use of the plant protection product with other plant protection products and/or with adjuvants as a tank mix, Member States shall evaluate the appropriateness of the mix and of its conditions of use.

- 2.4.7. Where the available data indicate that the micro-organism or significant relevant metabolites/toxins, degradation and reaction products of the formulants persist in soils and/or in or on plant substances in significant quantities after use of the plant protection product according to the proposed conditions of use, Member States shall evaluate the degree of adverse effects on subsequent crops.
- 2.4.8. Where the proposed use of a plant protection product is intended to have an effect on vertebrates, Member States shall evaluate the mechanism by which this effect is obtained and the observed effects on the behaviour and health of the target animals. When the intended effect is to kill the target animal they shall evaluate the time necessary to obtain the death of the animal and the conditions under which death occurs.

This evaluation will take into consideration the following information:

- (a) all relevant information as provided for in Annex IIB and the results of the evaluation thereof, including the toxicological studies;
- (b) all relevant information on the plant protection product as provided for in Annex IIIB, including toxicological studies and efficacy data.

#### 2.5. *Identification/detection and quantification methods*

Member States shall evaluate the analytical methods proposed for post-registration control and monitoring purposes of the viable and non-viable components both in the formulation and as residues in or on treated crops. Sufficient validation is required for pre-authorisation methods and post-authorisation monitoring methods. Methods that are considered suitable for post-authorisation monitoring must be clearly identified.

##### 2.5.1. Analytical methods for the plant protection product

###### 2.5.1.1. Non-viable components

Member States shall evaluate the analytical methods proposed to identify and quantify the toxicologically, ecotoxicologically or environmentally significant non-viable components resulting from the micro-organism and/or present as impurity or co-formulant (including eventually resulting breakdown and/or reaction products thereof).

This evaluation will take into consideration the information on analytical methods provided for in Annex IIB and IIIB and the results of the evaluation thereof. In particular, the following information must be taken into account:

- (a) the specificity and linearity of the proposed methods,

- (b) the precision (repeatability) of the proposed methods,
- (c) the importance of interferences,
- (d) the accuracy of the proposed methods at appropriate concentrations,
- (e) the limit of quantification of the proposed methods.

#### 2.5.1.2. Viable components

Member States shall evaluate the methods proposed to quantify and identify the specific strain concerned and especially methods that discriminate that strain from closely related strains.

This evaluation will take into consideration the information on analytical methods provided for in Annex IIB and IIIB and the results of the evaluation thereof. In particular, the following information must be taken into account:

- (a) the specificity of the proposed methods,
- (b) the precision (repeatability) of the proposed methods,
- (c) the importance of interferences,
- (d) the quantifiability of the proposed methods.

#### 2.5.2. Analytical methods for the determination of residues

##### 2.5.2.1. Non-viable residues

Member States shall evaluate the analytical methods proposed to identify and quantify the toxicologically, ecotoxicologically or environmentally significant non-viable residues resulting from the micro-organism (including eventually resulting breakdown and/or reaction products thereof).

This evaluation will take into consideration the information on analytical methods provided for in Annex IIB and IIIB and the results of the evaluation thereof. In particular, the following information must be taken into account:

- (a) the specificity and linearity of the proposed methods,
- (b) the precision (repeatability) of the proposed methods,
- (c) the reproducibility (independent laboratory validation) of the proposed methods,
- (d) the importance of interferences,
- (e) the accuracy of the proposed methods at appropriate concentrations,
- (f) the limit of quantification of the proposed methods.

##### 2.5.2.2. Viable residues

Member States shall evaluate the methods proposed to identify the specific strain concerned and especially methods that discriminate that strain from closely related strains.

This evaluation will take into consideration the information on analytical methods provided for in Annex IIB and IIIB and the results of the evaluation thereof. In particular, the following information must be taken into account:

- (a) the specificity of the proposed methods,
- (b) the precision (repeatability) of the proposed methods,
- (c) the importance of interferences,
- (d) the quantifiability of the proposed methods.

#### 2.6. *Impact on human or animal health*

The impact on human or animal health must be evaluated. In particular, Member States must take account of the following principles:

- (a) due to the ability of micro-organisms to replicate, there is a clear difference between chemicals and micro-organisms used as plant protection products. Hazards arising are not necessarily of the same nature as those presented by chemicals, especially in relation to the capacity of micro-organisms to persist and multiply in different environments;
- (b) the pathogenicity of the micro-organism to humans and non-target animals, the infectiveness of the micro-organism, the ability of the micro-organism to colonise, the toxicity of metabolites/toxins as well as the toxicity of the residual growth medium, contaminants and co-formulants, are important endpoints in assessing adverse effects arising from the plant protection product;
- (c) colonisation, infectiveness and toxicity comprise a complex set of interactions between micro-organisms and hosts and these endpoints may not be resolved easily as independent endpoints;
- (d) in combining these endpoints, the most important aspects of the micro-organism that must be assessed are:
  - ability to persist and multiply in a host (indicative of colonisation or infectivity),
  - ability to produce non-adverse or adverse effects in a host, indicative of infectivity, pathogenicity, and/or toxicity;
- (e) moreover, the complexity of the biological issues should be taken into account in evaluating the hazards and risks presented by use of these plant protection products for human and animals. An assessment of pathogenicity and infectiveness is necessary even if the potential of exposure is deemed low;
- (f) for risk assessment purposes the acute toxicity studies used should, where available, include at least two doses (e.g. one very high dose and one corresponding to the expected exposure under practical conditions).

##### 2.6.1. Effects on human or animal health arising from the plant protection product

2.6.1.1. Member States shall evaluate operator exposure to the micro-organism, and/or to toxicologically relevant compounds in the plant protection product (e.g. their metabolites/toxins, residual growth medium, contaminants and co-formulants), likely to occur under the proposed conditions of use (including in particular dose, application method and climatic conditions). Realistic data on exposure levels must be used and, if such data are not available, a suitable, validated calculation model. When available, a European harmonised generic exposure database for plant protection products should be used.

(a) This evaluation will take into consideration the following information:

- (i) the medical data and the toxicity, infectivity and pathogenicity studies as provided for in Annex IIB, and the results of the evaluation thereof. Tier 1 tests should permit an evaluation to be made of a micro-organism with respect to its ability to persist or grow in the host and its ability to cause effects/reactions in the host. Parameters that indicate the absence of ability to persist and multiply in the host, and the absence of ability to produce non-adverse or adverse effects in a host, include fast and complete clearance from the body, no activation of the immune system, no histopathological changes, and for replication temperatures far below or far above mammalian body temperatures. These parameters can in some cases be assessed using acute studies and existing human data, and sometimes can only be assessed using repeated dose studies.

Evaluation based on relevant parameters of Tier 1 tests should lead to an assessment of the possible effects of occupational exposure, taking into account the intensity and duration of exposure including exposure due to repeated use during practical use.

The toxicity of certain metabolites/toxins can only be assessed, if it has been demonstrated that the test animals are actually exposed to these metabolites/toxins;

- (ii) other relevant information on the micro-organism, the metabolites/toxins, residual growth medium, contaminants and co-formulants in the plant protection product, such as their biological, physical and chemical properties (e.g. survival of the micro-organism at the body temperature of humans and animals, ecological niche, behaviour of the micro-organism and/or metabolites/toxins during application);

(iii) the toxicological studies provided for in Annex IIIB;

(iv) other relevant information provided for in Annex IIIB such as:

- composition of the preparation,
- nature of the preparation,
- size, design and type of packaging,
- field of use and nature of the crop or target,
- method of application including handling, loading and mixing of the plant protection product,
- exposure reduction measures recommended,
- protective clothing recommendations,
- maximum application rate,
- minimum spray application volume stated on the label,
- number and timing of applications.

(b) On the basis of the information mentioned in (a) the following overall end-points should be established for single or repeated operator exposure following the intended use:

- persistence or growth of the micro-organism in the host,
- adverse effects observed,
- observed or expected effects of contaminants (including contaminating micro-organisms),
- observed or expected effects of relevant metabolites/toxins.

If there are indications of colonisation in the host and/or if any adverse effects, indicative of toxicity/infectivity are observed, taking into account the exposure scenario (i.e. acute or repeated exposure), further testing is indicated.

(c) This evaluation shall be made for each type of application method and application equipment proposed for use of the plant protection product as well as for the different types and sizes of containers to be used, taking into account mixing, loading operations, application of the plant protection product and cleaning and routine maintenance of application equipment. Where relevant, other authorised uses of the plant protection product in the area of envisaged use containing the same active substance or which give rise to the same residues may also be taken into account. It should be taken into account that if replication of the micro-organism is expected, exposure assessment could be highly speculative.

(d) The absence or presence of the potential for colonisation or the possibility of effects in operators at the tested dose levels as provided for in Annex IIB and IIIB should be assessed with regard to measured or estimated levels of human exposure. This risk assessment, preferably quantitative, should include consideration of e.g. mode of action, biological, physical and chemical properties of the micro-organism and other substances in the formulation.

2.6.1.2. Member States shall examine information relating to the nature and characteristics of the packaging proposed with particular reference to the following aspects:

- (a) the type of packaging,
- (b) its dimensions and capacity,
- (c) the size of the opening,
- (d) the type of closure,
- (e) its strength, leakproofness and resistance to normal transport and handling,
- (f) its resistance to and compatibility with the contents.

2.6.1.3. Member States shall examine the nature and characteristics of the protective clothing and equipment proposed with particular reference to the following aspects:

- (a) obtainability and suitability,
- (b) effectiveness,
- (c) ease of wearing taking into account physical stress and climatic conditions,
- (d) resistance to and compatibility with the plant protection product.

2.6.1.4. Member States shall evaluate the possibility of exposure of other humans (workers exposed after the application of the plant protection product, such as re-entering workers, or bystanders) or animals to the micro-organism and/or to other toxicologically relevant compounds in the plant protection product under the proposed conditions of use. This evaluation will take into consideration the following information:

- (a) the medical data and the toxicity, infectivity and pathogenicity studies provided for in Annex IIB, and the results of the evaluation thereof. Tier 1 tests should permit an evaluation to be made of a micro-organism with respect to its ability to persist or grow in the host and its ability to cause effects/reactions in the host. Parameters that indicate the absence of ability to persist and multiply in the host, and the absence of ability to produce non-adverse or adverse effects in a host, include rapid and complete clearance from the body, no activation of the immune system, no histopathological changes, and inability to replicate at mammalian body temperatures. These parameters can in some cases be assessed using acute studies and existing human data, and sometimes can only be assessed using repeated dose studies.

Evaluation based on relevant parameters of Tier 1 tests should lead to an assessment of the possible effects of occupational exposure, taking into account the intensity and duration of exposure, including exposure due to repeated use during practical use.

The toxicity of certain metabolites/toxins can only be assessed, if it has been demonstrated that the test animals are actually exposed to these metabolites/toxins;

- (b) other relevant information on the micro-organism, the metabolites/toxins, residual growth medium, contaminants and co-formulants in the plant protection product, such as their biological, physical and chemical properties (e.g. survival of the micro-organism at the body temperature of humans and animals, ecological niche, behaviour of the micro-organism and/or metabolites/toxins during application);
- (c) the toxicological studies provided for in Annex IIIB;
- (d) other relevant information on the plant protection product as provided for in Annex IIIB such as:
- re-entry periods, necessary waiting periods or other precautions to protect humans and animals,
  - method of application, in particular spraying,
  - maximum application rate,
  - minimum spray application volume,
  - composition of the preparation,
  - excess remaining on plants and plant products after treatment, taking into account the influence of factors such as temperature, UV light, pH and the presence of certain substances,
  - further activities whereby workers are exposed.

2.6.2. Effects on human or animal health arising from residues

In the evaluation, non-viable and viable residues must be addressed separately. Viruses and viroids should be considered as viable residues since they are capable of transferring genetic material, although strictly speaking they are not living.

#### 2.6.2.1. Non-viable residues

- (a) Member States shall evaluate the possibility of exposure of humans or animals to non-viable residues and their degradation products via the food chain due to the possible occurrence of such residues in or on edible parts of treated crops. In particular, the following information should be taken into account:
- the stage of development of the micro-organism at which non-viable residues are produced,
  - the development stages/life cycle of the micro-organism under typical environmental conditions; in particular, attention shall be paid to the assessment of the likelihood of survival and multiplication of the micro-organism in or on crops, food or feed, and, as a consequence, the likelihood of the production of non-viable residues,
  - the stability of relevant non-viable residues (including the effects of factors such as temperature, UV light, pH and the presence of certain substances),
  - any experimental study showing whether or not relevant non-viable residues are translocated in plants,
  - data concerning the proposed good agricultural practice (including number and timing of applications, maximum application rate and minimum spray application volume, proposed pre-harvest intervals for envisaged uses, or withholding periods or storage periods, in the case of post-harvest uses) and additional data on application as provided for in Annex IIIB,
  - where relevant, other authorised uses of plant protection products in the area of envisaged use, i.e. containing the same residues, and
  - the natural occurrence of non-viable residues on edible plant parts as a consequence of naturally occurring micro-organisms.
- (b) Member States shall evaluate the toxicity of non-viable residues and their degradation products having regard in particular to the specific information provided in accordance with Annex IIB and IIIB.
- (c) Where non-viable residues or their degradation products are considered toxicologically relevant for humans and/or animals and when exposure is not considered negligible, the actual levels in or on the edible parts of treated crops should be determined, taking into consideration:
- analytical methods for the non-viable residues,
  - the growth curves of the micro-organism under optimal conditions,
  - the production/formation of non-viable residues at relevant moments (e.g. at the anticipated harvest time).

#### 2.6.2.2. Viable residues

- (a) Member States shall evaluate the possibility of exposure of humans or animals to viable residues via the food chain due to the possible occurrence of such residues in or on edible parts of treated crops. In particular, the following information should be taken into account:
- the likelihood of survival, the persistence and multiplication of the micro-organism in or on crops, food or feed. The various development stages/life cycle of the micro-organism should be addressed,
  - information concerning its ecological niche,

- information on fate and behaviour in the various parts of the environment,
  - the natural occurrence of the micro-organism (and/or a related micro-organism),
  - data concerning the proposed good agricultural practice (including number and timing of applications, maximum application rate and minimum spray application volume, proposed pre-harvest intervals for envisaged uses, or withholding periods or storage periods in the case of post-harvest uses) and additional data on application as provided for in Annex IIB,
  - where relevant, other authorised uses of plant protection products in the area of envisaged use, i.e. containing the same micro-organism or which result in the same residues.
- (b) Member States shall evaluate the specific information concerning the ability of viable residues to persist or grow in the host and the ability of such residues to cause effects/reactions in the host. In particular, the following information should be taken into account:
- the medical data and toxicity, infectivity and pathogenicity studies provided for in Annex IIB, and the results of the evaluation thereof,
  - the development stages/life cycle of the micro-organism under typical environmental conditions (e.g. in or on the treated crop),
  - the mode of action of the micro-organism,
  - the biological properties of the micro-organism (e.g. host specificity).

The various development stages/life cycle of the micro-organism should be addressed.

- (c) In the event that viable residues are considered to be toxicologically relevant for humans and/or animals and if exposure is not considered negligible, the actual levels in or on the edible parts of treated crops should be determined, taking into consideration:
- analytical methods for the viable residues,
  - the growth curves of the micro-organism under optimal conditions,
  - the possibilities of extrapolating data from one crop to another.

#### 2.7. *Fate and behaviour in the environment*

The biocomplexity of the ecosystems and interactions in the microbial communities concerned must be taken into account.

Information on the origin and properties (e.g. specificity) of the micro-organism/its residual metabolites/toxins and its intended use forms the basis for an assessment of environmental fate and behaviour. The mode of action of the micro-organism should be taken into consideration.

An assessment shall be made of the fate and behaviour of any known relevant metabolite that is produced by the micro-organism. The assessment shall be made for each environmental compartment, and shall be triggered on the basis of the criteria specified in section 7 (iv) of Annex IIB.

In the assessment of the environmental fate and behaviour of plant protection products, Member States shall have regard to all aspects of the environment, including biota. The potential for persistence and multiplication of micro-organisms has to be assessed in all environmental compartments unless it can be justified that particular micro-organisms will not reach a specific compartment. The mobility of micro-organisms and their residual metabolites/toxins must be considered.

- 2.7.1. Member States shall evaluate the possibility of contamination of ground water, surface water and drinking water under the proposed conditions of use of the plant protection product.

In the overall assessment, Member States should pay particular attention to potential adverse effects on humans through groundwater contamination, when the active substance is applied in regions with vulnerable conditions, such as drinking water abstraction areas.

- 2.7.2. Member States shall evaluate the risk for the aquatic compartment where the possibility of the exposure of aquatic organisms has been established. A micro-organism may give rise to risks because of its potential through multiplication to establish itself in the environment and can therefore have a long-lasting or permanent impact on microbial communities or their predators.

This evaluation will take into consideration the following information:

- (a) the biological properties of the micro-organism,
- (b) the survival of the micro-organism in the environment,
- (c) its ecological niche,
- (d) the natural background level of the micro-organism, where it is indigenous,
- (e) information on fate and behaviour in the various parts of the environment,
- (f) where relevant, information on potential interference with analytical systems used for the control of the quality of drinking water as provided for in Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption <sup>(1)</sup>,
- (g) where relevant, other authorised uses of plant protection products in the area of envisaged use, e. g. containing the same active substance or which gives rise to the same residues.

- 2.7.3. Member States shall evaluate the possibility of exposure of organisms in the atmosphere to the plant protection product under the proposed conditions of use; if this possibility exists they shall evaluate the risk for the atmosphere. The transport, short-range and long-range, of the micro-organism in the atmosphere should be taken into account.

- 2.7.4. Member States shall evaluate the possibility of exposure of organisms in the terrestrial compartment to the plant protection product under the proposed conditions of use; if this possibility exists they shall evaluate the risks arising for the terrestrial compartment. A micro-organism may give rise to risks because of its potential through multiplication to establish itself in the environment and can therefore have a long-lasting or permanent impact on microbial communities or their predators.

This evaluation will take into consideration the following information:

- (a) the biological properties of the micro-organism,
- (b) the survival of the micro-organism in the environment,
- (c) its ecological niche,
- (d) the natural background level of the micro-organism, where it is indigenous,
- (e) information on fate and behaviour in the various parts of the environment,

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<sup>(1)</sup> OJ L 330, 5.12.1998, p. 32. Directive as last amended by Regulation (EC) No 1882/2003 of the European Parliament and of the Council (OJ L 284, 31.10.2003, p. 1).

- (f) where relevant, other authorised uses of plant protection products in the area of envisaged use, e. g. containing the same active substance or which gives rise to the same residues.

#### 2.8. *Effects on and exposure of non-target organisms*

Information on the ecology of the micro-organism and effects on the environment should be assessed as well as possible exposure levels and the effects of its relevant metabolites/toxins. An overall assessment of the environmental risks that the plant protection product may cause, taking into account the normal levels of exposure to micro-organisms both in the environment as well as in the body of organisms, is necessary.

Member States shall evaluate the possibility of exposure of non-target organisms under the proposed conditions of use and if this possibility exists they shall evaluate the risks arising for the non-target organisms concerned.

Where applicable, an assessment of infectivity and pathogenicity is necessary, unless it can be justified that non-target organisms will not be exposed.

To assess the possibility of exposure the following information should also be taken into consideration:

- (a) the survival of the micro-organism in the respective compartment,
- (b) its ecological niche,
- (c) the natural background level of the micro-organism, where it is indigenous,
- (d) information on fate and behaviour in the various parts of the environment,
- (e) where relevant, other authorised uses of the plant protection product in the area of envisaged use containing the same active substance or which give rise to the same residues.

##### 2.8.1. Member States shall evaluate the possibility of exposure of and effects on terrestrial wildlife (non-domestic birds, mammals and other terrestrial vertebrates).

2.8.1.1. A micro-organism may give rise to risks because of its potential to infect and multiply in avian and mammalian host systems. Whether or not identified risks could be changed due to the formulation of the plant protection product shall be assessed, taking into account the following information on the micro-organism:

- (a) its mode of action,
- (b) other biological properties,
- (c) studies on mammalian toxicity, pathogenicity and infectivity,
- (d) studies on avian toxicity, pathogenicity and infectivity.

2.8.1.2. A plant protection product may give rise to toxic effects due to the action of toxins or co-formulants. For the assessment of such effects, the following information should be taken into consideration:

- (a) studies on mammalian toxicity,
- (b) studies on avian toxicity,
- (c) information on fate and behaviour in the various parts of the environment.

If mortality or signs of intoxication are observed in the tests the evaluation must include a calculation of toxicity/exposure ratios based on the quotient of the  $LD_{50}$  value and the estimated exposure expressed in mg/kg body weight.

2.8.2. Member States shall evaluate the possibility of exposure of and effects on aquatic organisms.

2.8.2.1. A micro-organism may give rise to risks because of its potential to infect and multiply in aquatic organisms. Whether or not identified risks could be changed due to the formulation of the plant protection product shall be assessed, taking into account the following information on the micro-organism:

- (a) its mode of action,
- (b) other biological properties,
- (c) studies on toxicity, pathogenicity and infectivity.

2.8.2.2. A plant protection product may give rise to toxic effects due to the action of toxins or co-formulants. For the assessment of such effects the following information should be taken into consideration:

- (a) studies on toxicity to aquatic organisms,
- (b) information on fate and behaviour in the various parts of the environment.

If mortality or signs of intoxication are observed in the tests the evaluation must include a calculation of toxicity/exposure ratios based on the quotient of the  $EC_{50}$  value and/or the NOEC value and the estimated exposure.

2.8.3. Member States shall evaluate the possibility of exposure of and effects on bees.

2.8.3.1. A micro-organism may give rise to risks because of its potential to infect and multiply in bees. Whether or not identified risks could be changed due to the formulation of the plant protection product shall be assessed, taking into account the following information on the micro-organism:

- (a) its mode of action,
- (b) other biological properties,
- (c) studies on toxicity, pathogenicity and infectivity.

2.8.3.2. A plant protection product may give rise to toxic effects due to the action of toxins or co-formulants. For the assessment of such effects the following information should be taken into consideration:

- (a) studies on toxicity to bees,
- (b) information on fate and behaviour in the various parts of the environment.

If mortality or signs of intoxication are observed in the tests the evaluation must include a calculation of the hazard quotient, based on the quotient of the dose in g/ha and the  $LD_{50}$  value in  $\mu\text{g}/\text{bee}$ .

2.8.4. Member States shall evaluate the possibility of exposure of and effects on arthropods other than bees.

2.8.4.1. A micro-organism may give rise to risks because of its potential to infect and multiply in arthropods other than bees. Whether or not identified risks could be changed due to the formulation of the plant protection product shall be assessed, taking into account the following information on the micro-organism:

- (a) its mode of action,
- (b) other biological properties,

(c) studies on toxicity, pathogenicity and infectivity to honeybees and other arthropods.

2.8.4.2. A plant protection product may give rise to toxic effects due to the action of toxins or co-formulants. For the assessment of such effects the following information should be taken into consideration:

- (a) studies on toxicity to arthropods,
- (b) information on fate and behaviour in the various parts of the environment,
- (c) available data from biological primary screening.

If mortality or signs of intoxication are observed in the tests the evaluation must include a calculation of toxicity/exposure ratios based on the quotient of the  $ER_{50}$  value (effective rate) and the estimated exposure.

2.8.5. Member States shall evaluate the possibility of exposure of and effects on earthworms.

2.8.5.1. A micro-organism may give rise to risks because of its potential to infect and multiply in earthworms. Whether or not identified risks could be changed due to the formulation of the plant protection product shall be assessed, taking into account the following information on the micro-organism:

- (a) its mode of action,
- (b) other biological properties,
- (c) studies on earthworm toxicity, pathogenicity and infectivity.

2.8.5.2. A plant protection product may give rise to toxic effects due to the action of toxins or co-formulants. For the assessment of such effects the following information should be taken into consideration:

- (a) studies on earthworm toxicity,
- (b) information on fate and behaviour in the various parts of the environment.

If mortality or signs of intoxication are observed in the tests the evaluation must include a calculation of toxicity/exposure ratios based on the quotient of the  $LC_{50}$  value and the estimated exposure expressed in mg/kg dry weight soil.

2.8.6. Member States shall evaluate the possibility of exposure of and effects on soil micro-organisms.

2.8.6.1. A micro-organism may give rise to risks because of its potential to interfere with nitrogen and carbon mineralisation in the soil. Whether or not identified risks could be changed due to the formulation of the plant protection product shall be assessed, taking into account the following information on the micro-organism:

- (a) its mode of action,
- (b) other biological properties.

Experimental data are not normally required, i.e. where it can be justified that a proper risk assessment can be performed with the available information.

2.8.6.2. Member States shall evaluate the impact of exotic/non-indigenous micro-organisms on non-target micro-organisms and on their predators following use of the plant protection product according to the proposed conditions of use. Experimental data are not normally required, i.e. where it can be justified that a proper risk assessment can be performed with the available information.

2.8.6.3. A plant protection product may give rise to toxic effects due to the action of toxins or co-formulants. For the assessment of such effects the following information should be taken into consideration:

- (a) information on fate and behaviour in the various parts of the environment,
- (b) all available information from biological primary screening.

#### 2.9. *Conclusions and proposals*

Member States shall draw conclusions on the need for further information and/or testing and the need for measures to limit the risks arising. Member States shall justify proposals for the classification and labelling of plant protection products.

### C. **DECISION-MAKING**

#### 1. **General principles**

- 1.1. Where appropriate, Member States shall impose conditions or restrictions on the authorisations they grant. The nature and severity of these conditions or restrictions must be selected on the basis of, and be appropriate to, the nature and extent of the expected advantages and the risks likely to arise.
- 1.2. Member States shall ensure that decisions taken to grant authorisations, take account of the agricultural, plant health or environmental (including climatic) conditions in the areas of envisaged use. Such considerations may result in specific conditions and restrictions on use, and, in authorisation being granted for some but not other areas within the Member State in question.
- 1.3. Member States shall ensure that the authorised amounts, in terms of rates and number of applications, are the minimum necessary to achieve the desired effect even where higher amounts would not result in unacceptable risks to human or animal health or to the environment. The authorised amounts must be differentiated according to, and be appropriate to, the agricultural, plant health or environmental (including climatic) conditions in the various areas for which an authorisation is granted. However, the rates and the number of applications may not give rise to undesirable effects such as the development of resistance.
- 1.4. Member States shall ensure that decisions respect the principles of integrated pest control if the plant protection product is intended for use in conditions where these principles are relied on.
- 1.5. Since the evaluation is to be based on data concerning a limited number of representative species, Member States shall ensure that use of plant protection products does not have any long-term repercussions for the abundance and diversity of non-target species.
- 1.6. Before issuing an authorisation, Member States shall ensure that the label of the plant protection product:
  - (a) fulfils the requirements of Article 16 of this Directive,
  - (b) also contains the information on protection of users required by Community legislation on worker protection,
  - (c) specifies in particular the conditions or restrictions under which the plant protection product may or may not be used as referred to in points 1.1 to 1.5,

- (d) The authorisation shall mention the particulars indicated in Article 16(1)(g) and (h) of this Directive and Article 10(1.2), (2.4), (2.5) and (2.6) of Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations <sup>(1)</sup>.

1.7. Before issuing authorisations, Member States shall:

- (a) ensure that the proposed packaging is in accordance with the provisions of Directive 1999/45/EC;
- (b) ensure that:
- the procedures for destruction of the plant protection product,
  - the procedures for neutralisation of any adverse effects of the plant protection product if it is accidentally dispersed, and
  - the procedures for the decontamination and destruction of the packaging,

are in accordance with the relevant regulatory provisions.

1.8. No authorisation shall be granted unless all the requirements referred to in point 2 are satisfied. However, when one or more of the specific decision-making requirements referred to in point 2.4 are not fully satisfied, authorisations shall be granted only where the advantages of the use of the plant protection product under the proposed conditions of use outweigh the possible adverse effects of its use. Any restrictions on use of the plant protection product relating to non-compliance with some of the requirements referred to in point 2.4 must be mentioned on the label. These advantages can be in terms of:

- (a) advantages for and compatibility with integrated control measures or organic farming,
- (b) facilitating strategies to minimise the risk of development of resistance,
- (c) reduced risk for operators and consumers,
- (d) reduced contamination of the environment and reduced impact on non-target species.

1.9. Where an authorisation has been granted according to the requirements provided for in this Annex, Member States may, by virtue of Article 4(6):

- (a) define, where possible, preferably in close cooperation with the applicant, measures to improve the performance of the plant protection product, and/or
- (b) define, where possible, in close cooperation with the applicant, measures to reduce further the exposure that could occur during and after use of the plant protection product.

Member States shall inform applicants of any measures identified under (a) or (b) and shall invite applicants to provide any supplementary data and information necessary to demonstrate performance or potential risks arising under the changed conditions.

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<sup>(1)</sup> OJ L 200, 30.7.1999, p. 1. Directive as last amended by Directive 2004/66/EC (OJ L 168, 1.5.2004, p. 35).

- 1.10. Member States shall ensure, as far as is practically possible, that for all micro-organisms that are considered for an authorisation, the applicant has taken into account all available relevant knowledge and information in literature at the time of submission.
- 1.11. Where the micro-organism has been genetically modified, as defined in Directive 2001/18/EC, no authorisation shall be granted unless the evaluation conducted in accordance with Directive 2001/18/EC has been submitted, as required under Article 1(3) of that Directive. The relevant decision taken by the competent authorities in accordance with Directive 2001/18/EC must be provided.
- 1.12. In accordance with Article 1(3) of this Directive, no authorisation shall be granted for a plant protection product containing a genetically modified organism unless authorisation is granted according to the provisions in Directive 2001/18/EC, part C, under which that organism can be released into the environment.
- 1.13. No authorisation shall be granted if relevant metabolites/toxins (i.e. those expected to be of concern for human health and/or the environment) known to be formed by the micro-organism, and/or by microbial contaminants are present in the plant protection product, unless it can be shown that the amount present is at an acceptable level before and after its proposed use.
- 1.14. Member States shall ensure that adequate quality control measures are applied to ensure the identity of the micro-organism and contents of the plant protection product. Such measures must include a Hazard Analysis Critical Control Point (HACCP) system or equivalent system.

## 2. **Specific principles**

The specific principles shall apply without prejudice to the general principles referred to in Section 1.

### 2.1. *Identity*

For each authorisation granted the Member States shall ensure that the micro-organism concerned is deposited at an internationally recognised culture collection and has an accession number. Each micro-organism must be identified and named at the species level and characterised at the strain level. There must also be information as to whether or not the micro-organism is a wild type or a spontaneous or induced mutant, or a genetically modified organism.

### 2.2. *Biological and technical properties*

- 2.2.1. There must be sufficient information to permit assessment of the minimum and maximum content of the micro-organism in the material used for the manufacturing of plant protection products, as well as in the plant protection product. The content of other components and formulants in the plant protection product and contaminating micro-organisms derived from the production process must to the extent possible be defined. Member States shall ensure that the level of contaminating organisms is controlled to an acceptable level. In addition: the physical nature and state of the plant protection product must be specified, preferably according to the 'Catalogue of pesticide formulation types and international coding system (CropLife International Technical Monograph No 2, 5th Edition, 2002)'.
- 2.2.2. No authorisation shall be granted if, at any stage in the development of a microbial plant protection product, it becomes apparent, on the basis of a build-up of resistance, or transfer of resistance, or other mechanism, that there may be interference with the effectiveness of an anti-microbial agent used in human or animal medicine.

### 2.3. *Further information*

No authorisation shall be granted unless full information is provided on the continuous quality control of the production method, production process and plant protection product. In particular, the occurrence of spontaneous changes in major characteristics of the micro-organism and the absence/presence of contaminating organisms shall be considered. The quality assurance criteria for production and the techniques used to ensure a uniform plant protection product must to the extent possible be described and specified.

### 2.4. *Efficacy*

#### 2.4.1. Performance

2.4.1.1. No authorisation shall be granted where the proposed uses include recommendations for the control of or protection against organisms which are not considered to be harmful on the basis of experience acquired or scientific evidence under normal agricultural, plant health and environmental (including climatic) conditions in the areas of proposed use or where the other intended effects are not considered to be beneficial under those conditions.

2.4.1.2. The level, consistency and duration of control or protection or other intended effects must be similar to those resulting from the use of suitable reference products. If no suitable reference product exists, the plant protection product must be shown to give a defined benefit in terms of the level, consistency and duration of control or protection or other intended effects under the agricultural, plant health and environmental (including climatic) conditions in the area of proposed use.

2.4.1.3. Where relevant, yield response when the plant protection product is used and reduction of loss in storage must be quantitatively and/or qualitatively similar to those resulting from the use of suitable reference products. If no suitable reference product exists, the plant protection product must be shown to give a consistent and defined quantitative and/or qualitative benefit in terms of yield response and reduction of loss in storage under the agricultural, plant health and environmental (including climatic) conditions in the area of proposed use.

2.4.1.4. Conclusions as to the performance of the preparation must be valid for all areas of the Member State in which it is to be authorised, and for all conditions under which its use is proposed, except where the proposed label specifies that the preparation is intended for use in certain specified circumstances (e.g. light infestations, particular soil types or particular growing conditions).

2.4.1.5. Where proposed label claims include requirements for use of the preparation with other specified plant protection products or adjuvants as a tank mix, the mixture must achieve the desired effect and comply with the principles referred to in points 2.4.1.1 to 2.4.1.4.

Where proposed label claims include recommendations for use of the preparation with specified plant protection products or adjuvants as a tank mix, Member States shall not accept the recommendations unless they are justified.

2.4.1.6. If there is evidence of a development of resistance of pathogens towards the plant protection product, the Member State shall decide if the submitted resistance management strategy addresses this adequately and sufficiently.

2.4.1.7. Only plant protection products containing non-viable micro-organisms may be authorised for use to control vertebrate species. The intended effect on vertebrates to be controlled shall be obtained without unnecessary suffering and unnecessary pain for these animals.

#### 2.4.2. Absence of unacceptable effects on plants and plant products

- 2.4.2.1. There must be no relevant phytotoxic effects on treated plants or plant products except where the proposed label indicates appropriate limitations of use.
- 2.4.2.2. There must be no reduction of yield at harvest due to phytotoxic effects below that which could be obtained without the use of the plant protection product, unless this reduction is compensated for by other advantages such as an enhancement of the quality of the treated plants or plant products.
- 2.4.2.3. There must be no unacceptable adverse effects on the quality of treated plants or plant products, except in the case of adverse effects on processing where proposed label claims specify that the preparation should not be applied to crops to be used for processing purposes.
- 2.4.2.4. There must be no unacceptable adverse effects on treated plants or plant products used for propagation or reproduction, such as effects on viability, germination, sprouting, rooting and establishment, except where proposed label claims specify that the preparation should not be applied to plants or plant products to be used for propagation or reproduction.
- 2.4.2.5. There must be no unacceptable impact on succeeding crops, except where proposed label claims specify that particular crops, which would be affected, should not be grown following the treated crop.
- 2.4.2.6. There must be no unacceptable impact on adjacent crops, except where proposed label claims specify that the preparation should not be applied when particular sensitive adjacent crops are present.
- 2.4.2.7. Where proposed label claims include requirements for use of the preparation with other plant protection products or adjuvants, as a tank mix, the mixture must comply with the principles referred to in points 2.4.2.1 to 2.4.2.6.
- 2.4.2.8. The proposed instructions for cleaning the application equipment must be both practical and effective so that they can be applied with ease so as to ensure the removal of residual traces of the plant protection product which could subsequently cause damage.

#### 2.5. *Identification/detection and quantification methods*

The methods proposed must reflect the latest techniques. Methods for post-authorisation monitoring should involve the use of commonly available reagents and equipment.

- 2.5.1. No authorisation shall be granted unless there is an adequate method of sufficient quality to identify and quantify the micro-organism and non-viable components (e.g. toxins, impurities and co-formulants) in the plant protection product. In the case of a plant protection product containing more than one micro-organism, the recommended methods should be capable of identifying and determining the content of each one.
- 2.5.2. No authorisation shall be granted unless there are adequate methods for post-registration control and monitoring of viable and/or non-viable residues. Methods must be available for analysis of:
  - (a) plants, plant products, foodstuffs of plant and animal origin and feedingstuffs if toxicologically relevant residues occur. Residues are considered relevant if a maximum residue level (MRL) or a waiting or re-entry safety period or other such precaution is required,
  - (b) soil, water, air and/or body tissues if toxicologically, ecotoxicologically or environmentally relevant residues occur.

2.6. *Impact on human and animal health*

2.6.1. Effects on human and animal health arising from the plant protection product

2.6.1.1. No authorisation shall be granted if on the basis of the information provided in the dossier it appears that the micro-organism is pathogenic to humans or non-target animals under the proposed conditions of use.

2.6.1.2. No authorisation shall be granted if the micro-organism and/or the plant protection product containing the micro-organism might, under the recommended conditions of use, including a realistic worst case scenario, colonise or cause adverse effects in humans or animals.

When making a decision on the authorisation of the microbial plant protection product, Member States shall consider possible effects on all human populations, namely professional users, non-professional users and humans exposed directly or indirectly through the environment and at work, and animals.

2.6.1.3. All micro-organisms should be regarded as potential sensitisers, unless it is established by means of relevant information that there is no risk of sensitisation, taking into account immuno-compromised and other sensitive individuals. Authorisations granted shall therefore specify that protective clothing and suitable gloves be worn and that the plant protection product containing the micro-organism should not be inhaled. Moreover, the proposed conditions of use may require use of additional items of protective clothing and equipment.

Where the proposed conditions of use require use of items of protective clothing, no authorisation shall be granted unless those items are effective and in accordance with relevant Community provisions, and are readily obtainable by the user and unless it is feasible to use them under the conditions of use of the plant protection product, taking into account climatic conditions in particular.

2.6.1.4. No authorisation shall be granted if it is known that transfer of genetic material from the micro-organism to other organisms may lead to adverse effects on human and animal health, including resistance to known therapeutic substances.

2.6.1.5. Plant protection products which, because of particular properties, or which, if mishandled or misused, could lead to a high degree of risk must be subject to particular restrictions such as restrictions on the size of packaging, formulation type, distribution, use or manner of use. Moreover, plant protection products which are classified as very toxic may not be authorised for use by non-professional users.

2.6.1.6. Waiting and re-entry safety periods or other precautions must be established in such a way that no colonisation of or adverse effects on bystanders or workers exposed after application of the plant protection product are expected.

2.6.1.7. Waiting and re-entry safety periods or other precautions must be established in such a way that no colonisation of or adverse effects on animals are expected.

2.6.1.8. Waiting and re-entry periods or other precautions to ensure that no colonisation or adverse effects are expected must be realistic; if necessary, special precautionary measures must be prescribed.

2.6.1.9. The conditions of authorisation shall be in compliance with Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work <sup>(1)</sup>, and Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work <sup>(2)</sup>. The experimental data and information relevant to the recognition of the symptoms of infection or pathogenicity and on the effectiveness of first aid and therapeutic measures provided shall be considered. The conditions of authorisation shall also be in compliance with Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work <sup>(3)</sup>. The conditions of authorisation shall also be in compliance with Council Directive 89/656/EEC of 30 November 1989 on the minimum health and safety requirements for the use by workers of personal protective equipment at the workplace <sup>(4)</sup>.

#### 2.6.2. Effects on human and animal health arising from residues

2.6.2.1. No authorisation shall be granted unless there is sufficient information for plant protection products containing the micro-organism, to decide that there is no harmful effect on human or animal health arising from exposure to the micro-organism, its residual traces and metabolites/toxins remaining in or on plants or plant products.

2.6.2.2. No authorisation shall be granted unless viable residues and/or non-viable residues occurring reflect the minimum quantities of the plant protection product necessary to achieve adequate control corresponding to good agricultural practice, applied in such a manner (including pre-harvest intervals or withholding periods or storage periods) that the viable residues and/or toxins at harvest, slaughter or after storage are reduced to a minimum.

#### 2.7. *Fate and behaviour in the environment*

2.7.1. No authorisation shall be granted if the available information indicates that there may be unacceptable adverse environmental effects due to the fate and behaviour of the plant protection product in the environment.

2.7.2. No authorisation shall be granted if contamination of ground water, surface water or drinking water expected as a result of the use of a plant protection product under the proposed conditions of use, may cause interference with the analytical systems for the control of the quality of drinking water provided for in Directive 98/83/EC.

2.7.3. No authorisation shall be granted if the contamination of groundwater expected as a result of the use of a plant protection product under the proposed conditions of use contravenes or exceeds whichever of the following is the lower:

(a) the parameters or maximum permissible concentrations laid down by Directive 98/83/EC, or

(b) the parameters or maximum permissible concentrations laid down for components in the plant protection product such as relevant metabolites/toxins in accordance with Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy <sup>(5)</sup>, or

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<sup>(1)</sup> OJ L 131, 5.5.1998, p. 11.

<sup>(2)</sup> OJ L 262, 17.10.2000, p. 21.

<sup>(3)</sup> OJ L 158, 30.4.2004 p. 50.

<sup>(4)</sup> OJ L 393, 30.12.1989, p. 18.

<sup>(5)</sup> OJ L 327, 22.12.2000, p. 1. Directive as amended by Decision No 2455/2001/EC.

- (c) the parameters for the micro-organism or the maximum concentration laid down by the Commission for components in the plant protection product such as relevant metabolites/toxins when including the micro-organism in Annex I, on the basis of appropriate data, in particular, toxicological data, or, where that concentration has not been laid down, the concentration corresponding to 1/10 of the acceptable daily intake (ADI) laid down when the micro-organism was included in Annex I,

unless it is scientifically demonstrated that under relevant field conditions the lower of the parameters or concentrations is not contravened or exceeded.

2.7.4. No authorisation shall be granted if the contamination of surface water expected as a result of the use of a plant protection product under the proposed conditions of use:

- (a) exceeds, where the surface water in or from the area of envisaged use is intended for the extraction of drinking water, the parameters or values established in accordance with Council Directive 75/440/EEC of 16 June 1975 concerning the quality required of surface water intended for the abstraction of drinking water in the Member States <sup>(1)</sup>, or
- (b) exceeds the parameters or values for components in the plant protection product, such as relevant metabolites/toxins, established in accordance with Directive 2000/60/EC or
- (c) has an impact deemed unacceptable on non-target species, including animals, according to the relevant requirements provided for in point 2.8.

The proposed instruction for use of the plant protection product, including procedures for cleaning application equipment, must be such that the likelihood of accidental contamination of surface water is reduced to a minimum.

2.7.5. No authorisation shall be granted if it is known that transfer of genetic material from the micro-organism to other organisms, may lead to unacceptable effects on the environment.

2.7.6. No authorisation shall be granted unless there is sufficient information on the possible persistence/competitiveness of the micro-organism and relevant secondary metabolites/toxins in or on the crop under the environmental conditions prevailing at and following the intended use.

2.7.7. No authorisation shall be granted if it can be expected that the micro-organism and/or its possible relevant metabolites/toxins will persist in the environment in concentrations considerably higher than the natural background levels, taking into account repeated applications over the years, unless a robust risk assessment indicates that the risks from accumulated plateau concentrations are acceptable.

## 2.8. *Effects on non-target organisms*

Member States shall ensure that the available information is sufficient to permit a decision to be taken as to whether or not there may be unacceptable effects on non-target species (flora and fauna), due to exposure to the plant protection product containing the micro-organism following its intended use.

Member States shall pay special attention to possible effects on beneficial organisms used for biological control and organisms playing an important role in integrated control.

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<sup>(1)</sup> OJ L 194, 25.7.1975, p. 26. Directive to be repealed from 22.12.2007 by Directive 2000/60/EC (OJ L 327, 22.12. 2000, p. 1).

- 2.8.1. Where there is a possibility of birds and other non-target terrestrial vertebrates being exposed, no authorisation shall be granted if:
- (a) the micro-organism is pathogenic to birds and other non-target terrestrial vertebrates,
  - (b) in case of toxic effects due to components in the plant protection product, such as relevant metabolites/toxins, the toxicity/exposure ratio is less than 10 on the basis of the acute LD<sub>50</sub> value or the long-term toxicity/exposure ratio is less than 5, unless it is clearly established through an appropriate risk assessment that under field conditions no unacceptable effects occur — directly or indirectly — after use of the plant protection product according to the proposed conditions of use.
- 2.8.2. Where there is a possibility of aquatic organisms being exposed, no authorisation shall be granted if:
- (a) the micro-organism is pathogenic to aquatic organisms,
  - (b) in case of toxic effects due to components in the plant protection product such as relevant metabolites/toxins, the toxicity/exposure ratio is less than 100 in case of acute toxicity (EC<sub>50</sub>) to daphnia and fish and 10 for long-term/chronic toxicity to algae (EC<sub>50</sub>), daphnia (NOEC) and fish (NOEC), unless it is clearly established through an appropriate risk assessment that under field conditions no unacceptable impact on the viability of exposed species occurs — directly or indirectly — after use of the plant protection product according to the proposed conditions of use.
- 2.8.3. Where there is a possibility of bees being exposed, no authorisation shall be granted:
- (a) if the micro-organism is pathogenic to bees,
  - (b) in case of toxic effects due to components in the plant protection product such as relevant metabolites/toxins, the hazard quotients for oral or contact exposure of honeybees are greater than 50, unless it is clearly established through an appropriate risk assessment that under field conditions there are no unacceptable effects on honeybee larvae, honeybee behaviour, or colony survival and development after use of the plant protection product according to the proposed conditions of use.
- 2.8.4. Where there is a possibility of arthropods other than bees being exposed, no authorisation shall be granted if:
- (a) the micro-organism is pathogenic to arthropods other than bees,
  - (b) in case of toxic effects due to components in the plant protection product such as relevant metabolites/toxins, unless it is clearly established through an appropriate risk assessment that under field conditions there is no unacceptable impact on those organisms after use of the plant protection product according to the proposed conditions of use. Any claims for selectivity and proposals for use in integrated pest management systems shall be substantiated by appropriate data.
- 2.8.5. Where there is a possibility of earthworms being exposed, no authorisation shall be granted if the micro-organism is pathogenic to earthworms or in the case of toxic effects due to components in the plant protection product such as relevant metabolites/toxins, the acute toxicity/exposure ratio is less than 10, or the long-term toxicity/exposure ratio is less than 5, unless it is clearly established through an appropriate risk assessment that under field conditions earthworm populations are not at risk after use of the plant protection product according to the proposed conditions of use.

- 2.8.6. Where there is a possibility of non-target soil micro-organisms being exposed, no authorisation shall be granted if the nitrogen or carbon mineralisation processes in laboratory studies are affected by more than 25 % after 100 days, unless it is clearly established through an appropriate risk assessment that under field conditions there is no unacceptable impact on the microbial community after use of the plant protection product according to the proposed conditions of use, taking account of the ability of micro-organisms to multiply.
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