[F1ANNEX VI U.K.

Textual Amendments

F1 Substituted by Council Directive 97/57/EC of 22 September 1997 establishing Annex VI to Directive 91/414/EEC concerning the placing of plant protection products on the market.

[F2PART II U.K.

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

B. EVALUATION U.K.

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 U.K.

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: U.K.

(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: U.K.

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. U.K.

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: U.K.

(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 U.K.

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 U.K.

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

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[1], 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 U.K.

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 U.K.

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

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: U.K.

(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;

(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: U.K.

(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). U.K.

(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 U.K.

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: U.K.

(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 U.K.

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

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 U.K.

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 U.K.

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: U.K.

(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: U.K.

(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. U.K.

(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. U.K.

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. U.K.

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 U.K.

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 U.K.

2.5.1.1. Non-viable components U.K.

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 U.K.

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 U.K.

2.5.2.1. Non-viable residues U.K.

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 U.K.

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 U.K.

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 U.K.

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. U.K.

(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: U.K.

(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: U.K.

(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: U.K.

(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 U.K.

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 U.K.

(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 U.K.

(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 IIIB,

— 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 U.K.

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. U.K.

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. U.K.

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[(2)],

(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. U.K.

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, 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 U.K.

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). U.K.

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: U.K.

(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: U.K.

(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. U.K.

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: U.K.

(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: U.K.

(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. U.K.

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: U.K.

(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: U.K.

(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 µg/bee.

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

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: U.K.

(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: U.K.

(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. U.K.

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: U.K.

(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: U.K.

(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. U.K.

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: U.K.

(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: U.K.

(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 U.K.

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.**]]**

Textual Amendments

F2 Inserted by 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).

(1) **[**[F1]**[**[F2]See definition of 'genetically modified' in Directive 2001/18/EC.

(2) 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).**]]**

Textual Amendments

F1 Substituted by Council Directive 97/57/EC of 22 September 1997 establishing Annex VI to Directive 91/414/EEC concerning the placing of plant protection products on the market.

F2 Inserted by 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).