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COUNCIL DIRECTIVE

of 23 April 1990

on the contained use of genetically modified micro-organisms

(90/219/EEC)

(OJ L 117, 8.5.1990, p. 1)

Amended by:

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►**M1**	Commission Directive 94/51/EC of 7 November 1994	L 297	29	18.11.1994
►**M2**	Council Directive 98/81/EC of 26 October 1998	L 330	13	5.12.1998
►**M3**	Council Decision 2001/204/EC of 8 March 2001	L 73	32	15.3.2001
►**M4**	Regulation (EC) No 1882/2003 of the European Parliament and of the Council of 29 September 2003	L 284	1	31.10.2003
►**M5**	Commission Decision 2005/174/EC of 28 February 2005	L 59	20	5.3.2005

Corrected by:

►**C1** Corrigendum, OJ L 93, 8.4.1999, p. 27 (98/81/EC)

►**C2** Corrigendum, OJ L 65, 11.3.2005, p. 39 (2005/174/EEC)

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COUNCIL DIRECTIVE

of 23 April 1990

on the contained use of genetically modified micro-organisms

(90/219/EEC)

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 130s thereof,

Having regard to the proposal from the Commission ([1]),

Having regard to the opinion of the European Parliament ([2]),

Having regard to the opinion of the Economic and Social Committee ([3]),

Whereas, under the Treaty, action by the Community relating to the environment shall be based on the principle that preventive action shall be taken and shall have as its objective to preserve, protect and improve the environment and to protect human health;

Whereas the Council Resolution of 19 October 1987 ([4]) concerning the Fourth Environmental Action Programme of the European Communities declares that measures concerning the evaluation and best use of biotechnology with regard to the environment are a priority area on which Community action should concentrate;

Whereas the development of biotechnology is such as to contribute to the economic expansion of the Member States; whereas this implies that genetically modified micro-organisms will be used in operations of various types and scale;

Whereas the contained use of genetically modified micro-organisms should be carried out in such way as to limit their possible negative consequences for human health and the environment, due attention being given to the prevention of accidents and the control of wastes;

Whereas micro-organisms, if released in the environment in one Member State in the course of their contained use, may reproduce and spread, crossing national frontiers and thereby affecting other Member States;

Whereas, in order to bring about the safe development of biotechnology throughout the Community, it is necessary to establish common measures for the evaluation and reduction of the potential risks arising in the course of all operations involving the contained use of genetically modified micro-organisms and to set appropriate conditions of use;

Whereas the precise nature and scale of risks associated with genetically modified micro-organisms are not yet fully known and the risk involved must be assessed case by case; whereas, to evaluate risk for human health and the environment, it is necessary to lay down requirements for risk assessment;

Whereas genetically modified micro-organisms should be classified in relation to the risks they present; whereas criteria should be provided for this purpose; whereas particular attention should be given to operations using the more hazardous genetically modified micro-organisms;

Whereas appropriate containment measures should be applied at the various stages of an operation to control emissions and to prevent accidents;

Whereas any person, before undertaking for the first time the contained use of a genetically modified micro-organism in a particular installation,

([1]) OJ No C 198, 28. 7. 1988, p. 9 and
OJ No C 246, 27. 9. 1989, p. 6.
([2]) OJ No C 158, 26. 6. 1989, p. 122 andOJ No C 96, 17. 4. 1990.
([3]) OJ No C 23, 30. 1. 1989, p. 45.
([4]) OJ No C 328, 7. 12. 1987, p. 1.

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should forward to the competent authority a notification so that the authority may satisfy itself that the proposed installation is appropriate to carry out the activity in a manner that does not present a hazard to human health and the environment;

Whereas it is also necessary to establish appropriate procedures for the case-by-case notification of specific operations involving the contained use of genetically modified micro-organisms, taking account of the degree of risk involved;

Whereas, in the case of operations involving high risk, the consent of the competent authority should be given;

Whereas it may be considered appropriate to consult the public on the contained use of genetically modified micro-organisms;

Whereas appropriate measures should be taken to inform any person liable to be affected by an accident on all matters relating to safety;

Whereas emergency plans should be established to deal effectively with accidents;

Whereas, if an accident occurs, the user should immediately inform the competent authority and communicate the information necessary for assessing the impact of that accident and for taking the appropriate action;

Whereas it is appropriate for the Commission, in consultation with the Member States, to establish a procedure for the exchange of information on accidents and for the Commission to set up a register of such accidents;

Whereas the contained use of genetically modified micro-organisms throughout the Community should be monitored and to this end Member States should supply certain information to the Commission;

Whereas a committee should be set up to assist the Commission on matters relating to the implementation of this Directive and to its adaptation to technical progress,

HAS ADOPTED THIS DIRECTIVE:

Article 1

This Directive lays down common measures for the contained use of genetically modified micro-organisms with a view to protecting human health and the environment.

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Article 2

For the purposes of this Directive:

(a) ‘micro-organism’ shall mean any microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material, including viruses, viroids, animal and plant cells in culture;

(b) ‘genetically modified micro-organism’ (GMM) shall mean a micro-organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

Within the terms of this definition:

(i) genetic modification occurs at least through the use of the techniques listed in Annex I, Part A;

(ii) the techniques listed in Annex I, Part B, are not considered to result in genetic modification;

(c) ‘contained use’ shall mean any activity in which micro-organisms are genetically modified or in which such GMMs are cultured, stored, transported, destroyed, disposed of or used in any other way, and for which specific containment measures are used ►C1 to limit their contact with, and to provide a high level of safety for, the general population and the environment; ◄

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(d) ‘accident’ shall mean any incident involving a significant and unintended release of GMMs in the course of their contained use which could present an immediate or delayed hazard to human health or the environment;

(e) ‘user’ shall mean any natural or legal person responsible for the contained use of GMMs;

(f) ‘notification’ shall mean the presentation of the requisite information to the competent authorities of a Member State.

Article 3

Without prejudice to Article 5(1) this Directive shall not apply:

— where genetic modification is obtained through the use of the techniques/methods listed in Annex II, Part A, or

— for contained uses involving only types of GMMs meeting the criteria listed in Annex II, Part B which establish their safety to human health and the environment. These types of GMMs shall be listed in Annex II, Part C.

Article 4

Article 5(3) and 5(6) and Articles 6 to 12 shall not apply to the transport of GMMs by road, rail, inland waterway, sea or air.

This Directive shall not apply to the storage, culture, transport, destruction, disposal or use of GMMs which have been placed on the market in accordance with Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms ([1]) or pursuant to other Community legislation, which provides for a specific environmental risk assessment similar to that laid down in the said Directive, provided that the contained use is in accordance with the conditions, if any, of the consent for placing on the market.

Article 5

1. Member States shall ensure that all appropriate measures are taken to avoid adverse effects on human health and the environment which might arise from the contained use of GMMs.

2. To this end the user shall carry out an assessment of the contained uses as regards the risks to human health and the environment that these contained uses may incur, using as a minimum the elements of assessment and the procedure set out in Annex III, sections A and B.

3. The assessment referred to in paragraph 2 shall result in the final classification of the contained uses in four classes applying the procedure set out in Annex III, which will result in the assignment of containment levels in accordance with Article 6:

Class 1: activities of no or negligible risk, that is to say activities for which level 1 containment is appropriate to protect human health as well as the environment.

Class 2: activities of low risk, that is to say activities for which level 2 containment is appropriate to protect human health as well as the environment.

Class 3: activities of moderate risk, that is to say activities for which level 3 containment is appropriate to protect human health as well as the environment.

Class 4: activities of high risk, that is to say activities for which level 4 containment is appropriate to protect human health as well as the environment.

([1]) OJ L 117, 8.5.1990, p. 15. Directive as last amended by Commission Directive 97/35/EC (OJ L 169, 27.6.1997, p. 72).

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4. Where there is doubt as to which class is appropriate for the proposed contained use, the more stringent protective measures shall be applied unless sufficient evidence, in agreement with the competent authority, justifies the application of less stringent measures.

5. The assessment referred to in paragraph (2) shall especially take into account the question of disposal of waste and effluents. Where appropriate, the necessary safety measures shall be implemented in order to protect human health and the environment.

6. A record of the assessment referred to in paragraph (2) shall be kept by the user and made available in an appropriate form to the competent authority as part of the notification pursuant to Articles 7, 9 and 10 or on request.

Article 6

1. The user shall apply, except to the extent that paragraph 2 of Annex IV allows other measures to be applied, the general principles and the appropriate containment and other protective measures set out in Annex IV corresponding to the class of the contained use, so as to keep workplace and environmental exposure to any GMMs to the lowest reasonably practicable level, and so that a high level of safety is ensured.

2. The assessment referred to in Article 5(2) and the containment and other protective measures applied shall be reviewed periodically, and forthwith if:

(a) the containment measures applied are no longer adequate or the class assigned to the contained uses is no longer correct, or

(b) there is reason to suspect that the assessment is no longer appropriate judged in the light of new scientific or technical knowledge.

Article 7

When premises are to be used for the first time for contained uses, the user shall be required to submit to the competent authorities, before commencing such use, a notification containing at least the information listed in Annex V, Part A.

Article 8

Following the notification referred to in Article 7, subsequent class 1 contained use may proceed without further notification. Users of GMMs in class 1 contained uses shall be required to keep the record of each assessment referred to in Article 5(6), which shall be made available to the competent authority on request.

Article 9

1. For first and subsequent class 2 contained uses to be carried out in premises notified in accordance with Article 7, a notification containing the information listed in Annex V, Part B shall be submitted.

2. If the premises have been the subject of a previous notification to carry out class 2 or a higher class of contained uses and any associated consent requirements have been satisfied, the class 2 contained use may proceed immediately following the new notification.

The applicant can, however, himself request a decision on a formal authorisation from the competent authority. The decision must be made within a maximum of 45 days from the notification.

3. If the premises have not been the subject of a previous notification to carry out class 2 or a higher class of contained uses, the class 2 contained use may, in the absence of any indication to the contrary from the competent authority, proceed 45 days after submission of the notification referred to in paragraph 1, or earlier with the agreement of the competent authority.

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Article 10

1. For first and subsequent class 3 or class 4 contained uses to be carried out in premises notified in accordance with Article 7, a notification containing the information listed in Annex V, Part C shall be submitted.

2. A class 3 or higher class of contained use may not proceed without the prior consent of the competent authority which shall communicate its decision in writing:

(a) at the latest 45 days after submission of the new notification, in the case of premises which have been the subject of a previous notification to carry out class 3 or a higher class of contained uses and where any associated consent requirements have been satisfied for the same or a higher class than the contained use with which it is intended to proceed;

(b) at the latest 90 days after submission of the notification, in other cases.

Article 11

1. Member States shall designate the authority or authorities competent to implement the measures which they adopt in application of this Directive and to receive and acknowledge the notifications referred to in Articles 7, 9 and 10.

2. The competent authorities shall examine the conformity of the notifications with the requirements of this Directive, the accuracy and completeness of the information given, the correctness of the assessment referred to in Article 5(2) and the class of contained uses and, where appropriate, the suitability of the containment and other protective measures, the waste management, and emergency response measures.

3. If necessary, the competent authority may:

(a) ask the user to provide further information or to modify the conditions of the proposed contained use or to amend the class assigned to the contained use(s). In this case the competent authority may require that the contained use, if proposed, does not begin, or, if in progress, is suspended or terminated, until the competent authority has given its approval on the basis of the further information obtained or of the modified conditions of the contained use;

(b) limit the time for which the contained use should be permitted or subject it to certain specific conditions.

4. For the purpose of calculating the periods referred to in Articles 9 and 10, any period of time during which the competent authority:

— is awaiting any further information which it may have requested from the notifier in accordance with paragraph 3(a), or

— is carrying out a public inquiry or consultation in accordance with Article 13

shall not be taken into account.

Article 12

If the user becomes aware of relevant new information or modifies the contained use in a way which could have significant consequences for the risks posed by it, the competent authority shall be informed as soon as possible and the notification pursuant to Articles 7, 9 and 10 shall be modified.

If information subsequently becomes available to the competent authority which could have significant consequences for the risks posed by the contained use, the competent authority may require the user to modify the conditions of, or suspend or terminate, the contained use.

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Article 13

Where a Member State considers it appropriate, it may provide that the public shall be consulted on aspects of the proposed contained use, without prejudice to Article 19.

Article 14

The competent authorities shall ensure that before a contained use commences:

(a) an emergency plan is drawn up for contained uses where failure of the containment measures could lead to serious danger, whether immediate or delayed, to humans outside the premises and/or to the environment, except where such an emergency plan has been drawn up under other Community legislation;

(b) information on such emergency plans, including the relevant safety measures to be applied, is supplied in an appropriate manner, and without their having to request it, to bodies and authorities liable to be affected by the accident. The information shall be updated at appropriate intervals. It shall also be made publicly available.

The Member States concerned shall at the same time make available to other Member States concerned, as a basis for all necessary consultation within the framework of their bilateral relations, the same information as that which is disseminated to their nationals.

Article 15

1. Member States shall take the necessary measures to ensure that, in the event of an accident, the user shall be required to inform immediately the competent authority specified in Article 11 and provide the following information:

— the circumstances of the accident,

— the identity and quantities of the GMMs concerned,

— any information necessary to assess the effects of the accident on the health of the general population and the environment,

— the measures taken.

2. Where information is given pursuant to paragraph 1, the Member States shall be required to:

— ensure that any measures necessary are taken, and immediately alert any Member States which could be affected by the accident,

— collect, where possible, the information necessary for a full analysis of the accident and, where appropriate, make recommendations to avoid similar accidents in the future and to limit the effects thereof.

Article 16

1. Member States shall be required to:

(a) consult with other Member States, likely to be affected in the event of an accident, on the proposed implementation of emergency plans;

(b) inform the Commission as soon as possible of any accident within the scope of this Directive, giving details of the circumstances of the accident, the identity and quantities of the GMMs concerned, the response measures taken and their effectiveness and an analysis of the accident, including recommendations to limit its effects and avoid similar accidents in the future.

2. The Commission, in consultation with the Member States, shall establish a procedure for the exchange of information pursuant to paragraph 1. It shall also set up and keep at the disposal of the Member States a register of accidents within the scope of this Directive, including an analysis of the causes of the accidents, experience gained and measures taken to avoid similar accidents in the future.

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Article 17

Member States shall ensure that the competent authority organizes inspections and other control measures to ensure user compliance with this Directive.

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Article 18

1. Member States shall send to the Commission, at the end of each year, a summary report on class 3 and class 4 contained uses notified during that year pursuant to Article 10 including the description, purpose and risks of the contained use(s).

2. Every three years, Member States shall send the Commission a summary report on their experience with this Directive, the first time being on 5 June 2003.

3. Every three years, the Commission shall publish a summary based on the reports referred to in paragraph 2, the first time being on 5 June 2004.

4. The Commission may publish general statistical information on the implementation of this Directive and related matters, as long as it contains no information likely to cause harm to the competitive position of a user.

Article 19

1. Where its disclosure affects one or more of the items mentioned in Article 3(2) of Council Directive 90/313/EEC of 7 June 1990 on the freedom of access to information on the environment [1], the notifier may indicate the information in the notifications submitted pursuant to this Directive that should be treated as confidential. Verifiable justification must be given in such cases.

2. The competent authority shall decide, after consultation with the notifier, which information will be kept confidential and shall inform the notifier of its decision.

3. In no case may the following information, when submitted according to Articles 7, 9 or 10, be kept confidential:

— the general characteristics of the GMMs, name and address of the notifier, and location of use,

— class of contained use and measures of containment,

— the evaluation of foreseeable effects, in particular any harmful effects on human health and the environment.

4. The Commission and the competent authorities shall not divulge to third parties any information decided to be confidential according to paragraph 2 and notified or otherwise provided pursuant to this Directive, and shall protect intellectual property rights relating to the data received.

5. If, for whatever reasons, the notifier withdraws the notification, the competent authority must respect the confidentiality of the information supplied.

Article 20

Amendments necessary to adapt Annex II, Part A, and Annexes III to V to technical progress and to adapt Annex II, Part C, shall be decided in accordance with the procedure laid down in Article 21.

Article 20a

Before 5 December 2000 Annex II, Part B, listing the criteria for inclusion of types of GMMs into Annex II, Part C, shall be adopted

[1] OJ L 158, 23.6.1990, p. 56.

▼M2

by the Council acting by qualified majority on a proposal from the Commission. Amendments to Annex II, Part B, shall be adopted by the Council acting by qualified majority on a proposal from the Commission.

▼M4

Article 21

1. The Commission shall be assisted by a committee.

2. Where reference is made to this Article, Articles 5 and 7 of Decision 1999/468/EC ([1]) shall apply, having regard to the provisions of Article 8 thereof.

The period laid down in Article 5(6) of Decision 1999/468/EC shall be set at three months.

3. The Committee shall adopt its rules of procedure.

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Article 22

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive not later than 23 October 1991. They shall forthwith inform the Commission thereof.

Article 23

This Directive is addressed to the Member States.

([1]) Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission (OJ L 184, 17.7.1999, p. 23).

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ANNEX I

PART A

Techniques of genetic modification referred to in Article 2(b)(i) are, *inter alia*:

1. Recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation.

2. Techniques involving the direct introduction into a micro-organism of heritable material prepared outside the micro-organism including micro-injection, macro-injection and micro-encapsulation.

3. Cell fusion or hybridisation techniques where live cells with new combinations of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally.

PART B

Techniques referred to in Article 2(b)(ii) which are not considered to result in genetic modification, on condition that they do not involve the use of recombinant-nucleic acid molecules or GMMs made by techniques/methods other than techniques/methods excluded by Annex II, PART A:

(1) *in vitro* fertilisation;

(2) natural processes such as: conjugation, transduction, transformation;

(3) polyploidy induction.

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ANNEX II

PART A

Techniques or methods of genetic modification yielding micro-organisms to be excluded from the Directive on the condition that they do not involve the use of recombinant-nucleic acid molecules or GMMs other than those produced by one or more of the techniques/methods listed below:

1. Mutagenesis.

2. Cell fusion (including protoplast fusion) of prokaryotic species that exchange genetic material by known physiological processes.

3. Cell fusion (including protoplast fusion) of cells of any eukaryotic species, including production of hybridomas and plant cell fusions.

4. Self-cloning consisting in the removal of nucleic acid sequences from a cell of an organism which may or may not be followed by reinsertion of all or part of that nucleic acid (or a synthetic equivalent) with or without prior enzymic or mechanical steps, into cells of the same species or into cells of phylogenetically closely related species which can exchange genetic material by natural physiological processes where the resulting micro-organism is unlikely to cause disease to humans, animals or plants.

   Self-cloning may include the use of recombinant vectors with an extended history of safe use in the particular micro-organisms.

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PART B

Criteria establishing the safety of GMMs for human health and the environment

This Annex describes in general terms the criteria to be met when establishing the safety of types of GMMs for human health and the environment and their suitability for inclusion in Part C. It will be supplemented by guidance notes for the easy application of such criteria, such notes being developed and, if necessary, amended by the Commission in accordance with the procedure referred to in Article 21.

1. INTRODUCTION

   Types of genetically modified micro-organisms (GMMs) listed in Part C in accordance with the procedure referred to in Article 21 are excluded from the scope of this Directive. GMMs will be added to the list on a case-by-case basis and exclusion will relate only to each clearly identified GMM. This exclusion applies only when the GMM is used under conditions of contained use as defined in Article 2(c). It does not apply to the deliberate release of GMMs. For a GMM to be listed in Part C, it must be proved that it meets the criteria given below.

2. GENERAL CRITERIA

2.1. **Strain verification/authentication**

   Identity of the strain must be precisely established. Modification must be known and verified.

2.2. **Documented and established evidence of safety**

   Documented evidence of the safety of the organism must be provided.

2.3. **Genetic stability**

   Where any instability could adversely affect safety, evidence of stability is required.

3. SPECIFIC CRITERIA

3.1. **Non-pathogenic**

   The GMM should not be capable of causing disease or harm to a healthy human, plant or animal. Since pathogenicity includes both toxigenicity and allergenicity, the GMM should therefore be:

3.1.1. *Non-toxigenic*

   The GMM should not produce increased toxigenicity as a result of the genetic modification nor be noted for its toxigenic properties.

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3.1.2. *Non-allergenic*

The GMM should not produce increased allergenicity as a result of the genetic modification nor be a noted allergen, having, for example, allergenicity comparable in particular with that of the micro-organisms identified in Council Directive 93/88/EEC of 12 October 1993 amending Directive 90/679/EEC on the protection of workers from risks related to exposure to biological agents at work [1].

3.2. **No harmful adventitious agents**

The GMM should not harbour known harmful adventitious agents such as other micro-organisms, active or latent, existing alongside or inside the GMM that could cause harm to human health and the environment.

3.3. **Transfer of genetic material**

The modified genetic material must not give rise to harm if transferred nor should it be self transmissible or transferable at a frequency greater than other genes of the recipient or parental micro-organism.

3.4. **Safety for the environment in the event of a significant and unintended release**

GMMs must not produce adverse effects on the environment, immediate or delayed, should any incident involving a significant and unintended release occur.

GMMs that do not meet the above criteria may not be included in Part C.

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Guidance notes supplementing part B of Annex II to Directive 90/219/EEC

INTRODUCTION

Types of GMMs are only judged to be suitable for inclusion in Annex II, part C when both the general and specific criteria set out in Annex II, part B are met.

All GMMs included in Annex IIC will be published in the Official Journal along with appropriate identifying characteristics or reference sources of the GMM. When considering whether a type of GMM is suitable for inclusion in Annex II, part C all components and where relevant the process used to construct the GMM should be considered. It should be noted that whilst consideration of all aspects must be undertaken it is only the properties of the GMM which will be judged against the criteria in Annex II, part B. If all the components of the GMM were individually considered and determined to be safe it is likely that the GMM will meet the safety criteria. This should not, however, be assumed and must be thoroughly examined.

If GMMs are produced as intermediate organisms in the production of a final GMM, these intermediates should also be judged against the criteria in Annex II, part B for each type to be exempt and thus de facto allow exemption of the whole contained use to be acceptable. Member States should ensure that the following guidelines are used, by users, to facilitate compliance with these criteria in producing appropriate dossiers establishing the safety, for human health and the environment, of types of GMMs to be included in part C to Annex II and by the national competent authorities to assess compliance.

Dossiers should include detailed and substantiated evidence to enable Member States to judge whether statements concerning the safety of GMMs in terms of the criteria are justified. A precautionary approach should be adopted where scientific uncertainty exists and only where there is convincing evidence to demonstrate that the criteria have been met will GMMs be considered for exemption.

The national competent authority receiving a dossier for this purpose should, following a positive appraisal as to compliance with the criteria, forward it to the Commission, which in turn should consult the committee, formed according to Article 21 of the Directive, as to inclusion of the GMM in question in its Annex II, part C. Definitions of the terms used are set out in Appendix 1.

1. GENERAL CRITERIA

1.1. *Strain verification/authentication*

The identity of the strain should be established and authenticated and the vector/insert should be well characterised for its structure and function as it occurs in the final GMM. A detailed strain history (including the history

[1] OJ L 268, 29.10.1993, p. 71.

▼C2

of genetic modifications) provides useful information for safety evaluation. The taxonomic relationship to closely related, known, harmful micro-organisms should be understood, as this can give information about possible harmful characteristics not normally expressed but which as a result of the genetic modification may be expressed. For eukaryotic cell and tissue culture systems these should be verified for their identity in accordance with international classifications (ATCC or others).

Relevant literature should be searched for history, safety records, taxonomic detail, phenotypic and genetic markers, e.g. Bergeys Manual of Determinative Bacteriology, scientific papers and journals, information from commercial companies supplying the DNA. Useful information can also be obtained from culture collections and culture collection organisations such as the World Federation of Culture Collections (WFCC), who publish the World Directory of Collections of Cultures of Micro-organisms, and the European Culture Collections Organisation (ECCO). Major European culture collections which maintain broad groups of micro-organisms should also be taken into account. In the case of a novel isolate or a strain that has not been extensively studied, any issues still unanswered should be addressed by the tests carried out to confirm identity of the GMM. This could well arise where the GMM strain differs appreciably from its parent strain(s), for instance if it is derived from cell fusion or is the result of multiple genetic modifications.

Where tests are necessary to confirm the identity of the strain, these tests can include morphology, staining, electron microscopy, serology, nutritional profiles based on utilisation and/or degradation, iso-enzyme analysis, protein and fatty acid profiles, % G + C, DNA/RNA fingerprints, amplification of taxon specific DNA/RNA sequences, gene probing, hybridisation with rRNA specific DNA probes and DNA/RNA sequencing. The results of such tests should be documented.

For the identification of the genes in the GMM, the optimum situation is where the complete nucleotide sequence of the vector and insert are known. The function of each genetic unit can then be accounted for. The vector and insert should be limited in size, where possible, to the genetic sequences required to perform the intended function. This decreases the probability of introduction and expression of cryptic functions, or the acquisition of unwanted traits.

1.2. *Documented and established safety*

Documented evidence of safe use of the GMM should be provided. This may include results from tests previously performed, data from a literature search or established record of the safety of the organism. It should be noted that a history of safe use does not necessarily establish safety, especially when the GMM has been used under highly controlled conditions for reasons of safety.

Documented evidence of established safety of the recipient or parental strain will be a key element of support in deciding whether a GMM meets this criterion. However, the GMM may have significant changes compared with the parent(s) which could affect safety and these must be investigated. In particular, care should be taken if the genetic modification was designed to remove a harmful or pathogenic trait from the recipient or parental strain. In such cases clear, documentary evidence of the successful removal of harmful or potentially harmful traits should be provided to prove safety. If data is not available for the particular recipient or parental strain, it may be possible to use data collected for the species. This data, supported by a literature survey and taxonomic investigation of the strain variation within the species, may provide evidence of the safety of the recipient or parental strain concerned.

If information to prove safety is not available, then appropriate tests would have to be carried out to establish the safety of the GMM.

1.3. *Genetic stability*

The genetic modification should not increase the stability of the GMM over the unmodified micro-organism in the environment if it could lead to harm.

Where any instability in the genetic modification could adversely affect safety, evidence of stability must be provided. This is especially so in cases where a disabling mutation has been introduced into the GMM to attenuate harmful properties.

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2. SPECIFIC CRITERIA

2.1. *Non-pathogenic*

The GMM should not be capable of causing disease or harm to healthy humans, plants or animals under any normal conditions or as the result of a reasonably foreseeable incident such as a needlestick injury, accidental ingestion, aerosol exposure, and escape leading to environmental exposure. Where there is an increased likelihood that immunocompromised individuals are exposed to the GMM, for example, where the GMM is to be used in a clinical setting, the possible effects of such exposure should be taken into account when judging the overall safety of that GMM.

The literature searches and background information gathered for the general criteria should provide much of the information required here. Historical data on handling and safety of the species and closely related strains should be investigated. Lists of human, animal and plant pathogens should also be searched.

Eukaryotic viral vectors, to be included in Annex IIC should not produce harmful effects on human health and the environment. Their origin should be known as well as the mechanism of their attenuation and the stability of the features concerned. Whenever practicable the presence of such features in the virus should be confirmed, before and after modification is carried out. Where such vectors are used, only deletion mutations should be employed. Constructs that use DNA or RNA vectors derived from viruses in cultured cells as hosts where no infective virus is involved or can be produced may also be appropriate.

Non-virulent strains of acknowledged pathogenic species, such as live human and animal vaccines, could be considered as unlikely to cause disease and as such satisfy the criteria for Annex IIB provided that:

1. the non-virulent strain has an established record of safety with no adverse effects on human, animal or plant health (lit. survey); or

2. the strain is stably deficient in genetic material that determines virulence or has stable mutations known to sufficiently reduce virulence (pathogenicity tests, genetic investigation, gene probes, phage and plasmid detection, restriction enzyme mapping, sequencing, protein probes) and for which good evidence of safety exists. The risk of reversal of gene deletion or mutation by any incoming gene transfer event should be considered.

To obtain the information required, if not revealed by a literature and taxonomic survey, pathogenicity tests appropriate to the micro-organism in question should be carried out. These tests should be carried out on the GMM, although in some cases tests on the recipient or parental strain could be adequate. However where the GMM is considerably different to its parental organism(s) care should be taken to avoid false conclusions of non-pathogenicity.

Examples of recipient or parental strains of micro-organisms for the production of GMMs that could be considered suitable for inclusion in part C to Annex II include:

— adequately disabled derivatives of bacterial strains, e.g. Escherichia coli K12 and Staphylococcus aureus 83254 whose growth and survival depends on the addition of nutrients not available in humans or in the environment outside of culture media, e.g. di aminopimelic acid requirement, thymine auxotrophy,

— Eukaryotic cell and tissue culture systems (plant or animal, including mammalian) can be considered as adequately disabled hosts. The GMMs based on the cells should meet the other criteria listed here (e.g. no harmful adventitious agents and non-mobilisable vectors),

— strains of non-pathogenic, wild type hosts may have extremely specialised ecological niches for which accidental escape from control would have minimal environmental impact or have very widespread benign occurrence for which accidental escape from control would have minimal human, animal, or plant health consequences. Examples of such hosts include lactic acid bacteria, rhizobacteria, extreme thermophiles, antibiotic-producing bacteria or fungi. The above must be micro-organisms with an established record of well-developed genetics and molecular knowledge.

The vector and insert as they occur in the final GMM, should not contain genes expressing an active protein or transcript (e.g. virulence determinants, toxins, etc.) at a level and in a form which endow the GMM with

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a phenotype likely to cause disease to humans, animals and plants or to cause adverse effects in the environment.

Use of a vector/insert containing sequences which code for harmful traits in certain micro-organisms, but which do not endow the GMM with a phenotype likely to cause disease to humans, animals and plants or adverse effects in the environment, should be avoided. Care should also be taken that the inserted genetic material does not encode a pathogenicity determinant capable of substituting for a disabling mutation present in the parental organism.

The phenotype resulting from a vector may be dependent on the recipient or parental organism; what is true for one host should not be automatically assumed when the construct is transferred to a different host. For example, a disabled retrovirus vector in bacteria or most cell lines would be incapable of producing infective virus particles. However, the same vector in a packaging cell line would produce infectious virus particles and, depending on the nature of the disablement and insert sequences, may endow the GMM with a phenotype likely to cause disease.

2.1.1. Non-toxigenic

The GMM should not produce unexpected toxins nor increased toxigenicity as a result of the genetic modification. Examples of microbial toxins are exotoxins, endotoxins and mycotoxins. Consideration of the recipient or parental strain would provide useful information on this point.

It should be considered that where the recipient or parental strain was toxin free, attention must be paid to any possibility of the vector/insert introducing toxins or stimulating/de-repressing toxin production. The presence of toxin should be carefully considered although it does not necessarily exclude the GMM from being included in Annex IIC.

2.1.2. Non-allergenic

Whilst all micro-organisms are to some degree potentially allergenic, some species are noted allergens, these can be found in Council Directive 93/88/EEC ([1]) and Commission Directive 95/30/EC ([2]) and amendments thereof. It should be considered whether the GMM belongs to this particular allergenic group. Allergenic components of micro-organisms can include cell walls, spores, naturally occurring metabolic products (e.g. proteolytic enzymes) and some antibiotics. If the vector and insert are expressed in the resulting GMM, the gene product must not possess biological activities which could lead to significant allergens. It should be noted that this criterion cannot be applied in absolute terms.

2.2. *No harmful adventitious agents*

The GMM should not harbour known adventitious agents such as mycoplasma, viruses, bacteria, fungi, other plant/animal cells, symbionts which can lead to harm. The use of a recipient or parental strain known to be free from harmful adventitious agents in the construction of the GMM is one method to avoid this. However, it must not be assumed that the GMM will be free of adventitious agents because the parent(s) were. New agents may have been introduced during the construction of the GMM.

Particular care should be taken when determining whether animal cell cultures contain potentially harmful adventitious agents such as lymphocytic chorio meningitus virus or mycoplasma such as *Mycoplasma pneumoniae*. Adventitious agents may be difficult to detect. Any limitations of screening efficiency should be taken into account.

2.3. *Transfer of genetic material*

The inserted genetic material in the GMM should not be transmissible or mobilisable if it could cause a harmful phenotype in a recipient micro-organism.

The vector and insert should not transfer any resistance markers to the GMM where resistance could compromise therapeutic treatment. Possession of such markers would not a priori exclude the inclusion of the GMM in Annex IIC but would place additional emphasis on the importance of non-mobilisation of such genes.

If the vector is a virus, cosmid or any type of virus-derived vector it should also be rendered non-lysogenic when used as a cloning vector (e. g. defective in the cI-lambda repressor). The insert should not be

([1]) OJ L 268, 29.10.1993, p. 71.
([2]) OJ L 155, 6.7.1995, p. 41.

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mobilisable, due to the presence of, for example, transferable provirus sequences or other functional transposing sequences.

Some vectors which are integrated into the host chromosome may also be considered non-mobilisable but should be investigated case by case particularly in consideration of mechanisms that may facilitate chromosome mobility (e.g. the presence of a chromosomal sex factor) or transposition to other replicons that may be present in the host.

2.4. *Safety for the environment in the event of an escape from containment*

Harm to the environment will normally only arise if a GMM can persist and possesses hazardous characteristics. When considering harm to the environment, account should be taken of the different environmental conditions that exist within Member States and where necessary, extreme case scenarios should be considered. Details of previous releases (deliberate or otherwise) and any associated impact on the environment should also be provided where available.

2.4.1. Organism survival

In deciding whether the GMM is likely to cause adverse effects on the environment or disease to plants and animals, consideration should be given to whether the biological characteristics of the GMM will enhance, leave unaltered or decrease the ability of the GMM to survive in the environment. If the GMMs are biologically disabled for survival in the environment these micro-organisms will not survive for any significant periods outside of the containment, and therefore the likelihood of interaction with the environment is reduced.

In considering possible adverse effects on the environment, the possible fate of GMMs that escape from containment into food webs should also be taken into account.

2.4.2. Dispersal

To be able to establish itself in the environment a GMM would have to survive dispersal to, and establish itself in, a suitable niche. Consideration should be given to the method of dispersal and the likelihood of survival during dispersal. Many micro-organisms survive, for example, when dispersed in aerosols and droplets and also via insects and worms.

2.4.3. Organism establishment in the environment

Establishment in a particular environment is dependent upon the nature of the environment into which the GMM escapes and its ability to survive transmission to the new environment. The potential for establishment in a suitable niche varies with the size of the viable population, the size of the niche and the frequency of suitable niches for the species. The probability will be different for each species. In addition resistance or sensitivity to biotic or abiotic stresses will have a great influence on the establishment of a GMM in the environment. The persistence of a GMM in the environment over a significant period is linked to its ability to survive and adapt to environmental conditions or to initiate a competitive growth rate. These factors may be influenced by the genetic modification and the site of integration. There are examples where the genetic modification would be unlikely to produce this effect, for example when:

— the gene product contributing to the formation of a secondary metabolite, formed at the end of growth, cannot promote growth initiation.

2.4.4. Transfer of genetic material

More information is becoming available on transfer of genetic material between micro-organisms. Even if the GMM has a very limited capacity to survive it will be important to decide on the potential for the introduced genetic material to persist in the environment or be transferred to other organisms and cause harm. Transfer of genetic material has been shown to occur, for example, under experimental conditions in soil (including rhizospheres), animal guts and water by either conjugation, transduction or transformation.

The chance of genetic material transfer from GMMs, with a low probability of growth and limited survivability is very low. If the GMM did not carry self-transmissible plasmids or transducing phages, active transfer is practically excluded. The risk would be very small if the vector/insert are not self-transmissible and are poorly mobilisable.

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APPENDIX 1

Definitions of terms used in this document

Adventitious agents —other micro-organisms, active or latent, existing alongside/inside the required micro-organism.

Antigen —any molecule which induces B cells to produce a specific antibody. A molecule which can be specifically recognised by the adaptive elements of the immune system, that is by B cells or T cells or both.

Allergen —an antigen which can sensitise individuals such that a hypersensitivity reaction is provoked in individuals on subsequent exposure to this allergen.

Allergy —immediate hypersensitivity reactions, occurs when an IgE response is directed against an innocuous antigen such as a non-pathogenic, non-viable bacteria cell. The resulting release of pharmacological mediators by IgE sensitised mast cells produces an acute inflammatory reaction with symptoms such as asthma, eczema, or rhinitis.

Conjugation —the active transfer of DNA from one host to another.

Cosmid —type of cloning vector comprising a plasmid in which the *cos* sequences of a lambda phage have been inserted.

Disease —any disturbance of structure or function in an immunocompetent human, animal or plant of such a degree as to produce detectable illness or disorder.

Expression —the process of producing RNA transcripts, proteins and polypeptides using the information contained in the genes, of the GMM. In this guidance expression is also a measure of the anticipated or known level of expression of the inserted genetic material.

Mobilisation —the passive transfer from one host to another.

Mobilisation defective —vectors defective in one or more transfer functions and which are unlikely to be mobilised by other elements which supply the missing functions.

Pathogenicity —the ability of the micro-organism to cause disease which can be by infection, toxicity or allergenicity. Pathogenicity is a taxonomically significant attribute and is the property of a species.

Plasmid —an extrachromosomal self-replicating piece of DNA, found in many micro-organisms, that generally confer some evolutionary advantage to the host cell.

Recipient or parental micro-organism —the micro-organism(s) to which the genetic modification occurred.

Rhizobacteria —bacteria which inhabit the rhizosphere, i.e. the soil adhering to plant roots, eventually entering the roots either intracellularly or intercellularly. Rhizobacteria are often used as microbial/seed inoculants in agriculture.

Transduction —the incorporation of bacterial DNA in bacteriophage particles and their transfer to recipient bacteria.

Transformation —the uptake of naked DNA by a cell.

Vector —a carrier DNA or RNA molecule, e.g. plasmid, bacteriophage into which a genetic material sequence can be inserted for introduction into a new host cell where it will be replicated *and* in some cases expressed.

Virulence —the capacity to cause harm. Individual strains of a micro-organism can vary widely in their ability to harm the host species.

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PART C

Types of GMMs which meet the criteria listed in Part B:

… (to be completed in accordance with the procedure in Article 21)

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ANNEX III

PRINCIPLES TO BE FOLLOWED FOR THE ASSESSMENT REFERRED TO IN ARTICLE 5(2)

This Annex describes in general terms the elements to be considered and the procedure to be followed to perform the assessment referred to in Article 5(2). It will be supplemented, as regards in particular section B, by guidance notes to be developed by the Commission in accordance with the procedure set out in Article 21.

These guidance notes shall be completed no later than 5 June 2000.

A. ELEMENTS OF ASSESSMENT

1. The following should be considered as potentially harmful effects:

   — disease to humans including allergenic or toxic effects,

   — disease to animals or plants,

   — deleterious effects due to the impossibility of treating a disease or providing an effective prophylaxis,

   — deleterious effects due to establishment or dissemination in the environment,

   — deleterious effects due to the natural transfer of inserted genetic material to other organisms.

2. The assessment referred to in Article 5(2) should be based on the following:

   (a) the identification of any potentially harmful effects, in particular those associated with:

      (i) the recipient micro-organism;

      (ii) the genetic material inserted (originating from the donor organism);

      (iii) the vector;

      (iv) the donor micro-organism (as long as the donor micro-organism is used during the operation);

      (v) the resulting GMM;

   (b) the characteristics of the activity;

   (c) the severity of the potentially harmful effects;

   (d) the likelihood of the potentially harmful effects being realised.

B. PROCEDURE

3. The first stage in the assessment process should be to identify the harmful properties of the recipient and, where appropriate, the donor micro-organism, any harmful properties associated with the vector or inserted material, including any alteration in the recipient's existing properties.

4. In general, only GMMs which show the following characteristics would be considered appropriate for inclusion in class 1 as defined in Article 5:

   (i) the recipient or parental micro-organism is unlikely to cause disease to humans, animals or plants ([1]);

   (ii) the nature of the vector and the insert is such that they do not endow the GMM with a phenotype likely to cause disease to humans, animals or plants ([2]), or likely to cause deleterious effects in the environment;

   (iii) the GMM is unlikely to cause disease to humans, animals or plants ([3]) and is unlikely to have deleterious effects on the environment.

5. In order to obtain the necessary information to implement this process the user may firstly take into account relevant Community legislation (in particular Council Directive 90/679/EEC ([4])). International or national classification

([1]) This would only apply to animals and plants in the environment likely to be exposed.
([2]) This would only apply to animals and plants in the environment likely to be exposed.
([3]) This would only apply to animals and plants in the environment likely to be exposed.
([4]) OJ L 374, 31.12.1990, p. 1. Directive as last amended by Commission Directive 97/59/EC (OJ L 282, 15.10.1997, p. 33).

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schemes (e.g. WHO, NIH, etc.) and their revisions due to new scientific knowledge and technical progress may also be considered.

These schemes concern natural micro-organisms and as such are usually based on the ability of micro-organisms to cause disease to humans, animals or plants and on the severity and transmissibility of the disease likely to be caused. Directive 90/679/EEC classifies micro-organisms, as biological agents, into four classes of risk on the basis of potential effects on a healthy human adult. These classes of risk can be used as guidance to the categorisation of the contained use activities in the four classes of risk referred to in Article 5(3). The user may also take into consideration classification schemes referring to plant and animal pathogens (which are usually established on a national basis). The abovementioned classification schemes give only a provisional indication of the risk class of the activity and the corresponding set of containment and control measures.

6. The hazard identification process carried out in accordance with paragraphs 3 to 5, should lead to the identification of the level of risk associated with the GMM.

7. Selection of the containment and other protective measures should then be made on the basis of the level or risk associated with the GMMs together with consideration of:

   (i) the characteristics of the environment likely to be exposed (e.g. whether in the environment likely to be exposed to the GMMs there are known biota which can be adversely affected by the micro-organisms used in the contained use activity);

   (ii) the characteristics of the activity (e.g. its scale; nature);

   (iii) any non-standard operations (e.g. the inoculation of animals with GMMs; equipment likely to generate aerosols).

   Consideration of items (i) to (iii) for the particular activity may increase, reduce or leave unaltered the level of risk associated with the GMM as identified under paragraph 6.

8. The analysis carried out as described above will finally lead to the assignment of the activity to one of the classes described in Article 5(3).

9. The final classification of the contained use should be confirmed by reviewing the completed assessment referred to in Article 5(2).

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ANNEX IV

CONTAINMENT AND OTHER PROTECTIVE MEASURES

General principles

1. These tables present the normal minimum requirements and measures necessary for each level of containment.

   Containment is also achieved through the use of good work practices, training, containment equipment and special installation design. For all activities involving GMMs the principles of good microbiological practice and the following principles of good occupational safety and hygiene, shall apply:

   (i) to keep workplace and environmental exposure to any GMM to the lowest practicable level;

   (ii) to exercise engineering control measures at source and to supplement these with appropriate personal protective clothing and equipment when necessary;

   (iii) to test adequately and maintain control measures and equipment;

   (iv) to test, when necessary, for the presence of viable process organisms outside the primary physical containment;

   (v) to provide appropriate training of personnel;

   (vi) to establish biological safety committees or subcommittees, if required;

   (vii) to formulate and implement local codes of practice for the safety of personnel, as required;

   (viii) where appropriate to display biohazard signs;

   (ix) to provide washing and decontamination facilities for personnel;

   (x) to keep adequate records;

   (xi) to prohibit eating, drinking, smoking, applying cosmetics or the storing of food for human consumption in the work area;

   (xii) to prohibit mouth pipetting;

   (xiii) to provide written standard operating procedures where appropriate to ensure safety;

   (xiv) to have effective disinfectants and specified disinfection procedures available in case of spillage of GMMs;

   (xv) to provide safe storage for contaminated laboratory equipment and materials, when appropriate.

2. The titles of the tables are indicative:

   Table I A presents minimum requirements for laboratory activities.

   Table I B presents additions to and modifications of Table I A for glasshouse/growth-room activities involving GMMs.

   Table I C presents additions to and modifications of Table I A for activities with animals involving GMMs.

   Table II presents minimum requirements for activities other than laboratory activities.

   In some particular cases, it might be necessary to apply a combination of measures, from Table I A and Table II, of the same level.

   In some cases users may, with the agreement of the competent authority, not apply a specification under a particular containment level or combine specifications from two different levels.

   In these tables ‘optional’ means that the user may apply these measures on a case-by-case basis, subject to the assessment referred to in Article 5(2).

3. Member states may, in implementing this Annex, incorporate in addition the general principles in paragraphs 1 and 2 in the following tables for the sake of clarity of the requirements.

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Table I A

Containment and other protective measures for laboratory activities

Specifications		Containment levels			
		1	2	3	4
1	Laboratory suite: isolation ([1])	Not required	Not required	Required	Required
2	Laboratory: sealable for fumigation	Not required	Not required	Required	Required
Equipment					
3	Surfaces resistant to water, acids, alkalis, solvents, disinfectants, decontamination agents and easy to clean	Required (bench)	Required (bench)	Required (bench, floor)	Required (bench, floor, ceiling, walls)
4	Entry to lab via airlock ([2])	Not required	Not required	Optional	Required
5	Negative pressure relative to the pressure of the immediate environment	Not required	Not required	Required except for ([3])	Required
6	Extract and input air from the laboratory should be HEPA-filtered	Not required	Not required	Required (HEPA) ([4]) — extract air except for ([3])	Required (HEPA) ([5]) — input and extract air
7	Microbiological safety post	Not required	Optional	Required	Required
8	Autoclave	On site	In the building	En suite ([6])	In lab = double-ended
System of work					
9	Restricted access	Not required	Required	Required	Required
10	Biohazard sign on the door	Not required	Required	Required	Required
11	Specific measures to control aerosol dissemination	Not required	Required minimise	Required prevent	Required prevent
13	Shower	Not required	Not required	Optional	Required
▼C1 14	Protective clothing	Suitable protective clothing	Suitable protective clothing	Suitable protective clothing and (optional) footwear	Complete change of clothing and footwear before entry and exit
▼M2 15	Gloves	Not required	Optional	Required	Required
18	Efficient vector control (e.g. for rodents and insects)	Optional	Required	Required	Required

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	Specifications	Containment levels			
		1	2	3	4
Waste					
19	Inactivation of GMMs in effluent from hand-washing sinks or drains and showers and similar effluents	Not required	Not required	Optional	Required
20	Inactivation of GMMs in contamined material and waste	Optional	Required	Required	Required
Other measures					
21	Laboratory to contain its own equipment	Not required	Not required	Optional	Required
23	An observation window or alternative is to be present so that occupants can be seen	Optional	Optional	Optional	Required

([1]) Isolation = the laboratory is separated from other areas in the same building or is in a separated building.

([2]) Airlock = entry must be through an airlock which is a chamber isolated from the laboratory. The clean side of the airlock must be separated from the restricted side by changing or showering facilities and preferably by interlocking doors.

([3]) Activities where transmission does not occur via airborne route.

([4]) HEPA = High efficiency particulate air.

([5]) Where viruses which are not retained by HEPA filters are used, extra requirements will be necessary for extract air.

([6]) With validated procedures, allowing the safe transfer of material into an autoclave outside the lab, and providing an equivalent level of protection.

Table I B

Containment and other protective measures for glasshouses and growth-rooms

The terms ‘glasshouse’ and ‘growth-room’ refer to a structure with walls, a roof and a floor designed and used principally for growing plants in a controlled and protected environment.

All provisions of Table I A shall apply with the following additions/modifications:

	Specifications	Containment levels			
		1	2	3	4
Building					
1	Greenhouse: permanent structure ([1])	Not required	Required	Required	Required
Equipment					
3	Entry via a separated room with two interlocking doors	Not required	Optional	Optional	Required
4	Control of contaminated run-off water	Optional	Minimise ([2]) run-off	Prevent run-off	Prevent run-off
System of work					
6	Measures to control undesired species such as insects, rodents, arthropods	Required	Required	Required	Required
7	Procedures for transfer of living material between the glasshouse/growth-room, protective structure and laboratory shall control dissemination of genetically modified micro-organisms	Minimise dissemination	Minimise dissemination	Prevent dissemination	Prevent dissemination

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(1) The glasshouse shall consist of a permanent structure with a continuous waterproofed covering, located on a site graded to prevent entry of surface-water run-off having self-closing lockable doors.

(2) Where transmission can occur through the ground.

Table I C

Containment and other protective measures for activities in animal units

All provisions of Table I A shall apply with the following additions/modifications:

Specifications		Containment levels			
		1	2	3	4
Facilities					
1	Isolation of animal unit (1)	Optional	Required	Required	Required
2	Animal facilities (2) separated by lockable doors	Optional	Required	Required	Required
3	Animal facilities designed to facilitate decontamination (waterproof and easily washable material (cages, etc.))	Optional	Optional	Required	Required
4	Floor and/or walls easily washable	Optional	Required (floor)	Required (floor and walls)	Required (floor and walls)
5	Animals kept in appropriate containment facilities such as cages, pens or tanks	Optional	Optional	Optional	Optional
6	Filters on isolators or isolated room (3)	Not required	Optional	Required	Required

(1) Animal unit: a building, or separate area within a building containing facilities and other areas such as changing rooms, showers, autoclaves, food storage areas, etc.

(2) Animal facility: a facility normally used to house stock, breeding or experimental animals or one which is used for the performance of minor surgical procedures.

(3) Isolators: transparent boxes where small animals are contained within or outside a cage; for large animals, isolated rooms may be more appropriate.

Table II

Containment and other protective measures for other activities

Specifications		Containment levels			
		1	2	3	4
General					
1	Viable micro-organisms should be contained in a system which separates the process from the environment (closed system)	Optional	Required	Required	Required
2	Control of exhaust gases from the closed system	Not required	Required, minimise dissemination	Required, prevent dissemination	Required, prevent dissemination
3	Control of aerosols during sample collection, addition of material to a closed system or transfer of material to another closed system	Optional	Required, minimise dissemination	Required, prevent dissemination	Required, prevent dissemination
4	Inactivation of bulk culture fluids before removal from the closed system	Optional	Required, by validated means	Required, by validated means	Required, by validated means

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Specifications		Containment levels			
		1	2	3	4
5	Seals should be designed so as to minimise or prevent release	No sepecific requirement	Minimise dissemination	Prevent dissemination	Prevent dissemination
6	The controlled area should be designed to contain spillage of the entire contents of the closed system	Optional	Optional	Required	Required
7	The controlled area should be sealable to permit fumigation	Not required	Optional	Optional	Required
Equipment					
8	Entry via airlock	Not required	Not required	Optional	Required
9	Surfaces resistant to water, acids, alkalis, solvents, disinfectants, decontamination agents and easy to clean	Required (bench if any)	Required (bench if any)	Required (bench if any, floor)	Required (bench, floor, ceiling, walls)
10	Specific measures to adequately ventilate the controlled area in order to minimise air contamination	Optional	Optional	Optional	Required
11	The controlled area should be maintained at an air pressure negative to the immediate surroundings	Not required	Not required	Optional	Required
12	Extract and input air from the controlled area should be HEPA filtered	Not required	Not required	Required (extract air, optional for input air)	Required (input and extract air)
System of work					
13	Closed systems should be located within a controlled area	Not required	Optional	Required	Required
14	Access should be restricted to nominated personnel only	Not required	Required	Required	Required
15	Biohazard signs should be posted	Not required	Required	Required	Required
17	Personnel should shower before leaving the controlled area	Not required	Not required	Optional	Required
18	Personnel should wear protective clothing	Required (work clothing)	Required (work clothing)	Required	Complete change before exit and entry
Waste					
22	Inactivation of GMMs in effluent from handwashing sinks and showers or similar effluents	Not required	Not required	Optional	Required

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	Specifications	Containment levels			
		1	2	3	4
23	Inactivation of GMMs in contaminated material and waste including those in process effluent before final discharge	Optional	Required, by validated means	Required, by validated means	Required, by validated means

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ANNEX V

PART A

Information required for the notification referred to in Article 7:

— name of user(s) including those responsible for supervision and safety,

— information on the training and qualifications of the persons responsible for supervision and safety,

— details of any biological committees or subcommittees,

— address and general description of the premises,

— a description of the nature of the work which will be undertaken,

— the class of the contained uses,

— only for class 1 contained uses, a summary of the assessment referred to in Article 5(2) and information on waste management.

PART B

Information required for the notification referred to in Article 9:

— the date of submission of the notification referred to in Article 7,

— the name of the persons responsible for supervision and safety and information on the training and qualification,

— the recipient, donor and/or parental micro-organism(s) used and, where applicable, the host-vector system(s) used,

— the source(s) and the intended function(s) of the genetic material(s) involved in the modification(s),

— identity and characteristics of the GMM,

— the purpose of the contained use including the expected results,

— approximate culture volumes to be used,

— description of the containment and other protective measures to be applied, including information about waste management including the wastes to be generated, their treatment, final form and destination,

— a summary of the assessment referred to in Article 5(2),

— the information necessary for the competent authority to evaluate any emergency response plans if required under Article 14.

PART C

Information required for the notification referred to in Article 10:

(a) — the date of submission of the notification referred to in Article 7,

— the name of the persons responsible for supervision and safety and information on the training and qualification;

(b) — the recipient or parental micro-organism(s) to be used,

— the host-vector system(s) to be used (where applicable),

— the source(s) and intended functions(s) of the genetic material(s) involved in the modification(s),

— identity and characteristics of the GMM,

— the culture volumes to be used;

(c) — description of the containment and other protective measures to be applied, including information about waste management including the type and form of wastes to be generated, their treatment, final form and destination,

— the purpose of the contained use including the expected results,

— description of the parts of the installation;

(d) information about accident prevention and emergency response plans, if any:

— any specific hazards arising from the location of the installation,

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— the preventive measures applied such as safety equipment, alarm systems and containment methods,

— procedures and plans for verifying the continuing effectiveness of the containment measures,

— a description of information provided to workers,

— the information necessary for the competent authority to evaluate any emergency response plans if required under Article 14;

(e) a copy of the assessment referred to in Article 5(2).