This is an unofficial translation - please note that only the Danish version has validity

Statutory Order on the approval of production using genetically modified micro-organisms[1)]

In pursuance of sections 8(2), 13(1), 19, 20(2), 27(1), 31(5) and 38(4) of Act no. 356 of 6 June 1991 concerning the environment and genetic engineering the following provisions are laid down:

Part 1

Scope

Article 1.-(1) This Statutory Order concerns:

1) approval in pursuance of section 8 of the Act on Environment and Genetic Engineering, of installations and genetically modified microorganisms for production; and
2) reporting of new production using other genetically modified microorganisms within the framework of a previous approval.

(2) Genetically modified microorganisms shall mean microorganisms, including cells in cultures and viruses, featuring genetic material that has been altered in a way that does not occur naturally (see Annex 1).

(3) Production using genetically modified microorganisms shall be classified in four classes (see Annex 3).

Part 2

Authorities

Article 2.-(1) Decisions concerning approval shall be made by the Danish Forest and Nature Agency.

(2). Applications for approval or reporting of new production shall be sent to the Danish Forest and Nature Agency with a copy of the application or the report to the relevant county council and municipal or city council.

(3) In cases concerning approval the county councils shall provide the Danish Forest and Nature Agency with an assessment of whether special circumstances apply in the case in question which may have an impact on the assessment of potential risks.

(4) In the City of Copenhagen and in Frederiksberg Municipality the city council and the municipal council respectively shall carry out the tasks which are otherwise to be carried out by county councils according to the provisions of this Statutory Order. In Bornholm Municipality these tasks shall be carried out by the regional council.

[1)] This Statutory Order contains provisions implementing Council Directive 98/81/EC of 26 October 1998 amending Directive 90/219/EEC on contained use of genetically modified micro-organisms, Official Journal 1998 L 330, p 13.

Part 3

Risk assessment and classification

Article 3.-(1) Before any production is initiated, the person in charge of production shall carry out an assessment of environmental risks and health risks (see Annex 2 and Annex 6). The risk assessment shall lead to classification in one of the classes mentioned in Annex 3. The general principles and relevant protective measures for the various containment levels appear in Annex 4.

(2) The first time production is initiated in class 1, the genetically modified microorganism and the production plant shall obtain overall prior approval. New production using other genetically modified microorganisms within the framework of a previously granted approval shall be reported in accordance with the rules specified in Article 10 below.

(3) The first time production is initiated in class 2, the genetically modified organism and the production plant shall obtain overall prior approval. New production using other genetically modified microorganisms within the framework of a previously granted approval shall be reported in accordance with the rules specified in Article 10 below.

(4) Initiation of production in class 3 and class 4 shall always be subject to prior approval.

Part 4

Content of application, etc

Article 4.-(1) Applications concerning approval of production in class 1 and class 2 shall contain the information stated in part A and part B of Annex 5.

(2) Applications concerning approval of production in class 3 and class 4 shall contain the information stated in part A and part C of Annex 5.

(3) The information submitted shall be accompanied by all necessary documentation.

Article 5.-(1) The competent authority may require additional information to the extent deemed necessary for the processing of the application.

(2) The competent authority may fix a deadline for the submission of further information and may state that an application will lapse if the information required has not been submitted on or before the final date for submission.

Part 5

Decisions concerning approval

Article 6.-(1) The competent authority shall verify that the risk assessment of production that has been prepared has been carried out in accordance with Annex 2 and Annex 6 and that the risk assessment leads to correct classification.

(2) Approvals shall contain information about the location, layout and operation of the production plant, including information concerning discharge-limiting measures and emergency response plans in the event of accidents. In addition approvals shall include a description of the genetically modified production organism as well as a summary of the risk assessment.

(3) As stated in section 16 of the Act, the competent authority shall lay down provisions concerning:

1) the layout and operation of the enterprise and concerning discharge conditions;
2) limitations in the contact of genetically modified production organisms with the surroundings;

3) measures taken to prevent and avoid undesirable impacts the environment, nature and human health; and
4) the enterprise's own control, supervision, limitations in use and submission of information to the supervisory authority.

(4) According to section 16 of the Act, the competent authority may stipulate a time limit for the approval.

(5) Approvals concerning production in class 3 and class 4 shall contain conditions to the effect that the holder of the approval shall prepare an emergency response plan which contains information about measures to be taken to limit the impacts on the environment, nature and human health in the event of accidents, including guidelines for sampling.

Article 7. The competent authority may decide that an approval for production in class 1 and class 2 may not be used until the period set aside for complaints has expired and that, in the event of a complaint, the approval shall not be used until the appeal authority has made a decision. The grounds on which such decisions are based shall be be stated.

Article 8. Approval of production in class 3 and class 4 may not be used until the period set aside for complaints has expired. If a complaint is filed concerning an approval within the period set aside for complaints, the approval may not be used until the appeal authority has made a decision.

Article 9.-(1) The competent authority shall make a decision concerning approval of production in class 1 and class 2 within 45 days after receipt of the application. As regards production in class 3 and class 4, the competent authority shall make a decision within 90 days after receipt of the application.

(2) The time during which the competent authority awaits further information from the applicant or carries out a public hearing shall not be included in the number of days stated in subsection (1) hereof.

Part 6

Reporting

Article 10.-(1) Reports of new production in class 1 and class 2 using genetically modified microorganisms within the framework of a previously granted approval shall be in writing and shall contain the information stated in part B of Annex 5.

(2) New production in class 1 which is covered by paragraph (1) hereof may be initiated 14 days after the competent authority has received the report, unless otherwise stated by the competent authority.

(3) As regards production in class 2 covered by paragraph (1) hereof, the competent authority shall within 45 days after receipt of the report (see, however, paragraph (6)) inform the enterprise of the following:

1) that production may be commenced; or
2) that it is not deemed to have been shown that production will take place within the framework of a previously granted approval, and that production may therefore not be initiated.

(4) The competent authority may request further information to the extent deemed necessary to process the application.

(5) The competent authority may fix a deadline for submission of further information and state that the report will lapse if the information requested has not been submitted on or before the deadline date.

(6) The time during which the competent authority awaits further information from the applicant or carries out a public hearing shall not be included in the number of days stated in paragraph (3) hereof.

Part 7

Charges

Article 11.-(1) On the submission of an application for approval or of a report, the competent authority shall fix a charge to be paid in accordance with the Statutory Order on Fees in pursuance of the Act on Environment and Genetic Engineering.

(2) This charge shall cover actual costs incurred in relation to the processing of the application. The charge may never exceed a sum of DKK 100,000 for processing of an application for approval see Article 3 above or DKK 50,000 for a report see Article 10 above.

Part 8

Notification

Article 12.-(1) The person in charge of production shall immediately notify the county council and the County Public Health Medical Officers about breakdowns or accidents which have resulted in or may result in the release of genetically modified organisms that may be harmful to the environment, nature and human health, or which may constitute a risk hereof.

(2) In the event of an accident in the City of Copenhagen or in Frederiksberg Municipality notification shall be made to the city council or municipal council respectively as well as to the municipal officer of health. In Bornholm Municipality notification shall be made to the regional council and to the medical officer of health.

(3) Notifications shall include information about the following:

1) special circumstances relating to the accident;
2) the identity and quantity of genetically modified organisms;
3) all details necessary to assess the impact of the accident the environment, nature and human health; and
4) the measures taken in order to prevent the consequences of the accident.

(4) Notification does not imply any limitation in the duty of the person in charge to try to prevent the consequences of the accident, just as it does not constitute any exemption from the duty to ensure that the former situation is restored to the greatest possible extent.

Part 9

Supervision

Article 13.-(1). County councils shall carry out supervisory activities to ensure that:

1) section 8 of the Act and the provisions of this Statutory Order are observed;
2) conditions laid down in approvals issued in pursuance of section 8 of the Act are observed; and
3) that orders and injunctions are observed.

(2) The rules in Parts 3 and 4 of the Act shall also apply to supervision and enforcement.

Part 10

Entry into force and transitional provisions

Article 14.-(1). This Statutory Order shall enter into force on 17 October 2002.

(2) Statutory order no 379 of 17 May 2000 concerning approval of production using genetically modified micro-organisms shall be repealed.

(3) Decisions made in pursuance of the Statutory Order mentioned in paragraph (2) hereof shall remain valid until the deadline fixed for the decision expires or until a new decision is made in accordance with the provisions of this Statutory Order. Reports of new production activities for decisions made in pursuance of the Statutory Order mentioned in paragraph (2) hereof may still be made

(4) Decisions made in pursuance of Statutory Order no 84 of 3 February 1995 on approval of production organisms and production plants and reporting of production organisms according to the Act on Environment and Genetic Engineering shall remain valid until the deadline fixed for the decision expires or until a new decision is made in accordance with the provisions of this Statutory Order. New reports of production organisms for decisions made in pursuance of Statutory Order no 84 of 3 February 1995 may not be made.

(5) Outstanding cases concerning approval or reports which are not concluded on the day on which this Statutory Order enters into force shall be concluded in accordance with the provisions of this Statutory Order.

Ministry of the Environment, 3 October 2002,
Hans Christian Schmidt
/Hans Henrik Christensen

Annex 1

Scope of application of the Statutory Order

An organism is any microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material, including viruses and viroids and animal and plant cells in culture.

A genetically modified organism is a microorganism 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, genetic modification occurs at least through the use of:

1) Recombinant DNA-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 (including protoplast fusion) or hybridisation techniques where live cells with new combinations of heritable genetic material are formed through the fusion or two or more cells by means of methods that do not occur naturally.

The following techniques are not considered to result in genetic modification, on condition that that they do not involve the use of recombinant DNA molecules or GMMs:

1) *in vitro* fertilisation;
2) conjugation, transduction, transformation or any other natural process;
3) polypoloidy induction.

The Statutory order does not apply to micro-organisms produced by application of the following techniques for genetic modification on the condition that they do not involve the use of GMMs as recipient or parental organisms:

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.

Annex 2

Principles governing risk assessment of genetically modified microorganisms

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 3 (1).

Guidelines for the carrying out of risk analyses are given in Annex 6.

A. Elements of the assessment mentioned in Article 3(1)

1. The following should be considered potentially harmful effects:

- disease to humans including allergenic or toxic effects;
- disease to animals or plants;
- adverse effects resulting from the inability to treat disease or offer effective prophylaxis;
- adverse effects resulting from establishment or dissemination in the environment;
- adverse effects resulting from the natural transfer of inserted genetic material to other organisms.

2. The assessment referred to in Article 3(1) should be based on the following:

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

(i) the recipient microorganism;

(ii) the inserted (donated) genetic material;

(iii) the vector;

(iv) the donor microorganism (as long as the donor microorganism is used during the operation);

(v) the resulting GMM;

(b) the characteristics of the activity;

(c) the severity of the potentially harmful effects;

(vi) 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 microorganism, as well as 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:

(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 and plants ([1]) , or likely to cause adverse effects in the environment;

(iii) the GMM is unlikely to cause disease to humans, animals or plants ([1]) and is unlikely to have adverse effects on the environment.

5. In order to inform this process the person in charge of transport and import may first take into account relevant Community legislation, especially Council Directive 90/679/EEC (˙). International and national classification schemes (for example WHO, NIH) and their adaptation to scientific and technological development may also be taken into account.

These schemes concern natural microorganisms and as such are usually based on the ability of microorganisms to cause disease in humans, animals or plants and on the severity and transmissibility of the disease likely to be caused. Council Directive 90/679/EEC classifies microorganisms, as biological agents, into four classes of risk on the basis of potential effects on a healthy human adult.

The classes of risk can be used as guidance to the categorisation of the contained use activities in the four classes, as stated in Article 3(1). The person in charge of transport and import may also take classification systems into account which refer to plant and animal pathogens (and which are normally prepared on a national basis). These classification systems give only a

([1]) This would only apply to animals and plants in the environment likely to be exposed.
( ) 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)

preliminary indication of the risk class of an activity and the associated set of containment and control measures.

6. The hazard identification process carried out in accordance with paragraphs 3 to 5 above, 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 of risk associated with the GMMs, including especially consideration of disposal of waste and discharge of waste water, together with the 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) above for the particular activity may increase, reduce or leave unaltered the level of risk associated with the GMM as identified under paragraph 6.

6. The analysis carried out as described above will finally lead to the assignment of the activity to one of the classes described in Article 3 and Annex 3. In case of doubt as to the class which is suitable for the proposed containment, the strictest protective measures shall be applied unless adequate documentation submitted by agreement with the competent authority justifies less strict measures.

7. The final classification of the contained use should be confirmed by reviewing the completed assessment referred to in Article 3 (1).

Annex 3

Criteria for classification of production using genetically modified micro-organisms

Class 1: Production which implies 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: Production which implies 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: Production which implies 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: Production which implies high risk, that is to say activities for which level 4 containment is appropriate to protect human health as well as the environment.

Annex 4

General principles and relevant containment and other protective measures

General principles:

The table presents 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

Containment and other protective measures for production:

In the table “optional” means that the user may apply these measures on a case-by-case basis, subject to the assessment referred to in Article 3. After a concrete estimation the competent authority can demand that the measures stated as “optional” in the table shall be applied.

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 release	required, prevent release	required, prevent release
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 release	required, prevent release	required, prevent release
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
5	Seals should be designed so as to minimise or prevent release	no specific requirement	minimise release	prevent release	prevent release
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 the 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 air should be HEPA filtered	not required	not required	required (extract air, optional for input air)	required (input, and extract air)

Specifications		Containment levels			
		1	2	3	4
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
17	Personnel should shower before leaving the controlled area	not required	not required	optional	required
18	Personnel should wear protective clothing	required (work cloth-ing)	required (work cloth-ing)	required	complete change be-fore exit and entry
Waste					
19	Inactivation of GMMs in effluent from handwashing sinks and showers or similar effluents	not required	not required	optional	required
20	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

Annex 5

Information requirements

PART A

Information required for the notification referred to in Article 4:

1. 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;
- a copy of the risk assessment mentioned in Article 3(1) as well as information concerning inactivation and disposal of waste.

PART B

Information required in relation to the application mentions in Article 4(1) and the notification mentioned in Article 10(1):

- the date of submission of the notification referred to in Part A;
- 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 systems(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, ultimate form and destination;

- a copy of the risk assessment referred to in Article 3(1);

PART C

A. Information required for the application referred to in Article 4(2):

- the date of submission of the notification referred to in Part A
- the name of the persons responsible for supervision and safety and information on the training and qualification;

- 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 function(s) of the genetic material(s) involved in the modification(s);

- identity and characteristics of the GMM;

- the culture volumes to be used;

- 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, ultimate form and destination;

- the purpose of the contained use including the expected results;

- description of the sections of the installation;

B. Information about accident prevention and emergency response plans, if any:

- any specific hazards arising from the location of the installation;

- 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 prepared in pursuance of Article 6(5), including agreements made by the enterprise with bodies and authorities that may be affected by an accident.

C. A copy of the assessment referred to in Article 3(1).

Annex 6

Guidelines for risk assessment as mentioned in Annex 2

1. INTRODUCTION

The elements of the risk assessment outlined in paragraphs 1 and 2 of Annex 2 require consideration of potentially harmful effects to human health and the environment. Potentially harmful effects are defined as those effects which may give rise to disease, render prophylaxis or treatment ineffective, promote establishment and/or dissemination in the environment which gives rise to harmful effects on organisms or natural populations present or harmful effects arising from gene transfer to other organisms. The assessment requires that the risk of these potentially harmful effects are considered for each activity and allocated to a class as defined in Article 3, taking into account both the nature and scale of operations, to determine the final containment facilities required. The degree of risk arising from contained uses with a genetically modified organism (GMO), and their construction, is determined by consideration of the severity of the potential harmful effects, to human health or the environment, with the possibility of those effects occurring. The risk assessment considers the exposure of humans or the environment to GMOs during the operation of, or possible unintended release from, a contained use facility. The classification level determined by the risk assessment defines the containment requirements for the activities involving GMOs. The containment requirements are listed in Annex 4.

2. RISK ASSESSMENT

The full risk assessment process consists of the two procedures outlined below:

2.1 Procedure 1

Identification of potential harmful properties (hazards) of the GMO and allocation of the GMO to an initial class (class 1 – class 4), taking into account the severity of the potential harmful effects.

AND

Assessment of possible harmful effects occurring by consideration of exposure (both human and environmental), taking into account the nature and scale of the work, with containment measures appropriate to the initial class allocated.

4.1 Procedure 2

Determination of final classification and containment measures required for the activity. Confirmation that final classification and containment measures are adequate by revisiting Procedure 1.

3. PROCEDURE 1

4.1 Identification of harmful properties (hazards) of the GMO.

The risk assessment process requires the identification of any potentially harmful properties of the GMO as a result of the genetic modification or any alteration of the recipient organisms' existing properties. Potentially harmful properties associated with the GMO must be determined. This should be done by consideration of the recipient organism, the donor organism, the characteristics and location of the inserted genetic material and any vector. It is important to appreciate that the genetic modification of a microorganism can affect its ability to cause harm to human health and the environment. Genetic modifications can result in a decreased, unchanged or increased ability to cause harm.

.2 Aspects that should be considered where relevant are:

3.2.1The recipient organism

- nature of pathogenicity and virulence, infectivity, allergenicity, toxicity and vectors of disease transmission;
- nature of indigenous vectors and adventitious agents, where they could mobilise the inserted genetic material, and the frequency of mobilisation;
- nature and stability of disabling mutations, if any;
- any prior genetic modifications;
- host range (if relevant);
- any significant physiological traits which may be altered in the final GMO and if relevant their stability;
- natural habitat and geographic distribution;
- significant involvement in environmental processes (such as nitrogen fixation or pH regulation);
- interaction with, and effects on, other organisms in the environment (including likely competitive pathogenic or symbiotic properties);
- ability to form survival structures (such as spores or sclerotia).

4.1.1 The donor organism (for fusion experiments or "shotgun" experiments where the insert is not well characterised)

- nature of pathogenicity and virulence, infectivity, toxicity and vectors or disease transmission;
- nature of indigenous vectors:
  - sequence;
  - frequency of mobilisation and specificity;
  - presence of genes which confer resistance to anti-microbials including antibiotics.
- host range;
- other relevant physiological traits.

3.2.3 The insert

- specific identify and function of the insert (genes);
- level of expression of inserted genetic material;
- source of the genetic material, identity of the donor organism(s) and characteristics where appropriate;
- history of prior genetic modifications if appropriate;
- location of inserted genetic material (possibility of insertional activation/deactivation of host genes).

4.1.1 The vector

- nature and source of the vector;
- structure and amount of any vector and/or donor nucleic acid remaining in the final construction of the modified microorganism;
- if present in the final GMO frequency of mobilisation of inserted vector and/or capability of transfer of genetic material.

4.1.1 The resulting GMO

4.1.1.1 Human health considerations

- expected toxic or allergenic affects of the GMO and/or its metabolic products;
- comparison of the modified microorganism to the recipient or (where appropriate) parental organism regarding pathogenicity;
- expected capacity for colonisation;
- if the microorganism is pathogenic to humans who are immunocompetent:

- Diseases caused and mechanism of transmission including invasiveness and virulence;
- infective dose;
- possible alteration of route of infection or tissue specificity;
- possibility of survival outside of human host;
- biological stability;
- antibiotic-resistance patterns;
- allergenicity;
- toxigenicity;
- availability of appropriate therapies and prophylactic measures.

4.1.1.1 Environmental considerations

- ecosystems to which the micro-organism could be unintentionally released from the contained use;
- expected survivability, multiplication and extent of dissemination of the modified microorganism in the identified ecosystems;
- anticipated result of interaction between the modified micro-organism and the organisms or microorganisms which might be exposed in case of unintentional release into the environment;
- known or predicted effects on plants and animals such as pathogenicity, toxicity, allergenicity, vector for a pathogen, altered antibiotic-resistance patterns, altered tropism or host specificity, colonisation;

- known or predicted involvement in biogeochemical processes.

4.1 Initial classification of the GMO

Paragraphs 3 – 5 of Annex 2 indicate that the first stage of the risk assessment process for a GMO is to identify the potential harmful properties of the GMO, to determine an initial classification of the GMO. This is achieved by the identification of hazards associated with the recipient, donor organism, vector and insert where appropriate. This process can be aided by taking into account the general characteristics for class 1 set out in paragraph 4 of Annex 2 and appropriate up to date national and international classification schemes (including Directive 90/679/EEC[3] and amendments thereof). The corresponding set of containment and other protection measures indicated in Annex 4 are used as a reference set of measures to determine whether more stringent containment and control measures are required to control identified harmful effects.

The risk of harm arising from any harmful property of the GMO is obtained by the consideration of the severity of the harm and any biological properties (e.g. disabling mutations) which limit the possibility of harm occurring. The estimation of the severity of the harmful effects is performed independently of the possibility of the harmful effect occurring. The severity of any possible harm is determined by considering what the result could be, not whether it is likely to occur in the particular case. For instance, for a pathogen it would be estimated how serious the disease would be assuming that the susceptible species was infected. The allocation of the GMO to an initial class includes consideration of severity. Classification schemes such as the scheme in Directive 90/679/EEC take severity into account. However many schemes are based only on either human health or environmental considerations. Care must be taken to ensure that the severity of harmful effects on human health and the environment from the GMO have been fully considered.

3.4 Assessment of possibility of harmful effects occurring

The key factor that affects the possibility of a harmful event occurring is the level and nature of exposure of humans or the environment to a particular GMO. Exposure is, in most cases, of primary importance to risk assessment as it will often determine whether a harmful effect could occur. The possibility of humans or the environment being exposed to a GMO depends upon what operations are being carried out (for example the scale of the operations) and the containment measures appropriate to the initial classification as determined in paragraphs 5 and 6 of Annex 2 applied to the work.

Paragraph 7 (ii & iii) of Annex 2 requires that the characteristics of the operation be taken into account when the final classification and selection of control measures are made. The nature and scale of the activity need to be considered in order to estimate the possibility of exposure of humans and the environment and will also affect the choice of appropriate risk management procedures.

[3] OJ L 374, 31.12.1990, p. 1

The characteristics of the operation that could affect the risk assessment and so should be taken into account as appropriate include the actual activities to be undertaken, work practices, scale and containment measures applied.

The assessment should especially take into account the question of disposal of waste and effluents. Where appropriate, the necessary safety measures should be implemented in order to protect human health and the environment.

4.1.1 Nature of activities to be undertaken

The degree of risk and application of control measures to reduce the risk from the GMO to an appropriate level will be influenced by the nature of the activities to be undertaken, since these will affect human and environmental exposure and hence possibility of harm occurring.

The nature of the activities will also determine the most appropriate containment and control measures to be considered, cfr. Annex 4.

In practice, for laboratory scale work where the effect of standard laboratory procedures on exposure are well known, detailed risk assessment of each individual procedure would be unlikely to be required unless a highly hazardous organism was being used. More detailed consideration however may be necessary for non-routine procedures or procedures which might have a significant effect on the degree of risk, for example, procedures which generate aerosols.

4.1.1 Concentration and scale

The density of a culture can lead to a risk of exposure to high concentrations of the GMO, particularly in downstream processing operations. The effects of concentration on the possibility of a harmful event occurring must be considered.

Scale is also a factor that must be taken into account in the risk assessment. Scale may be in terms of the absolute volume of a single operation or the frequent repetition of a process, because both could give rise to an increased possibility of exposure if the containment and control measures failed and thus affect the possibility of a harmful event occurring.

While large scale does not necessarily mean high risk, increased scale may lead to an increased possibility of exposure both in terms of the number of humans and the amount of environmental exposure that might occur in the event of containment failure.

The scale of the work will also influence the most appropriate containment and control measures, cfr. Annex 4.

4.1.1 Culture conditions

In many contained use activities, the culture conditions are rigorously contained to protect the work, however, the nature and design of the growth vessels or other culture equipment will also influence the degree of risk to human health and the environment. Highly engineered and sealed fermentation vessels can significantly reduce exposure and hence risk from a GMO. Consideration of reliability and possible failure rates for such equipment is important where failure could lead to high levels of exposure to harmful GMOs. Where such loss is reasonably foreseeable, additional containment measures may be required. The standard operating procedures of individuals undertaking work with cultured GMOs such as centrifugation or sonication will have a significant impact on the effectiveness of any containment measures employed.

In combination with physical culture conditions that act as containment measures, both biological and chemical measures that are employed to protect the work can also contribute significantly to the containment measures that may be required. Examples of biological containment could well be auxotrophic mutants that require specific growth factors to be supplied to grow. Examples of chemical containment measures could be disinfectant solutions maintained in drainage systems.

Paragraph 7 (i) of Annex 2 requires that the characteristics of the environment likely to be exposed and the severity of the effect be taken into account when assessing the possibility of harmful effects occurring and their severity.

There are a number of aspects to this consideration of the environment that are important, such as the extent and nature of environmental exposure and whether there are biota which can be adversely affected by the particular GMO in the area exposed.

The following factors should be considered, as appropriate, when assessing how the characteristics of the receiving environment will affect the possibility that the potentially harmful effect will be realised and hence the level of risk and selection of control measures.

4.1.1.1 Environmental considerations

The environment likely to be exposed will in most cases probably be limited to the workplace environment and the area immediately surrounding the facility, but depending on the specific characteristics of the contained use and the facility, a wider environment may need to be considered. The extent of the environmental exposure may be influenced by the nature and scale of the activity, but consideration should also be given to all possible modes of transmission into the wider environment. These can include physical modes (such as local drains, watercourses,

waste disposal, air movement) and biological vectors (such as movement of infected animals and insects).

4.1.1.1 Presence of susceptible species

The possibility of harm actually occurring will depend on whether there are susceptible species, including humans, animals and plants, in the environment that is likely to be exposed.

4.1.1.1 Whether the environment can support the survival of the GMO

The extent to which the GMO can survive and persist in the environment is a strong consideration in the risk assessment. The possibility of harm occurring will be significantly reduced if a GMO cannot survive in the environment to which it might gain access.

4.1.1.1 Effects on the physical environment

In addition to direct harmful effects of a GMO, indirect harmful effects from significantly altering the physico-chemical properties and/or ecological balance of the soil or water components of the environment must be considered.

4. PROCEDURE 2

4.1 Determination of final classification of containment measures

When all potentially harmful characteristics have been reviewed for their severity and possibility of occurrence, with the effect of the containment and control measures indicated by the initial classification of the recipient considered, the final classification and containment measures for the GMO can be determined. In considering the final classification and containment measures, the initial classification should be revisited to determine if it was correct bearing in mind the activities and characteristics of the operations proposed. A comparison of the initial classification and associated containment measures with the final class and containment requirements can give rise to three results:

- there are harmful effects which are not adequately taken into account in the initial classification, these would not be adequately contained by the provisional containment considered under Procedure 1. This would require the application of additional containment measures and possibly revision of the classification of the activity;

- the initial classification was correct and the attendant containment measures adequately prevent or minimise harm to human health and the environment;

- the initial classification is higher than the activity warrants and accordingly a lower classification with its attendant containment conditions would be appropriate.

4.1 Confirmation of adequacy of final containment measures

Once the proposed final classification and containment conditions have been determined, the level of human and environmental exposure should be reassessed (Procedure 1). This should confirm that the possibility of any harmful effects occurring, taking into account the nature and scale of the work and the proposed containment conditions are acceptably low. When this has been done the risk assessment process has been completed.

If the nature or scale of the work changes significantly or new scientific or technical knowledge becomes available, such that the risk assessment is no longer adequate, the risk assessment must be reviewed in the light of the changes. Any alteration in containment conditions indicated as a result of the review of the risk assessment must be applied forthwith to maintain adequate protection for human health and the environment.

The classification and the containment and control measures identified in the risk assessment as required to adequately contain the GMO during the proposed operations, leads to the classification of the contained use activities into classes 1 to 4. The containment and control measure for each class of contained use are detailed in Annex 4.

The classification of the contained use activities for the GMO defines the administration requirements.

If there are any uncertainties in the final classification and containment conditions, it is advisable to contact the competent authority.