

## Executive Order on Genetic Engineering and the Working Environment<sup>(1)</sup>

Pursuant to Sections 17(3), 22(1), 35, 39(1) and (2), 40, 41(1), 43, 44, 46, 49, 49a(1) and (2), 49c, 73, 75(1) and 84 of the [Danish] Working Environment Act, cf. Consolidation Act No. 784 of 11 October 1999 as amended by Act No. 331 of 16 May 2001, and as authorised by the Minister for the Environment and Energy pursuant to Sections 7, 27(3) and 36(4) of Act No. 356 of 6 June 1991 on the Environment and Genetic Engineering as amended by Act No. 921 of 25 November 1992, it is laid down as follows:

### Part 1

#### *Scope*

**1.—**(1) The present Order covers work, including development work, involving genetically modified organisms, cf. Annex 1, in:

- 1) laboratories and laboratory zones, including animal sheds, greenhouses, aquaria, and similar
- 2) facilities for large-scale experiments or production.

(2) The Order shall apply whether or not the work is performed for an employer.

**2.—**(1) The Order shall not apply to exhibition and other information activities etc. which the Environment and Energy Minister has determined can take place outside classified laboratories and laboratory zones, as provided by the Environment and Genetic Engineering Act.

(2) The Director General of the Danish Working Environment Authority shall have the power to determine that work with the genetically modified organisms excepted by the Minister for the Environment and Energy as provided by the Environment and Genetic Engineering Act shall also be excepted from the Order.

**3.—**(1) The ordinary rules laid down in health and safety legislation and any rules laid down on genetic engineering in pursuance of other legislation shall apply in addition to the rules set out in the present Order.

(2) For genetically modified micro-organisms, the provisions laid down in the Executive Order on Biological Agents and the Working Environment concerning the duty to maintain lists of employees who are exposed to biological agents in risk group 3 or 4 and the duty to ensure the employees' access to an occupational medical examination, shall also apply.

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1) The Order contains provisions implementing Council Directive 90/219/EEC, Official Journal of the European Communities 1990, L 117, p. 1, as amended by Council Directive 98/81/EC, Official Journal of the European Communities 1998, L 330, p. 13.

### *Definitions*

4. For the purposes of the present Order, genetically modified organisms are plants, animals, micro-organisms, cells in cultures and viruses in which there occur new combinations of genetic material that do not arise naturally (see Annex 1).

5. The application of the provisions laid down in the present Order shall be based on the following definitions:

- 1) 'Research projects and other laboratory work' means work with genetically modified animals or plants and work with genetically modified micro-organisms or cell cultures where the volume of culture fluid does not exceed 15 litres per vessel.
- 2) 'Large-scale experiments' means work with genetically modified micro-organisms or cell cultures that is not actual production but which takes place in similar facilities. The definition does not cover work with genetically modified plants or animals.
- 3) 'Donor' means the organism or cell/cell material from which the genetic material utilised originates.
- 4) 'Host' means the cell or organism into which the genetic material is introduced.
- 5) 'Vector' means the biological material used to introduce genetic material into a host.
- 6) 'Biologically active material' means donors, hosts, genetically modified cells and organisms or tissue thereof, viruses and genetically modified animals and plants that are capable of self-replication.
- 7) 'Laboratories' and 'laboratory zones' mean the working space(s) in which biologically active material is handled, i.e., indoor areas where work of one or another form involving biologically active material takes place. Laboratory zones are such indoor areas as animal sheds, greenhouses and aquaria.

### Part 2

#### *Health and Safety Assessment*

6.—(1) An overall assessment of the possible hazards posed by the biological systems to human health and safety and to the external environment shall be performed prior to notification of work.

(2) For work with genetically modified micro-organisms, the assessment must include at least the elements and the procedure given in Annex 3a, Part A, and Annex 3b. This assessment will form the basis for determining under which class the work shall be performed, cf. Annex 3a, Part B.

(3) For work with genetically modified animals, plants, etc., the principles contained in Annex 3a, Part A, and Annex 3b must enter into the assessment.

(4) A written report of the assessment must be retained and made available to the Danish Working Environment Authority.

(5) The assessment must be brought up to date when there are changes in the work, working methods, work processes, etc., that affect the working environment at the enterprise or the external environment, if:

- 1) the protective measures used are no longer adequate, or the class under which the activity takes place is no longer the correct one, or

- 2) there are grounds to suppose that the assessment is no longer appropriate in the light of the latest scientific and technical knowledge.

### Part 3

#### *Classification of Laboratories, Laboratory Zones and Facilities for Large-Scale Experiments or Production*

**7.**—(1) Laboratories, laboratory zones and facilities for large-scale experiments or production at which work with genetically modified organisms is to be carried out require prior classification by the Danish Working Environment Authority. For the purposes of this Order, ‘classification’ means the Danish Working Environment Authority’s approval of a zone as satisfying the requirements laid down for that zone.

(2) The classification shall remain in force until the Danish Working Environment Authority gives notification to the contrary.

**8.**—(1) Laboratories and laboratory zones, including greenhouses, animal sheds, aquaria, etc., shall be classified using four classes in accordance with Annex 2, Parts A and B, but see subsection (2) hereof.

(2) Laboratories and laboratory zones where work will not be performed with genetically modified micro-organisms but only with genetically modified plants and animals shall be classified not by four classes but only on the basis of an individual assessment.

(3) Classification of laboratories where work with genetically modified plants or animals is to be performed, and of laboratory zones, shall take place following consultation with the Danish Forest and Nature Agency.

**9.**—(1) Facilities for large-scale experiments or production shall be classified using four classes in accordance with Annex 2, Parts A and C, but see subsection (2) hereof. Classification of facilities for large-scale experiments shall take place following consultation with the Danish Forest and Nature Agency.

(2) Production facilities where work will not be performed with genetically modified micro-organisms but only with genetically modified plants and animals shall be classified not by four classes but only on the basis of an individual assessment.

**10.** The Director General of the Danish Working Environment Authority shall have the power to lay down rules or determine that specific experiments using genetically modified organisms may be carried out for educational purposes outside classified laboratories or laboratory zones.

**11.** Notification for the purpose of classification under Section 7(1) of this Order shall be submitted to the Danish Working Environment Authority and must contain the information specified in Annex 2. Additionally, the Danish Working Environment Authority may demand information concerning the equipment and the building.

**12.** Should it be desired to have a laboratory, laboratory zone, or facility for large-scale experiments or production reclassified in a lower class, or should it be desired to cease maintaining the classification, the Danish Working Environment Authority shall first be notified accordingly.

**13.** Work in classified laboratories, laboratory zones, and facilities for large-scale experiments or production shall always be carried out in accordance with the requirements laid down for the relevant class, see Annex 2, and in accordance with any specific conditions attached to the grant of classification.

**14.—(1)** Classification under Section 7(1) shall be granted in writing no later than 45 days after submission of the notification.

(2) However, classification of laboratories, laboratory zones and facilities for large-scale experiments or production in classes 3 and 4 shall be granted in writing no later than 90 days after submission of the notification.

(3) The period during which the Danish Working Environment Authority is awaiting further information it has requested from the notifier shall not be taken into account in the number of days stated in subsections (1) and (2) hereof.

#### Part 4

##### *Notification and Approval of Research Projects and other Laboratory Work*

**15.** Research projects and other laboratory work involving work with genetically modified organisms require approval from the Danish Working Environment Authority prior to their commencement.

**16.—(1)** Work with genetically modified micro-organisms shall be carried out only in laboratories or laboratory zones of the class required for the type of work concerned, or a higher class.

(2) In case of doubt as to the required class for the work concerned, the higher class shall apply.

**17.—(1)** Notification of research projects and other laboratory work shall be submitted to the Danish Working Environment Authority and must include the information specified in Annex 4, Part A, but see subsection (2) hereof.

(2) Notification of research projects and other laboratory work covered by Annex 5 must include:

- 1) The information specified in Annex 4, Parts A and B;
- 2) Identification of the health hazards both under normal working conditions and in the event of accidents: and
- 3) Details of the planned safety measures additional to those following from the laboratory classification.

**18.** The Danish Working Environment Authority shall lay notifications of research projects and other laboratory work before the Danish Forest and Nature Agency if:

- 1) they involve work with genetically modified reproducing plants, genetically modified animals or genetically modified organisms in animal sheds, greenhouses, aquaria or similar; or
- 2) an assessment in accordance with Section 6 of this Order shows that there is an environmental hazard.

**19.—**(1) The notification and accordingly the approval shall lapse after five years unless it is renewed; but see subsection (2) hereof.

(2) Approval of research projects and other laboratory work covered by Annex 5 shall remain in force until the Danish Working Environment Authority gives notification to the contrary.

**20.—**(1) Approval under Section 15 shall be granted by the Danish Working Environment Authority in writing no later than 45 days after submission of the notification. The period during which the Danish Working Environment Authority is awaiting further information it has requested from the notifier shall not be taken into account in the number of days here stated.

(2) However, research projects and other laboratory work that is not covered by Annex 5 can be commenced 45 days after submission of the notification, unless the Danish Working Environment Authority has indicated to the contrary.

(3) The Director General of the Danish Working Environment Authority shall have the power to authorise work with certain genetically modified organisms to commence on submission of the notification.

## Part 5

### *Notification and Approval of Large-Scale Experiments and Production*

**21.** Large-scale experiments and production involving work with genetically modified organisms require approval from the Danish Working Environment Authority prior to their commencement.

**22.—**(1) Work with genetically modified micro-organisms shall be carried out only in facilities for large-scale experiments or production of the class required for the type of work concerned, or a higher class.

(2) In case of doubt as to the required class for the work concerned, the higher class shall apply.

**23.** Notification of large-scale experiments and production shall be submitted to the Danish Working Environment Authority and must include the information specified in Annex 4, Parts A and B.

**24.** The Danish Working Environment Authority shall lay notifications of large-scale experiments in class 2 and above before the Danish Forest and Nature Agency.

**25.—**(1) The notification and accordingly the approval of large-scale experiments in class 1 shall lapse after five years unless it is renewed.

(2) Approval of large-scale experiments in class 2 or above, and production, shall remain in force until the Danish Working Environment Authority gives notification to the contrary.

**26.—**(1) Approval under Section 21 shall be granted by the Danish Working Environment Authority in writing no later than 45 days after submission of the notification. The period during which the Danish Working Environment Authority is awaiting further information it has requested from the notifier shall not be taken into account in the number of days here stated.

(2) However, large-scale experiments in class 1 can be commenced 45 days after submission of the notification, unless the Danish Working Environment Authority has communicated to the contrary.

(3) The Director General of the Danish Working Environment Authority shall have the power to lay down rules for a notification system for production involving genetically modified organisms in class 1.

## Part 6

### *Substitution*

**27.—**(1) A donor or a host-vector system must not be used if it is possible to substitute a less hazardous donor or host-vector system.

(2) Where the use of a substitute donor or substitute host-vector system would entail significant differences in technical properties or costs, an overall assessment of the technical and financial consequences weighed against the health and safety considerations must be undertaken.

(3) The Danish Working Environment Authority may demand proof of compliance with subsections (1) and (2) hereof.

## Part 7

### *General Provisions*

**28.—**(1) The employer shall ensure that instructions to employees and safety rules are produced in writing and displayed as necessary.

(2) Emergency response plans shall be drawn up in accordance with the Executive Order on the Performance of Work.

(3) Emergency response plans shall also be drawn up if there is a particular hazard to the external environment.

**29.** The Director General of the Danish Working Environment Authority shall be authorised to require that notifications in accordance with Sections 7(1), 17(1) and 23 shall be made on special forms to be obtained from the Danish Working Environment Authority.

**30.—**(1) Any significant change in the information furnished as required by Sections 11, 17 and 23 shall be notified to the Danish Working Environment Authority.

(2) Approval of the changes shall be granted in writing no later than 45 days after submission of the notification. The period during which the Danish Working Environment Authority is awaiting further information it has requested from the notifier shall not be taken into account in the number of days here stated.

**31.** To the extent that it may be deemed necessary for assessment of the safety of the genetic engineering work, or when circumstances otherwise give cause for it, the Danish Working Environment Authority shall have the power to demand further information. The Danish Working Environment Authority may require the information to be evaluated by experts, cf. Section 21 of the Working Environment Act.

**32.** The internal safety organisation of the enterprise concerned shall be involved in the preparation of the assessment required under Section 6 and the internal emergency response plan required under Section 28 of this Order. In enterprises not required to have an internal safety organisation, the employees must be involved in a similar way.

**33.—**(1) Classification under Section 7(1) and approvals under Sections 15 or 21 can be granted subject to specific conditions, and can also be granted for a limited period.

(2) The Danish Working Environment Authority shall have the power to revoke classifications under Section 7(1) and approvals under Sections 15 and 21 of this Order if the conditions are not observed or if new information of importance for health and safety renders it necessary.

## Part 8

### *Exemption and Appeals*

**34.** The Director General of the Danish Working Environment Authority shall have the authority where special circumstances obtain to permit deviations from the provisions of the present Order where this is deemed reasonable and entirely safe to the extent consistent with Directive 90/219/EEC on the contained use of genetically modified micro-organisms as amended by Directive 98/81/EC.

**35.** Appeals against decisions made by the Danish Working Environment Authority pursuant to this Order may be lodged in accordance with Section 81 of the Working Environment Act.

## Part 9

### *Penalties*

**36.—**(1) Unless a more severe penalty is incurred under the Working Environment Act or other legislation, the following offences shall be punishable by fine or imprisonment for up to two years:

- 1) Infringement of Section 6, 7(1), 11, 12, 13, 15, 17, 21, 23, 27(1) or (2), 28, 30 or 32 of this Order;
- 2) Failure to observe conditions attached to a classification under Section 7(1) or an approval under Section 15 or 21 of this Order;
- 3) Failure to comply with a notice or prohibition issued in accordance with the provisions of this Order.

(2) A fine may be imposed upon an employer for infringement of Section 7(1), 15 or 21 of this Order even where the infringement cannot be ascribed to his intent or negligence. No alternative sentence shall be set in lieu of the fine.

(3) Companies etc. (legal persons) may be held criminally liable in accordance with the rules set out in Part 5 of the [Danish] Criminal Code.

## Part 10

### *Entry into Force and Transitional Provisions*

**37.—**(1) The present Order shall enter into force on 16 July 2001.

(2) Executive Order No. 384 of 26 May 2000 on Genetic Engineering and the Working Environment shall be repealed simultaneously.

**38.—**(1) Classifications, approvals and exemptions granted by the Director General of the Danish Working Environment Authority prior to 1 July 2001 shall remain valid, but cf. Section 30 of this Order.

(2) In the case of material changes in information relating to a classification, approval or exemption granted by the Director General of the Danish Working Environment Authority pursuant to Ministry of Labour Executive Order No. 578 of 1 September 1987 or No. 684 of 11 October 1991 on Genetic Engineering and the Working Environment as amended by Executive Order No. 705 of 22 July 1996, new notification must be made in accordance with the provisions of the present Order.

(3) Previously granted classifications of facilities for large-scale experiments or production in group 1 shall be valid after the entry into force of the present Order also for facilities for large-scale experiments or production in class 1.

*The [Danish] Ministry of Labour, 28 June 2001*

Ove Hygum

/ Morten Bergulf

**Annex 1****Techniques of Genetic Modification, cf. Sections 1 and 4****PART A**

For the purpose of the definition of genetically modified organisms mentioned in Section 1, techniques resulting in genetic modification include but are not limited to the following:

- 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 a 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 an organism of heritable material prepared outside the organism including microinjection, 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 of two or more cells by means of methods that do not occur naturally.

**PART B**

The following techniques are not considered to result in genetic modification, provided that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms:

- 1) *In vitro* fertilisation;
- 2) Conjugation, transduction, transformation or any other natural process; and
- 3) Polyploidy induction.

**PART C**

The present Order does not apply to organisms produced by application of the following techniques for genetic modification provided that they do not involve the use of genetically modified organisms 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; and
- 4) Traditional breeding methods.

**Annex 2****Notification and Classification of Laboratories, Laboratory Zones and Facilities for Large-Scale Experiments or Production, cf. Section 7(1)****PART A****General**

Premises are classified in four classes on the basis of:

- 1) their design and fitting out;
- 2) plans for the performance of the work, including emergency response plans;
- 3) the equipment at the premises; and
- 4) internal supervision and control.

Notification for the purpose of classification:

Information required for the notification referred to in Section 7(1):

- Name of user(s) and the persons responsible for supervision and safety;
- Information on the training and qualifications of the persons responsible for supervision and safety;
- Information on the internal safety organisation;
- Address and general description of the premises;
- Description of the nature of the work which will be undertaken;
- Class of the contained use;
- Information on waste management.

Tables 1a, 1b, 1c and 2 present the normal minimum requirements and measures necessary for each level of containment.

In addition, containment is ensured through the use of good work practices, training, containment equipment and special installation design. For all activities involving genetically modified micro-organisms, the principles of good microbiological practice and the following principles of occupational safety and hygiene shall apply:

- i) To test adequately and maintain protective measures and protective equipment;
- ii) To test, as necessary, for the presence of viable process organisms outside the primary physical containment;
- iii) To provide appropriate training of personnel;
- iv) To formulate and implement local codes of practice for the safety of personnel, as required;
- v) To keep adequate records;
- vi) To provide written operating procedures where appropriate to ensure safety.

The table headings are indicative only.

Table 1a presents the minimum requirements for laboratories and laboratory zones where work is carried out with genetically modified organisms.

Table 1b presents additions to and variations of Table 1a applying to greenhouses and similar where work is carried out with genetically modified micro-organisms.

Table 1c presents additions to and variations of Table 1a applying to animal sheds and similar where work is carried out with genetically modified micro-organisms.

Table 2 presents the minimum requirements for facilities for large-scale experiments or production where work is carried out with genetically modified organisms.

In some cases it may be necessary to adopt a combination of measures from Table 1a and Table 2 for the same class.

In some cases the user may, by agreement with the Danish Working Environment Authority, omit to apply a stipulation for a given containment class or combine stipulations applying to two different classes.

In the tables ‘optional’ means that the user may apply these measures on a case-by-case basis, subject to the assessment referred to in Section 6. After a specific evaluation the Danish Working Environment Authority may demand that the measures stated as ‘optional’ in the table shall be applied.

Definitions:

**Autoclaving:**

‘Autoclaving’ means treatment with saturated steam at 121°C for 20 minutes or other combinations of temperature and time that have at least the same inactivating effect on biological material.

**Disinfection:**

‘Disinfection’ means reduction of the number of harmful micro-organisms to such a degree that no dissemination of significance for health or safety will occur. Disinfection is usually performed by heat or chemical action.

**PART B**

**Containment and other protective measures for laboratories and laboratory zones, cf.**

**Section 8**

In this Annex both laboratories and laboratory zones are termed ‘laboratories’.

In classes 2, 3 and 4, the requirements specified for the preceding class(es) shall apply as well as those specified for the class concerned. In addition to the general requirements set out in this Annex, classification of a laboratory in class 3 or 4 may be made subject to special requirements depending on the specific project to be carried out.

A horizontal line signifies that the requirement from the lower class is not to be carried into the higher class, as it would conflict with other requirements in the higher class.

**Table 1a: Containment and other protective measures for laboratories and laboratory zones**

| Stipulations                             | Containment level (Class)   |  |   |   |
|--|---|--|---|---|
|  | 1   | 2  | 3   | 4 |
| ADMINISTRATIVE MATTERS                   |   |  |   |   |
| Access and transport into the laboratory | Access to the laboratory by unauthorised persons must be restricted | Access only for personnel necessary to perform the work and appropriately instructed persons | Access only for specially nominated personnel who are necessary to perform the work |   |

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|  |   |  |  | A logbook must be kept recording the periods spent by personnel in the laboratory |
|  |   |  | Access only via airlock with shower and changing facilities  |   |
|  |   |  | All material must be brought in via an airlock designed on the same principles as the entry airlocks |   |
|  | Lab coats or other suitable dedicated work clothes must be worn in the laboratory   |  | Special requirements relating to work clothes and personal protective equipment                      |   |
|  |   | Suitable footwear must be used in the laboratory. Non-work clothes must not be kept in the laboratory. |  |   |
|  |   | Jewellery, wristwatches, handkerchiefs, and similar items must not be brought into the laboratory.     |  |   |
|  |   | Irrelevant materials are not permitted in the laboratory   |  |   |
|  | Tobacco use, eating, drinking and application of cosmetics are prohibited in the laboratory. If brought, such products must be kept in a special cabinet. However, food and drink must not be kept in the laboratory. | Tobacco, food, drinks and cosmetics must not be brought into the laboratory                            |  |   |
|  |   | Animals and plants not involved in the work must not be present  |  |   |
| Exit and transport out of the laboratory | The dedicated work clothes must be taken off before   | Personnel must remove the dedicated work   | Exit must be via airlock with shower and   |   |

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|  | eating and at the end of working hours  | clothes and footwear before leaving the laboratory   | changing facilities. Personnel must shower and change their clothes when leaving.                               |  |
|  |   | All persons must wash their hands before leaving the laboratory  |   |  |
|  |   |  | Transport of materials must take place via an airlock   |  |
|  | A procedure must be drawn up for transport of biologically active material out of the laboratory and for how transport containers are to be labelled                                    |  |   | No material may be removed without having been autoclaved. Appropriate equipment for this purpose must be present inside the zone. |
|  | All waste containing biologically active material must be collected in suitable containers and autoclaved or adequately disinfected before disposal                                     | All waste containing biologically active material must be collected in suitable containers and autoclaved before disposal  | All waste must be autoclaved within the classified area before disposal   |  |
|  | If waste containing biologically active material is to be transported outside the classified area in order to be autoclaved or disinfected, it must be transported in sealed containers | If waste containing biologically active material is to be transported outside the classified area in order to be autoclaved, it must be transported in sealed containers |   |  |
|  | If autoclaving and disinfection are impractical, waste may be transported directly for safe destruction. The transport must take place in suitable sealed packing.                      |  |   |  |
|  | Syringe needles, disposable syringes, sharp-edged objects and similar items must be placed in closed containers   | Syringe needles, disposable syringes, sharp-edged objects and similar items must be placed in closed containers  | Syringe needles, disposable syringes, sharp-edged objects and similar items must be placed in closed containers |  |

|                          |  |   |   |   |
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|                          | immediately after use and autoclaved or disinfected before disposal or cleaning  | immediately after use and autoclaved before disposal or cleaning  | immediately after use and autoclaved within the classified area before disposal or cleaning                             |   |
|                          | Utensils, glassware and similar items contaminated with biologically active material must be autoclaved or disinfected before cleaning                   | Utensils, glassware and similar items contaminated with biologically active material must be autoclaved before cleaning           | Utensils, glassware and similar items must be autoclaved in the classified area before cleaning                         |   |
|                          |  |   | Necessary auxiliary materials must not be removed from the classified area until it has been autoclaved                 |   |
|                          | Dedicated work clothes must be kept in a closed container or bag until washing. The dedicated work clothes must be cleaned effectively.                  | Dedicated work clothes must be collected in a closed container and properly autoclaved before or at the time of washing           | Dedicated work clothes must be collected in a closed container and autoclaved within the classified area before washing |   |
|                          |  | External surfaces of transport containers must be properly disinfected before the containers are taken out of the classified area |   |   |
| Training and instruction |  | The work must be specially supervised by a person with the requisite understanding of the relevant field of work                  | Special requirements relating to the professional qualifications of personnel   |   |
| Safety rules             | If experiments or similar activities are performed without relevantly qualified persons being present, it must be possible to call in a qualified person |   |   | Experiments or similar activities must not take place except in the presence of a relevantly qualified person |
|                          | A logbook must be kept recording all accidents and dangerous   |   | A logbook must be kept recording all accidents and dangerous  |   |

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|                         | situations that have given rise to a risk to human health or safety or to the external environment   |  | situations  |  |
|                         |  |  | The efficacy of the autoclaving must be monitored   |  |
|                         |  |  | Major accidents must be reported immediately to the Danish Working Environment Authority  |  |
| PERFORMANCE OF THE WORK | The work must be carried out in such a way that the formation of aerosols is minimised   |  |   |  |
|                         | Mouth pipetting is prohibited  |  |   |  |
|                         | The work must be carried out in a cabinet equipped with its own ventilation system if there is a danger of air pollution harmful to health | The work must be carried out in a cabinet equipped with its own ventilation system if there is a danger of air pollution harmful to health, including when:<br>1) there is a danger of the formation of aerosols containing biologically active material;<br>2) the work involves large quantities of liquid containing biologically active material; or<br>3) the work involves high concentrations of biologically active material | All work with biologically active material outside closed systems must be performed in a cabinet equipped with its own ventilation system |  |
|                         | The use of syringe needles, syringes, sharp-edged objects and similar items must be minimised  |  |   |  |
| Cleaning etc.           | Workstations in the laboratory must be cleaned and disinfected daily   | Workstations in the laboratory must be cleaned and disinfected daily   |   |  |

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|  |   | according to a special procedure  |   |                           |
|  | The workstation must be kept tidy   |   | The classified area must be cleaned at least once daily                             |                           |
|  | Suitable disinfectants must be present in the laboratory  |   |   |                           |
|  | Spills of biologically active material must be immediately disinfected with a suitable disinfectant   |   | All spills must immediately be effectively disinfected with a suitable disinfectant |                           |
| Dedicated work clothes and personal protective equipment |   | The dedicated work clothes and footwear must not be removed from the laboratory except for washing or destruction         |   |                           |
|  | Suitable gloves must be used for contact with biologically active material  | Suitable gloves must be used if there is a danger of contact with biologically active material or if working with animals |   |                           |
|  |   | Footwear must be thoroughly disinfected with a suitable disinfectant in the event of spillage                             |   |                           |
| Personal hygiene   | Hands must be washed after contamination with biologically active material and spills and contact with animals as well as before breaks and at the end of working hours |   |   | Special washing procedure |
| Doors/Windows  |   | Doors to the classified area must be closed when work is in progress  |   |                           |
| DESIGN AND FITTING OUT OF THE WORK-PLACE                 |   | Windows must either be closed or provided with insect screens   | _____   | _____                     |
| Signs  | Doors to the  | Doors to the  | Doors to the  | Doors to the              |

|   |  |  |   |   |
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|   | classified area must bear signs reading 'Gen-teknologisk område, klasse 1' ('Genetic Engineering Area Class 1')  | classified area must bear signs reading 'Gen-teknologisk område, klasse 2' ('Genetic Engineering Area Class 2')  | classified area must bear signs reading 'Gen-teknologisk område, klasse 3' ('Genetic Engineering Area Class 3') | classified area must bear signs reading 'Gen-teknologisk område, klasse 4' ('Genetic Engineering Area Class 4') |
|   |  |  | The classified area must be separated from the rest of the building by special means                            | The classified area must be in a separate or specially isolated part of the building                            |
| Design, equipment, fixtures, fittings and furniture | The laboratory must be designed and fitted out so that it is easy to clean and disinfect   |  | The classified area must be designed and fitted out so as to be very easily cleanable                           | Special requirements relating to cleaning procedure and qualifications of personnel                             |
|   |  | Only necessary equipment must be present at workstations where work with biologically active material is carried out in the laboratory                 |   |   |
|   | To the extent possible, equipment that may come into contact with biologically active material in the laboratory must be of a design that is easy to clean and disinfect | Equipment in the laboratory must be of a design that is easy to disinfect and clean  |   |   |
|   | The surface of workbenches, chairs etc. in the laboratory must be smooth and easy to clean   |  |   |   |
|   |  | Floors must have a smooth unbroken surface and a rounded transition to the walls   |   |   |
|   |  | Laboratory wall surfaces must be smooth and easy to wash. Transitions between fixtures and fittings and structure must either be completely sealed, or |   |   |

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|  |  | provide sufficient access to permit effective cleaning. |   |   |
|  | Movable furniture in the laboratory must be easy to move during cleaning and disinfecting  |   |   |   |
|  | The surface of fixtures, fittings, furniture, and floors in the laboratory must be resistant to acids, bases, organic solvents and moderate heat |   |   |   |
|  | Decontamination and washing facilities, including easy access to a wash-hand basin, must be present in the working area                          |   | Facilities for decontamination and washing, including easy access to a wash-hand basin, must be present in the working area. A wash-hand basin must be mounted near the exit. |   |
|  |  |   | The taps must not be hand operated  |   |
|  |  |   | Windows must be closed and sealed   | Windows must be unbreakable   |
|  |  |   | Airlocks must have self-closing doors, and air pressure below that of the immediate surroundings and above that in the classified area  |   |
|  |  |   |   | An observation window or similar must be provided to allow persons within the classified area to be seen from outside |
|  |  |   |   | The airlock must have self-locking doors  |
|  |  |   |   | Special requirements relating to the design of the airlock  |
|  |  |   | The classified area   | The classified area   |

|                      |  |   |   |   |
|----------------------|--|---|---|---|
|                      |  |   | must be sealable to permit disinfection   | must be sealable to permit disinfection by fumigation   |
| Plumbing and heating |  |   |   | Special requirements relating to plumbing and heating installations   |
| Ventilation systems  | Extract air from general ventilation must not be returned to the same or other indoor areas. However, in special cases (e.g. sterile rooms) this is acceptable.                                    |   | Ventilation system air must not be conducted to the same or other indoor areas                                |   |
|                      | A cabinet with its own ventilation system must normally be present in the laboratory. However, in special cases (e.g. sterile benches) it is acceptable that extract air is conducted to the area. |   | Special requirements relating to ventilation systems  |   |
|                      |  |   | Special requirements relating to closed systems   |   |
|                      |  | Extract air from cabinets with own ventilation system must be filtered through absolute filters, and the filters must be autoclaved before disposal | All extract air must be filtered through absolute filters, and the filters must be autoclaved before disposal | All extract and input air must be filtered through absolute filters, and the filters must be autoclaved before disposal |
|                      | Procedures must exist for monitoring and maintenance of filters and for effectiveness-monitoring and maintenance of the ventilation systems  |   | Special requirements relating to monitoring and maintenance   |   |
| Effluent and drains  | Biologically active material must not be discharged into drains/sewers   | Physical measures must be taken against release into sewers from all drains. Means must exist for the   | Physical measures must be taken against release into sewers from all drains, including shower room            |   |

|  |  |  |  |  |
|--|--|--|--|--|
|  |  | collection and autoclaving of releases containing biologically active material. Drains from basins used exclusively for hand washing are excepted from this requirement. | drains. All effluent must be collected and autoclaved. |  |
|--|--|--|--|--|

**Table 1b: Containment and other protective measures for greenhouses and similar**

The expression ‘greenhouses and similar’ refers to structures with walls, a roof and a floor, that are designed and principally used for the growing of plants in a controlled and protected environment.

All the provisions of Table 1a apply, with the following additions/variations:

| Stipulations          |  | Containment level (Class)       |   |                                  |                                  |
|-----------------------|--|---------------------------------|---|----------------------------------|----------------------------------|
|                       |  | 1                               | 2   | 3                                | 4                                |
| <b>Building</b>       |  |                                 |   |                                  |                                  |
| 1                     | Greenhouse: permanent structure <sup>(1)</sup>   | Not required                    | Required  | Required                         | Required                         |
| <b>Equipment</b>      |  |                                 |   |                                  |                                  |
| 2                     | Access via a separate ante-room with two mutually dependent doors  | Not required                    | Optional  | Required                         | Required                         |
| 3                     | Control of contaminated effluent   | Optional                        | Water off-flow must be reduced as much as possible <sup>(2)</sup> | Water off-flow must be prevented | Water off-flow must be prevented |
| <b>System of Work</b> |  |                                 |   |                                  |                                  |
| 4                     | Measures to control undesirable species of e.g. insects, rodents, arthropods   | Required                        | Required  | Required                         | Required                         |
| 5                     | Procedures for transfer of living material between greenhouse, protective structure and laboratory must hinder the dissemination of genetically modified micro-organisms | Dissemination must be minimised | Dissemination must be minimised                                   | Dissemination must be prevented  | Dissemination must be prevented  |

- 1) The greenhouse must consist of a permanent structure with a continuous watertight covering, must be located on sloping terrain so that the entry of surface water is prevented, and must have self-closing lockable doors.
- 2) In cases where transfer could occur through the soil.

**Table 1c: Containment and other protective measures for animal sheds and similar**

All the provisions of Table 1a apply, with the following additions/variations:

| Stipulations      |  | Containment level (Class) |          |          |          |
|-------------------|--|---------------------------|----------|----------|----------|
|                   |  | 1                         | 2        | 3        | 4        |
| <b>Facilities</b> |  |                           |          |          |          |
| 1                 | Isolation of animal units <sup>(3)</sup> | Optional                  | Required | Required | Required |

|   |  |          |                            |  |   |
|---|--|----------|----------------------------|--|---|
| 2 | Animal facilities <sup>(4)</sup> , separated by lockable doors   | Optional | Required                   | Required                                 | Required  |
| 3 | Animal facility equipment suitable for decontamination (water-resistant and easily washable hardware (cages etc.)) | Optional | Optional                   | Required                                 | Required  |
| 4 | Floor and/or walls that are easy to wash   | Optional | Required (floor and walls) | Required (floor and walls)               | Required (floor and walls)  |
| 5 | Animals kept in suitable containment facilities such as cages, pens or tanks                                       | Optional | Optional                   | Optional                                 | Special requirements relating to cages and sheds for animals used for experimentation |
| 6 | Filters on isolators and isolated rooms <sup>(5)</sup>   | Optional | Required                   | Required                                 | Required  |
| 7 | Respiratory protection   |          |                            | Suitable filter respirators must be used | Suitable filter respirators must be used  |

3) Animal shed: A building or separate area within a building that contains facilities and other areas such as changing rooms, showers, autoclaves, feedstuff storage rooms, etc.

4) Animal facility: A facility that is normally used for housing animals for breeding or experiments or a facility that is used for carrying out minor surgical procedures.

5) Isolators: Transparent boxes in which the animal is contained either inside or outside a cage; for larger animals, isolated rooms may be more appropriate.

## PART C

### Containment and other protective measures for facilities for large-scale experiments or production, cf. Section 9

The notification must include all necessary information on the protective measures it is planned to establish in order to provide against the risks associated with the use of the facility, including:

- the expected culture volume;
- the quantities, nature and consumption of raw materials, auxiliary substances etc. that will be used;
- the processes to be used, including the formation of intermediate products, waste products and by-products relevant to health and safety; and
- the expected emissions from plant and equipment at the workplace of gaseous, liquid and solid substances and materials under normal operating conditions and in the event of accidents.

The requirements relating to measures for organism containment can be seen from the categories set out below, depending on the organism and the work concerned.

Each operation in the process must be assessed. The characteristics of each operation will dictate the physical containment to be used. This will allow selection and design of the process, the procedures relating to the facility, and the operating procedures best fitted to assure adequate and safe containment. Two important factors to be considered when selecting the equipment needed to implement the containment are the risk of, and the effects consequent on, equipment failure.

Increasingly stringent standards may be required of engineering practice to reduce the risk of failure as the consequences of a potential failure become more serious.

**Table 2.**

| Stipulations     |  | Containment level (Class) |                                |   |   |
|------------------|--|---------------------------|--------------------------------|---|---|
|                  |  | 1                         | 2                              | 3   | 4   |
| <b>General</b>   |  |                           |                                |   |   |
| 1                | Viable micro-organisms must be contained in a system which physically 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, introduction of material into 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 physical or chemical means | Required, by validated physical or chemical means |
| 5                | Seals should be designed so as to minimise or prevent release  | No specific requirements  | Minimise release               | Prevent release                                   | Prevent release                                   |
| 6                | The controlled area must be designed to contain spillage of the entire contents of the closed system   | Optional                  | Optional                       | Required  | Required  |
| 7                | The controlled area must be sealable to permit disinfection by fumigation  | Not required              | Optional                       | Optional  | Required  |
| <b>Equipment</b> |  |                           |                                |   |   |
| 8                | Entry via airlock  | Not required              | Not required                   | Optional  | Required  |
| 9                | Surfaces must be resistant to acids, alkalis, solvents, disinfectants and decontamination agents, and easy to clean                          | Required (bench if any)   | Required (bench if any, floor) | Required (bench if any, floor)                    | Required (bench if any, 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 must be maintained at an air pressure below that of the immediate surroundings   | Not required              | Not required                   | Optional  | Required  |
| 12               | Extract and input air from/to the controlled area must be HEPA filtered  | Not required              | Not required                   | Required (extract air; optional for input air)    | Required (input and extract air)                  |
| 13               | A closed system must not be  | Optional                  | Required                       | Required  | Required  |

|                |  |                          |                              |   |                                       |
|----------------|--|--------------------------|------------------------------|---|---------------------------------------|
|                | opened for maintenance unless sterilisation by a recognised method has been carried out  |                          |                              |   |                                       |
| 14             | Closed systems must be provided with monitoring and sensing devices that measure the integrity of containment during operation                     | Optional                 | Optional                     | Required  | Required                              |
| 15             | The integrity of containment of closed systems must be tested by use of the corresponding host organism before the system is put into use          | Optional                 | Optional                     | Required  | Required                              |
| System of Work |  |                          |                              |   |                                       |
| 16             | Closed systems must be located within a controlled area  | Not required             | Required                     | Required  | Yes, designed for the purpose         |
| 17             | Access restricted to nominated personnel only  | Not required             | Required                     | Required  | Yes, via airlock                      |
| 18             | The genetic engineering area must be signed  | Yes, Class 1             | Yes, Class 2                 | Yes, Class 3                                      | Yes, Class 4                          |
| 19             | Personnel must shower before leaving the controlled area   | Not required             | Not required                 | Optional  | Required                              |
| 20             | Decontamination and washing facilities must be provided for personnel  | Required                 | Required                     | Required  | Required                              |
| 21             | Personnel must wear protective clothing  | Required (work clothing) | Required (work clothing)     | Required  | Complete change before exit and entry |
| Waste          |  |                          |                              |   |                                       |
| 22             | Inactivation of genetically modified micro-organisms in effluent from hand-basins and showers or similar effluents                                 | Not required             | Not required                 | Optional  | Required                              |
| 23             | Inactivation of genetically modified micro-organisms in contaminated material and waste including those in process effluent before final discharge | Optional                 | Required, by validated means | Required, by validated physical or chemical means | Required, by validated physical means |

**Annex 3a****Assessment of Biological Systems under Section 6****PART A**

This Annex describes in general terms the elements to be considered and the procedure to be followed to perform the assessment. For detailed guidelines on the assessment, see Annex 3b.

Consideration is particularly given in the assessment to the questions of waste and effluent discharge.

**A. Elements of the assessment referred to in Section 6:**

1. The following should be considered potentially harmful effects:
  - Disease in humans, including allergenic or toxic effects;
  - Disease in animals or plants;
  - Harmful effects due to the inability to treat a disease or offer effective prophylaxis;
  - Harmful effects due to establishment in, or dissemination into, the environment;
  - Harmful effects due to the natural transfer of inserted genetic material to other organisms.
2. In assessing potential health and safety hazards presented by biological systems, the following parameters are to be taken into account, as far as they are relevant:
  - a) Identification of all potentially harmful effects, in particular those associated with:
    - i) donor, host or any parental organism(s) (whilst the organism is used during the activity);
    - ii) the inserted (donated) genetic material;
    - iii) the vector;
    - iv) the resulting genetically modified organism.
  - b) The characteristics of the activity.
  - c) The extent of the potentially harmful effects, including considerations of health.
  - d) The probability of potentially harmful effects actually occurring.
  - e) Monitoring techniques.

**B. Procedure**

3. The first stage in the assessment process should be to identify any harmful properties of the recipient and, where appropriate, the donor organism, 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 genetically modified organisms which show the following characteristics would be considered appropriate for inclusion in class 1:
  - i) Neither the recipient nor the parental organism is considered likely to be capable of causing disease in humans, animals or plants<sup>(6)</sup>;
  - ii) The nature of the vector and the insert is such that they do not endow the genetically modified organism with a phenotype considered likely to be capable of causing disease in humans, animals or plants<sup>(6)</sup>, or to have harmful effects on the environment;

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<sup>6</sup> This would only apply to animals and plants in the exposed environment

- iii) The genetically modified organism is considered unlikely to be capable of causing disease in humans, animals or plants<sup>(6)</sup> and is considered unlikely to have harmful effects on the environment.
5. In order to inform this process the notifier may first take into account relevant legislation, especially the Danish Working Environment Authority's Executive Order on Biological Agents and the Working Environment.  
International and national classification schemes (for example WHO, NIH) and their adaptation to scientific and technological development may also be taken into account.
  6. The hazard identification process carried out in accordance with points 3 to 5 above, should lead to the identification of the level of risk associated with the genetically modified organisms.
  7. Selection of the containment and other protective measures should then be made on the basis of the level of risk associated with the genetically modified organisms, together with the consideration of:
    - i) the characteristics of the environment which would be likely to be exposed (e.g., whether in the environment which would be likely to be exposed to the genetically modified organisms there are known biota which can be adversely affected by the organisms used in the contained use activity);
    - ii) the characteristics of the activity (e.g. its scale and nature);
    - iii) any non-standard operations (e.g. the inoculation of animals with genetically modified micro-organisms; 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 genetically modified organism as identified under point 6 above.
  8. When the analysis has been carried out as described above, the activity is assigned to one of the classes described below. The division into four classes is not applied to genetically modified animals and plants.
  9. The final classification of the contained use should be confirmed following a review of the completed assessment as described in Section 6.

## **PART B**

Criteria for selection of class.

The assessment described in Annex 3a, Part A, leads to a final classification of the contained use activities in four classes, and this classification determines the containment level, cf. Section 6(2).

Class 1: Work which entails no or negligible risk, that is to say activities for which class 1 containment is adequate to protect human health and the environment.

Class 2: Work which entails low risk, that is to say activities for which class 2 containment is adequate to protect human health and the environment.

Class 3: Work which entails moderate risk, that is to say activities for which class 3 containment is adequate to protect human health and the environment.

Class 4: Work which entails high risk, that is to say activities for which class 4 containment is adequate to protect human health and the environment.

## Risk Assessment Guidelines

### 1. Introduction

The elements that must be taken into account when assessing potentially harmful effects on human health and the environment are set out in points 1 and 2 of Annex 3a, Part A. Potentially harmful effects are defined as those effects which give rise to disease or render prophylaxis or treatment ineffective; harmful effects on organisms or natural populations in consequence of establishment and/or dissemination in the environment; and harmful effects arising from gene transfer to other organisms. The risk of these potentially harmful effects must be examined for each operation, which must be allocated to a particular class, taking into account both the nature and scale of the operation, to determine the containment measures required. The degree of risk arising from contained use of genetically modified organisms (GMOs) and their construction is determined by examining how severe the potential harmful effects to human health and the environment would be, and the probability of those effects occurring. The risk assessment considers the exposure of humans or the environment to GMOs in consequence of 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.

### 2. Risk Assessment

The full risk assessment process consists of the following two procedures:

#### 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), on the basis of the severity of the potential harmful effects;

AND

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

#### 2.2 Procedure 2

Determination of final classification and containment measures required for the activity.

Confirmation that the final classification and containment measures are adequate by revisiting Procedure 1.

### 3. Procedure 1

#### 3.1 Identification of harmful properties (hazards) of the GMO.

The risk assessment process requires the identification of any harmful properties of the GMO resulting from genetic modification or any alteration of the recipient organisms' properties. Potentially harmful properties associated with the GMO must be determined by consideration of the recipient organism, the donor organism, the properties and location of the inserted genetic material and any vector. It is important to appreciate that the genetic modification of an organism 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.

### 3.2 Aspects that should be considered where relevant are:

#### 3.2.1 The recipient organism

- Name, designation and origin;
- Information on the cycle of propagation (sexual/asexual) of the parental organism(s) or (where applicable) of the host organism;
- Nature of pathogenicity and virulence, infectivity, allergenicity, toxicity and vectors of disease transmission;
- Nature of indigenous vectors and adventitious agents, if they could mobilise the inserted genetic material, and the frequency of such mobilisation;
- Nature and stability of disabling mutations, if any;
- Stability of the parental or host organism(s) as regards relevant genetic traits;
- 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).

#### 3.2.2 The donor organism

- Name, designation and origin;
- Level of relationship with the host organism;
- Nature of pathogenicity and virulence, infectivity, toxicity and vectors for disease transmission;
- Nature of indigenous vectors:
  - Sequence;
  - Frequency of mobilisation and specificity;
  - Presence of genes which confer resistance to antimicrobials including antibiotics;
  - Host range;
  - Other relevant physiological traits.

#### 3.2.3 The insert

- Description of the modification, including the method of vector insertion into the host organism or the method which is to be used to achieve the genetic modification involved;
- Specific identify and function of the insert (genes);
- Level and rate of expression of inserted genetic material; Method and sensitivity of measurement;
- Source of the genetic material, identity and properties of the donor organism(s) where relevant;
- Prior genetic modifications, if relevant;
- Location of inserted genetic material (possibility of insertional activation/inactivation of host genes).

#### 3.2.4 The vector

- Nature and source of the vector;
- Structure and amount of vector and/or donor nucleic acid that may remain in the final construction of the modified micro-organism;

- If present in the final GMO, frequency of mobilisation of inserted vector and/or capability of transfer of genetic material.

### 3.2.5 The resulting GMO

- Stability of the organism as regards genetic traits;
- Nature of substances that are formed or might be formed as a consequence of the genetic manipulation;
- Activity of the expressed protein;
- Factors that may affect the survival, multiplication or dissemination of the modified organism outside the culture fluid.

#### 3.2.5.1 Health considerations

- Expected toxic or allergenic effects of the GMO and/or its metabolic products;
- Product hazards, including the formation of toxins or biologically highly active materials;
- Comparison of the modified micro-organism to the recipient or (where appropriate) parental organism with regard to pathogenicity;
- Expected capacity for colonisation;
- Known and expected habitats;
- If the micro-organism is pathogenic to humans who are immunocompetent:
  - Diseases caused and mechanism of transmission including invasiveness and virulence;
  - Communicability;
  - Infective dose;
  - Possible alteration of route of infection or tissue specificity;
  - Possibility of survival outside of human host;
  - Presence of vectors or other means of dissemination;
  - Biological stability;
  - Antibiotic resistance patterns;
  - Allergenicity;
  - Availability of appropriate therapies and prophylactic measures.

#### 3.2.5.2 Environmental considerations

- Ecosystems to which the organism could be unintentionally released from the contained use;
- Expected survivability, multiplication and extent of dissemination of the modified organism in the identified ecosystems;
- Anticipated result of interaction between the modified organism and the organisms or micro-organisms 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 of pathogen, altered antibiotic resistance patterns, altered tropism or host specificity, colonisation;
- Known or predicted involvement in biogeochemical processes.

#### 3.2.5.3 Monitoring techniques

- Techniques for detection, identification and monitoring of the modified organism;
- Techniques for detection of transfer of the new genetic material to other organisms;
- Possible methods for decontamination of the area in case of release.

### 3.3 Initial classification of the GMO

It is stated in points 3 to 5 of Annex 3a, Part A, that the first stage of the risk assessment process for a GMO is to identify the potential harmful properties of the GMO, in order to determine an

initial classification of the GMO. This is achieved by the identification of hazards associated with the recipient and donor organisms, the vector and the insert. The assessment can take into account the general characteristics for class 1 set out at 4 of Annex 3a, Part A, and appropriate up-to-date national and international classification schemes (including the Executive Order on Biological Agents and the Working Environment and amendments thereto). The corresponding set of containment and other protection measures indicated in Annex 2 are used as a point of departure in assessing whether more stringent containment and control measures are required to control the 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 probability of harm occurring. The estimation of the severity of the harmful effects is performed independently of the probability of the harmful effects actually occurring. The severity of any possible harm is assessed by considering what the consequences could be, and not the probability of its occurring in the particular case. For instance, for a pathogen it would be estimated how serious the disease would be if a susceptible species were infected. The allocation of the GMO to an initial class also includes consideration of severity. Classification schemes such as that in the Executive Order on Biological Agents and the Working Environment take severity into account. However, many schemes are based only on either human health or environmental considerations. It is important 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 probability of harmful effects occurring

The key factor that affects the probability of a harmful event occurring is the level and nature of exposure of humans or the environment to a particular GMO. The exposure aspect is, in most cases, of primary importance to the risk assessment as it will often determine whether a harmful effect could occur. The probability of humans or the environment being exposed to a GMO depends upon what operations are being carried out (for example, on what scale) and the containment measures applied to the work on the basis of the initial classification as determined in accordance with points 5 and 6 in Annex 3a, Part A.

It is required under point 7 (ii and iii) of Annex 3a 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 probability of exposure of humans and the environment and will also affect the choice of appropriate risk management procedures.

The characteristics of the operation that could affect the risk assessment and so should be taken into account as appropriate include the actual activity to be undertaken, working procedures, 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.

#### 3.4.1. 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 the probability of harm occurring.

The nature of the activities will also determine which of the tables in Annex 2 gives the most appropriate containment and control measures.

In practice, for laboratory scale work where the effects 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 were being used. More detailed consideration may however 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.

#### 3.4.2 Concentration and scale

High cell density can lead to a risk of exposure to high concentrations of the GMO, particularly in downstream processing operations. The effect of concentration on the probability of a harmful event occurring must be examined.

Scale must also be taken into account in the risk assessment – both the scale of single operations and scale in the form of frequent repetition of processes, since either could give rise to an increased probability of exposure if containment and control measures failed, thereby affecting the probability of a harmful event occurring.

While large scale does not necessarily mean high risk, increased scale may lead to an increased probability 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 activities will also be relevant to which of the tables in Annex 2 gives the most appropriate containment and control measures.

#### 3.4.3 Culture conditions

In many contained use activities, the culture takes place subject to rigorous containment conditions; however, the nature and design of the growth vessels and other culture equipment will also influence the degree of risk to human health and the environment. Technologically advanced and sealed fermentation vessels can significantly reduce exposure to, 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 releases are reasonably foreseeable, additional containment measures may be required. The standard working procedures of individuals undertaking work with cultured GMOs such as centrifugation or sonication will have a significant impact on the effectiveness of the containment measures.

In addition to physical culture conditions that act as containment measures, both biological and chemical measures that are employed to protect the work can contribute significantly to the containment measures. Examples of biological containment include auxotrophic mutants, that require specific growth factors to be supplied in order to grow. Examples of chemical containment measures include disinfectants in drainage systems.

It is required under point 7 of Annex 3a that the characteristics of the environment which might be exposed and the severity of the effects be taken into account when assessing the probability of harmful effects occurring and their severity.

Certain aspects of these environmental considerations are of particular importance, such as the extent and nature of environmental exposure and whether there are biota which can be harmed 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 probability that the potentially harmful effect will be realised and hence the level of risk and selection of control measures.

##### 3.4.3.1 The environment likely to be exposed

The environment that might be exposed will in most cases probably be limited to the workplace 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 in the wider environment. These can include physical modes (such as drains, watercourses, waste disposal, air movement) and biological vectors (such as infected animals and insects).

#### 3.4.3.2 Presence of susceptible species

The probability of harm occurring will depend on whether there are susceptible species, including humans, animals and plants, in the environment that might be exposed.

#### 3.4.3.3 Whether the environment can support the survival of the GMO

The extent to which the GMO can survive and persist in the environment is an important consideration in the risk assessment. The probability of harm occurring will be significantly reduced if a GMO cannot survive in the environment to which it might escape.

#### 3.4.3.4 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 and final containment measures

When all potentially harmful properties have been reviewed for their severity and the probability of harm following from them, taking into account the containment and control measures indicated by the initial classification, 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 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 certain harmful effects which are not adequately taken into account in the initial classification and which would not be adequately contained by the provisional containment arrived at under Procedure 1. Additional containment measures and possibly revision of the classification of the activity are therefore required.
- The initial classification was appropriate and the containment measures applicable to it 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 and the containment measures applicable to it would be appropriate.

### 4.2 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 is to confirm that the probability of harmful effects occurring, taking into account the nature and scale of the work and the proposed containment conditions, is acceptably low. When this has been done the risk assessment process has been completed.

Section 6(5) states that the assessment must be brought up to date when there are changes in the work, working methods, work processes, etc., that affect the working environment at the enterprise or the external environment, if:

- 1) the protective measures used are no longer adequate, or the class under which the activity takes place is no longer the correct one, or
- 2) there are grounds to suppose that the assessment is no longer appropriate in the light of the latest scientific and technical knowledge.

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 necessary to adequately contain the GMO for the purpose of the proposed activities, leads to the classification of the contained use activities into classes 1 to 4. The containment and control measures for each class of contained use are detailed in Annex 2.

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

If there are any uncertainties in the final classification and final containment conditions, the Danish Working Environment Authority should be contacted.

**Annex 4****Notification and Approval of Research Projects, Other Laboratory Work, Large-Scale Experiments and Production Involving Genetically Modified Organisms, cf. Sections 15 and 21****PART A**

## General

Information required for the notification referred to in Sections 15 and 21:

1. Date of classification under Section 7(1) or of submission of notification;
2. Name of the persons responsible for supervision and safety and information on their training and qualifications;
3. The recipient, donor and/or parental organisms used and, where applicable, the host-vector system(s) used;
4. Source and intended function of the genetic material involved in the genetic manipulations;
5. Identity and characteristics of the genetically modified organism;
6. Purpose of the contained use including the expected results;
7. For micro-organisms, approximate culture volumes;
8. Description of the containment and other protective measures planned, including information about management of the wastes that will be generated, their treatment, ultimate form and destination;
9. A copy of the assessment mentioned in Section 6;
10. The information necessary for the Danish Working Environment Authority to enable it to evaluate the emergency response plans drawn up in accordance with Section 28(2) and (3).

**PART B**

Notification of research projects in classes 3 and 4, large-scale experiments and production

The notification must contain the information specified in Annex 4, Part A.

The following information must also be supplied:

1. The culture volumes to be used;
2. Description of the containment and other protective measures that will be applied, including information about waste management, including the type and form of wastes that will be generated, their treatment, ultimate form and destination;
3. Description of the parts of the installation;
4. Details of accident prevention and emergency response plans, if any;
5. Any specific hazards arising from the location of the installation;
6. The preventive measures applied such as safety equipment, alarm systems and containment methods;
7. Procedures and plans for verifying the continuing effectiveness of the containment measures;
8. A description of information provided to workers, including safety rules.

In cases where it is not technically possible, or is considered unnecessary, to supply part of this information, the reasons must be stated.

In the case of production, the degree of detail required for each of the items specified will vary according to the nature and scale of the proposed production. Specifically, it will not normally be

necessary to give detailed biological information on host organisms that have previously been classified in class 1.

Where some of the information required has been supplied previously to the Danish Working Environment Authority, the notification can give a reference thereto.

**Annex 5****Approval of Research Projects and other Laboratory Work, cf. Section 20(2)**

The following research projects and other laboratory work must not be commenced without prior approval:

- 1) Research projects and other laboratory work to be carried out in laboratory class 3 or 4, cf. Annex 3a, Part B.
- 2) Research projects and other laboratory work entailing transfer of resistance markers to organisms not known to possess them naturally, if such transfer could compromise the use of antibiotics to control pathogenic agents.