SCHEDULE 1 Regulations 2(1) and 3(3)

DEFINITION OF GENETIC MODIFICATION

PART I

Examples of techniques constituting genetic modification

1. Examples of the techniques which constitute genetic modification which are referred to in sub-paragraph (a) of the definition of genetic modification in regulation 2(1) are—

(a) recombinant DNA techniques consisting of the formation of new combinations of genetic material by the insertion of nucleic acid molecules, produced by whatever means outside the cell, into any virus, bacterial plasmid or other vector system so as to allow their incorporation into a host organism in which they do not occur naturally but in which they are capable of continued propagation;

(b) techniques involving the direct introduction into an organism of heritable material prepared outside the organism including micro-injection, macro-injection and microencapsulation; and

(c) cell fusion (including protoplast fusion) or hybridization 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 II

Techniques which are not considered to result in genetic modification

2. The following techniques are not considered to result in genetic modification if they do not involve the use of recombinant-DNA molecules or genetically modified organisms—

(a) in vitro fertilization;

(b) conjugation, transduction, transformation or any other natural process; and

(c) polyploidy induction.

PART III

Techniques to which these Regulations do not apply

3. These Regulations shall not apply to the following techniques of genetic modification if they do not involve the use of genetically modified organisms as recipient or parental organisms—

(a) mutagenesis;

(b) the construction and use of somatic hybridoma cells (for example for the production of monoclonal antibodies);

(c) cell fusion (including protoplast fusion) of plant cells where the resulting organisms can also be produced by traditional breeding methods;

(d) self-cloning of non-pathogenic naturally occurring micro-organisms which fulfil the criteria of Group I for recipient micro-organisms; and

(e) self-cloning of non-pathogenic naturally occurring organisms other than micro-organisms which fulfil the criteria of Part III of Schedule 2.

SCHEDULE 2 Regulation 2(2)

CRITERIA FOR THE CLASSIFICATION OF ORGANISMS

PART I

Criteria as applicable for classification of micro-organisms in Group I

Recipient or parental organism

(a) (a) non-pathogenic;

(b) no adventitious agents;

(c) proven and extended history of safe use or built-in biological barriers, which, without interfering with optimal growth in the reactor or fermenter, confer limited survivability and replicability, without adverse consequences in the environment.

Vectors/Insert

(a) (a) well characterised and free from known harmful sequences;

(b) limited in size as much as possible to the genetic sequences required to perform the intended function;

(c) should not increase the stability of the construct in the environment (unless that is a requirement of intended function);

(d) should be poorly mobilisable;

(e) should not transfer any resistance markers to micro-organisms not known to acquire them naturally (if such acquisition could compromise use of drugs to control disease agents).

Genetically modified micro-organisms

(a) (a) non-pathogenic;

(b) as safe in the reactor or fermenter as recipient or parental organism, but with limited survivability and/or replicability without adverse consequences in the environment.

Other genetically modified micro-organisms that could be included in Group I if they meet the conditions in paragraph 3

(a) (a) those constructed entirely from a single prokaryotic recipient (including its indigenous plasmids and viruses) or from a single eukaryotic recipient (including its chloroplasts, mitochondria, plasmids, but excluding viruses);

(b) those that consist entirely of genetic sequences from different species that exchange these sequences by known physiological processes.

PART II

Guidelines as applicable for classification of micro-organisms in Group I

For classification into Group I the following guidelines should be used to further interpret Part I of this Schedule.

Characteristics of the recipient or parental organism(s)

5.—(1) Non-pathogenic

The recipient or parental organisms can be classified as non-pathogenic if they satisfy the conditions of one of the following sub-paragraphs—

(a) the recipient or parental strain should have an established record of safety in the laboratory and/or industry, with no adverse effects on human health and the environment;

(b) the recipient or parental strain does not meet the conditions of sub-paragraph (a) above but it belongs to a species for which there is a long record of biological work including safety in the laboratory and/or industry, showing no adverse effects on human health and the environment;

(c) if the recipient or parental organism is a strain which does not satisfy the conditions of sub-paragraph (a) above and belongs to a species for which there is no record of biological work including safe use in the laboratory and/or industry, appropriate testing (including, if necessary, animals) must be carried out, in order to establish non-pathogenicity and safety in the environment;

(d) if a non-virulent strain of an acknowledged pathogenic species is used, the strain should be as deficient as possible in genetic material that determines virulence so as to ensure no reversion to pathogenicity. In the case of bacteria, special attention should be given to plasmid or phage-borne virulence determinants.

(2) No adventitious agents

The recipient or parental strain/cell line should be free of known biological contaminating agents (symbionts, mycoplasms, viruses, viroids, etc.), which are potentially harmful.

(3) The recipient or parental strain/cell line should have proven and extended history of safe use or built-in biological barriers, which, without interfering with optimal growth in the reactor or fermenter, confer limited survivability and replicability, without adverse consequences in the environment (applicable only for Type B operations).

Characteristics of the vector

6.—(1) The vector should be well characterised

For this purpose the following characteristics should be taken into account.

(a) Information on composition and construction

(i) the type of the vector should be defined (virus, plasmid, cosmid, phasmid, transposable element, minichromosome, etc.);

(ii) the following information on the constituent fragments of the vector should be available—

(aa) the origin of each fragment (progenitor genetic element, strain of organism in which the progenitor genetic element naturally occurred),

(bb) if some fragments are synthetic, their functions should be known;

(iii) the methods used for construction should be known.

(b) Information on vector structure

(i) the size of the vector should be known and expressed in basepairs or D;

(ii) the function and relative positions of the following should be known—

(aa) structural genes,

(bb) marker genes for selection (antibiotic resistance, heavy metal resistance, phage immunity, genes coding for degradation of xenobiotics, etc.),

(cc) regulatory elements,

(dd) target sites (nic-sites, restriction endonuclease sites, linkers, etc.),

(ee) transposable elements (including provirus sequences),

(ff) enes related to transfer and mobilisation function (eg with respect to conjugation, transduction or chromosomal integration),

(gg) replicon(s).

(2) The vector should be free from harmful sequences

The vector should not contain genes coding for potentially harmful or pathogenic traits (eg virulence determinants, toxins, etc.) unless for Type A operations, such genes constitute an essential feature of the vector without, under any conditions or circumstances, resulting in a harmful or pathogenic phenotype of the genetically modified micro-organism.

(3) The vector should be limited in size as much as possible to the genetic sequences required to perform the intended function.

(4) The vector should not increase the stability of the genetically modified micro-organism in the environment (unless that is a requirement of the intended function).

(5) The vector should be poorly mobilisable

(a) If the vector is a plasmid—

(i) it should have a restricted host-range;

(ii) it should be defective in transfer-mobilisation factors eg Tra, MobS.036, for Type A operations or Tra, Mob, for Type B operations.

(b) If the vector is a virus, cosmid or phasmid—

(i) it should have a restricted host-range;

(ii) it should be rendered non-lysogenic when used as a cloning vector (eg defective in the cI-lambda repressor).

(6) It should not transfer any resistance markers to micro-organisms not known to acquire them naturally (if such acquisition could compromise use of drugs to control disease agents).

Required characteristics of the insert

7.—(1) The insert should be well characterised

For this purpose, the following characteristics should be taken into account.

(a) The origin of the insert should be known (genus, species, strain).

(b) The following information on the library from which the insert originated, should be known—

(i) the source and method for obtaining the nucleic acid of interest (cDNA, chromosomal, mitochondrial, etc.);

(ii) the vector in which the library was constructed (eg lambda gt 11, pBR322, etc.) and the site in which the DNA was inserted;

(iii) the method used for identification (colony, hybridization, immuno-blot, etc.);

(iv) the strain used for library construction.

(c) If the insert is synthetic, its intended function should be identified.

(d) The following information on the structure of the insert is required—

(i) information on structural genes, regulatory elements;

(ii) size of the insert;

(iii) restriction endonuclease sites flanking the insert;

(iv) information on transposable elements and provirus sequences.

(2) the insert should be free from harmful sequences—

(a) the function of each genetic unit in the insert should be defined (not applicable for Type A operations);

(b) the insert should not contain genes coding for potentially harmful or pathogenic traits (eg virulence determinants, toxins, etc.), (unless for Type A operations, such genes constitute an essential part of the insert without, under any circumstances, resulting in a harmful or pathogenic phenotype of the genetically modified microorganism).

(3) The insert should be limited in size as much as possible to the genetic sequences required to perform the intended function.

(4) The insert should not increase the stability of the construct in the environment (unless that is a requirement of intended function).

(5) The insert should be poorly mobilisable.

For instance, it should not contain transposing or transferable provirus sequences and other functional transposing sequences.

Required characteristics of the genetically modified micro-organism

8.—(1) The genetically modified micro-organism should be non-pathogenic.

This requirement is reasonably assured by compliance with all the requirements above.

(a) (2) (a) The genetically modified micro-organism should be as safe (to man and the environment) as the recipient or parental strains (applicable only for Type A operations);

(b) the genetically modified micro-organisms should be as safe in the reactor or fermentor as the recipient or parental strains, but with limited survivability and/or replicability outside the reactor or fermenter without adverse consequences in the environment (applicable only for Type B operations).

Other genetically modified micro-organisms that could be included in Group I if they meet the conditions in paragraph 8 above

9.—(1) Those constructed entirely from a single prokaryotic recipient (including its indigenous plasmids and viruses) or from a single eukaryotic recipient (including its chloroplasts, mitochondria, plasmids, but excluding viruses).

(2) Those that consist entirely of genetic sequences from different species that exchange these sequences by known physiological processes.

PART III

Criteria for the classification of organisms other than micro-organisms

10. An organism which satisfies the criteria of this Part is a genetically modified organism—

(a) which is not a genetically modified micro-organism; and

(b) which is as safe in the containment facility as any recipient or parental organism.

SCHEDULE 3

Regulation 7(3)

PARAMETERS TO BE TAKEN INTO ACCOUNT IN RISK ASSESSMENTS, AS FAR AS THEY ARE RELEVANT, UNDER REGULATION 7

Characteristics of the donor, recipient or (where appropriate) parental organism

1. The following matters shall be investigated and assessed in relation to any organism which is or will be a donor, recipient or parental organism—

(a) the name, species, subspecies and strain of the organism;

(b) the degree of relatedness between the donor, recipient (and where appropriate the parental) organism in relation to which the assessment is being carried out;

(c) the sources of the organism;

(d) the reproductive cycle of the organism;

(e) history of prior genetic modifications to the organism;

(f) the stability of the genetic traits of the organism;

(g) the nature of the pathogenicity, virulence, infectivity, toxicity, and vectors of disease transmission of the organism;

(h) the base sequence, frequency of mobilisation and specificity of the organism's indigenous vectors;

(i) the presence in the organism of genes which confer resistance;

(j) the host range of an organism which is a parasite or pathogen;

(k) the organism's other potentially significant physiological traits, and the stability of those traits;

(l) the organism's natural habitat and geographic distribution;

(m) the climatic characteristics of the organism's natural habitat;

(n) the significant involvement of the organism in environmental processes, including nitrogen fixation and pH regulation;

(o) the interaction of the organism with other organisms in the environment and its effect on those organisms, including its likely competitive or symbiotic properties;

(p) the ability of the organism to form survival structures, including seeds, spores or sclerotia.

Characteristics of the modified organism

2. The following matters shall be investigated and assessed in relation to an organism in relation to which a risk assessment under regulation 7 is carried out—

(a) the description of the modification, including the technique used or proposed to be used to introduce a vector or insert into the organism;

(b) the nature and source of the vector introduced into the organism;

(c) the function of the genetic modification and/or of the new nucleic acid;

(d) the structure and amount of any vector or donor nucleic acid remaining in the final construction of the modified organism;

(e) the stability of the genetic traits introduced into the organism;

(f) the frequency of mobilisation of inserted vector or genetic transfer capability;

(g) the rate and level of expression of the new genetic material in the organism, and the method and sensitivity of measurement of that rate and level;

(h) the activity of the expressed protein.

Health considerations

3. The following matters shall be investigated and assessed in relation to an organism in relation to which a risk assessment under regulation 7 is carried out—

(a) toxic or allergenic effects of non-viable organisms and/or their metabolic products;

(b) product hazards;

(c) comparison of the modified micro-organism to the donor, recipient or (where appropriate) parental organism regarding pathogenicity;

(d) capacity for colonization;

(e) if the organism is pathogenic to humans who are immunocompetent—

(i) diseases caused and mechanism of pathogenicity including invasiveness and virulence,

(ii) communicability,

(iii) infective dose,

(iv) host range, possibility of alteration,

(v) possibility of survival outside of human host,

(vi) presence of vectors or means of dissemination,

(vii) biological stability,

(viii) antibiotic-resistance patterns,

(ix) allergenicity,

(x) availability of appropriate therapies.

Environmental considerations

4. The following matters shall also be investigated and assessed in relation to an organism in relation to which a risk assessment under regulation 7 is carried out—

(a) the factors affecting survival, multiplication and dissemination of the modified organism in the environment;

(b) the available techniques for detection, identification, and monitoring of the modified organism in the environment;

(c) the available techniques for detecting transfer of the new genetic material to other organisms;

(d) the known and predicted habitats of the modified organism;

(e) the ecosystems to which the modified organism could be disseminated as a result of an escape;

(f) the anticipated mechanism and result of interaction between the modified organism and the organisms which might be exposed in case of the escape of the organism;

(g) the known or predicted effects of the organism on plants and animals, including pathogenicity, infectivity, toxicity, virulence, vector or pathogen allergenicity, colonisation, predation, parasitism, symbiosis and competition;

(h) the known or predicted involvement of the organism in biogeochemical processes, including nitrogen fixation and pH regulation;

(i) the availability of methods for decontamination of the area in case of release to the environment.

SCHEDULE 4

Regulation 8(1)

INFORMATION REQUIRED FOR A NOTIFICATION UNDER REGULATION 8(1)

A notification required for the purposes of regulation 8(1) shall include the following information—

(a) the name and address of the person responsible for carrying out the activity and the names of persons responsible for supervision, monitoring and safety together with details of their training and qualifications;

(b) address of the premises where the activity is to be carried on and its grid reference and, where appropriate, a description of the sections of the installation;

(c) a description of the nature of the activity to be undertaken, the likely scale of the operation and in particular, in the case of micro-organisms, their classification (whether in Group I or Group II);

(d) a summary of the risk assessment undertaken in accordance with regulation 7;

(e) the names and capacities of the members of the genetic modification safety committee;

(f) comments made by the genetic modification safety committee on the local arrangements for risk assessment;

(g) the names of the biological and deputy biological safety officers concerned with the intended activities (if any);

(h) the name of the supervisory medical officer (if any);

(i) the arrangements for health surveillance (if any); and

(j) any other information the Executive needs for the purpose of maintaining the register referred to in regulation 16.

SCHEDULE 5

Regulation 9

INFORMATION REQUIRED FOR A NOTIFICATION UNDER REGULATION 9

PART I

Information required under regulation 9(3)

1. A notification required for the purposes of regulation 9(3) shall include the following information—

(a) the name and address of the person responsible for carrying out the activity;

(b) address of the premises where the activity is to be carried out;

(c) the date of the notification referred to in regulation 8(1);

(d) the parental organism used, or where applicable the host-vector system used;

(e) the source and the intended function of the genetic material involved in the modification;

(f) the identity and characteristics of the genetically modified organism;

(g) the purpose of the activity including the expected results;

(h) where appropriate the culture volumes to be used or the scale of the activity;

(i) details of waste treatment including levels of live genetically modified micro-organisms in the waste; and

(j) a summary of the risk assessment required in accordance with regulation 7 and of the comments of the genetic modification safety committee on it.

PART II

Additional information required under regulation 9(4)

2. In addition to the information required under Part I a notification made for the purposes of regulation 9(4) shall contain the following information—

(a) a description of the sections of the installation involved and the methods for handling the organisms;

(b) a description of the predominant meteorological conditions and the potential sources of danger arising from the location of the installation;

(c) a description of the protective and supervisory methods to be applied throughout the duration of the activity; and

(d) in the case of micro-organisms, the containment level to which the micro-organism has been allocated in accordance with the risk assessment made in accordance with regulation 7(1) and in any case the safety precautions to be observed.

PART III

Additional information required under regulation 9(5)

3. In addition to the information required under Parts I and II a notification made for the purposes of regulation 9(5) shall contain the information specified in paragraph 5.

4. If it is not technically possible, or if it does not appear necessary to give the information specified in paragraph 5, the reason shall be stated. The level of detail required in response to each subset of considerations is likely to vary according to the nature and scale of the proposed activity. In the case of information already submitted to the Executive by the notifier under these Regulations (or the 1989 Regulations) reference can be made to that information by him.

5. The additional information required is—

(a) information about the genetically modified micro-organisms—

(i) the identity and characteristics of the genetically modified micro-organisms,

(ii) the purpose of the contained use or the nature of the product,

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

(iv) the culture volume to be used,

(v) behaviour and characteristics of the micro-organisms in the case of changes in the conditions of containment or release into the environment,

(vi) overview of the potential hazards associated with the release of the micro-organisms into the environment, and

(vii) substances which are or may be produced in the course of use of the microorganisms other than the intended product;

(b) information about personnel—

(i) the maximum number of persons working in the installation, and

(ii) the number of persons who will work directly with the micro-organisms;

(c) information about the installation—

(i) the activity in which the micro-organisms are to be used,

(ii) the technological processes used,

(iii) a description of the sections of the installation involved, and

(iv) the predominant meteorological conditions and specific hazards arising from the location of the installation;

(d) information about waste management—

(i) types, quantities and potential hazards arising from the use of the micro-organisms,

(ii) waste management techniques used including recovery of liquid or solid wastes and the inactivation techniques used, and

(iii) ultimate form and destination of inactivated wastes;

(e) information about accident prevention and emergency response plans—

(i) the sources of hazards and conditions under which accidents might occur,

(ii) the preventive measures applied such as safety equipment, alarm systems, containment methods and procedures and available resources,

(iii) a description of information given to workers, and

(iv) the information necessary for the Executive to evaluate any emergency plan prepared in accordance with regulation 13;

(f) he full risk assessment referred to in regulation 7; and

(g) any other information the Executive needs for the purpose of maintaining the register referred to in regulation 16.

SCHEDULE 6

Regulation 12(4)

CONTAINMENT MEASURES FOR MICRO-ORGANISMS OF GROUP II

1. The containment measures for Type B operations using micro-organisms from Group II shall be chosen by the user from the levels in the Table below as appropriate to the micro-organism and the operation in question in order to ensure the protection of health of the general population and the environment.

2. Type B operations shall be considered in terms of their unit operations. The characteristics of each operation will dictate the physical containment to be used at that stage. This will allow the selection and design of process, plant and operating procedures best fitted to ensure 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. Engineering practice may require increasingly stringent standards to reduce the risks of failure as the consequence of that failure becomes less tolerable.

	Containment Levels		
B2 SPECIFICATIONS	B3	B4	
1. Viable micro-organisms should be contained in a system which physically separates the process from the environment (closed system)	Yes	Yes	Yes
2. Exhaust gases from the closed system should be treated so as to:	Minimise release	Prevent release	Prevent release
3. Sample collection, addition of materials to a closed system and transfer of viable micro-organisms to another closed system, should be performed so as to:	Minimise release	Prevent release	Prevent release
4. Bulk culture fluids should not be removed from the closed system unless the viable micro-organisms have been:	Inactivated by validated means	Inactivated by validated chemical or physical means	Inactivated by validated chemical or physical means
5. Seals should be designed so as to:	Minimise release	Prevent release	Prevent release
6. Closed systems should be located within a controlled area	Optional	Optional	Yes, and purpose-built
(a) (a) Biohazard signs should be posted	Optional	Yes	Yes
(b) (b) Access should be restricted to nominated personnel only	Optional	Yes	Yes, via airlock
(c) (c) Personnel should wear protective clothing	Yes, work clothing	Yes	Yes, A complete change

	Containment Levels		
B2 SPECIFICATIONS	B3	B4	
(d) (d) Decontamination and washing facilities should be provided for personnel	Yes	Yes	Yes
(e) (e) Personnel should shower before leaving the controlled area	No	Optional	Yes
(f) (f) Effluent from sinks and showers should be collected and inactivated before release	No	Optional	Yes
(g) (g) The controlled area should be adequately ventilated to minimise air contamination	Optional	Optional	Yes
(h) (h) The controlled areas should be maintained at an air pressure negative to atmosphere	No	Optional	Yes
(i) (i) Input air and extract air to the controlled area should be HEPA filtered	No	Optional	Yes

	Containment Levels		
B2 SPECIFICATIONS	B3	B4	
(j) (j) The controlled area should be designed to contain spillage of the entire contents of the closed system	Optional	Yes	Yes
(k) (k) The controlled area should be sealable to permit fumigation	No	Optional	Yes
7. Effluent treatment before final discharge	Inactivated by validated means	Inactivated by validated chemical or physical means	Inactivated by validated physical means