

The Ministerial Ordinance Providing Containment Measures to Be Taken in the Industrial Use of Type 2 Use of Living Modified Organisms

(Tentative Translation)

(Purpose)

Article 1: This Ministerial Ordinance shall have the purpose of stipulating necessary matters concerning containment measures to be taken in the industrial use of Type 2 Use of living modified organisms (excluding use toward commercialization or practical use of living modified organisms preferred to be examined in accordance with the ideas shown in the recommendations, dated July 16, 1986, of the Council of the Organization for Economic Cooperation and Development concerning Considerations on the Safety in Using Recombinants in Industry, Agriculture and Environment) and concerning the confirmation of containment measures in the case where containment measures to be taken are not stipulated, and thereby to ensure proper implementation of industrial use of living modified organisms.

(Definition)

Article 2: In the Ministerial Ordinance, the terms mentioned in the following subparagraphs shall have the meanings stipulated respectively in these subparagraphs.

(1) Modified microorganisms: Of the living modified organisms that possess nucleic acid, or its replicated products, obtained by using technology provided in Article 2 Paragraph 2 Subparagraph 1 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (hereinafter the Law), living organisms belonging to Fungi (excluding mushrooms), those belonging to Protista, those belonging to Monera, virus and viroids.

(2) Modified animals: Of the living modified organisms that possess nucleic acid or its replicated products, obtained by using technology provided in Article 2 Paragraph 2 Subparagraph 1 of the Law, living organisms belonging to Animalia.

(Containment Measures to be taken in the Use in Production Processes of Genetically Modified Microorganisms)

Article 3: Containment measures to be taken in the use in production processes of genetically modified microorganisms (including storage and conveyance in production processes, the same applies to annexed table) in the industrial use of living modified organisms shall be as stipulated in the right columns of the annexed table for the categories of mentioned respectively in the left columns (excluding the cases set forth

in Article 16 Subparagraphs 1, 2 and 4 of the Regulations related to Enforcement of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organizations (Ordinance No. 1 of the Ministry of Finance; the Ministry of Education, Culture, Sports, Science and Technology; the Ministry of Health, Welfare and Labour; the Ministry of Agriculture, Forestry and Fisheries, the Ministry of Economy, Trade and Industry; and the Ministry of the Environment, 2003 (hereinafter “the Enforcement Regulations”) and cases where Type 2 Use is made without taking containment measures to be taken in Type 2 Use because of false information received).

(Containment Measures to Be Taken in Storage)

Article 4: Containment measures to be taken in storage (excluding storage in production processes) in the industrial use of living modified organisms shall be as follows (excluding the cases cited in Article 16 Subparagraphs 1, 2 and 4 of the Enforcement Regulations and cases where Type 2 Use is made without taking containment measures required to be taken in Type 2 Use because of false information received).

(1) A living modified organism shall be put in a container of the structure that prevents the living modified organism from leaking, escaping or other dispersion and it shall be indicated in an easily visible spot of the container that a living modified organism is contained.

(2) The container of the preceding subparagraph in which the living modified organism is put shall be stored clearly in distinction from other living organisms than living modified organisms, and it shall be indicated in a easily visible spot of the equipment for storage that the living modified organism is stored.

(Containment Measures to Be Taken in Conveyance)

Article 5: Containment measures to be taken in conveyance (excluding conveyance in production processes) in the industrial use of living modified organisms shall be as follows (excluding the cases set forth in Article 16 Subparagraphs 1, 2 and 4 of the Enforcement Regulations and cases where which Type 2 Use is made without taking containment measures required to be taken in Type 2 Use because of false information received).

(1) A living modified organism shall be put in a container of a structure that prevents the living modified organism from leaking, escaping or other dispersion.

(2) It shall be indicated in an easily visible spot of the container (in case the container is packed, the packing) of the preceding subparagraph in which the living modified organism is contained that care should be taken in handling.

(Matters Mentioned in Application)

Article 6: Matters to be stipulated by the ordinance of the competent ministries under Article 13 Paragraph 2 Subparagraph 4 of the Law shall be as follows:

- (1) The name of the type of a living modified organism
- (2) The name and the location of a place where Type 2 Use is intended.
- (3) The purpose and an outline of Type 2 Use

(Form of Application)

Article 7: The form of an application stipulated in Article 13 Paragraph 2 of the Law shall be forms stipulated in the following subparagraphs for the categories mentioned respectively in these subparagraphs:

1. Modified microorganisms: Form No. 1
2. Modified animals: Form No. 2

Supplementary Provision

This Ministerial Ordinance shall be enforced on the date of the enforcement of the Law (February 19, 2004).

Annexed Table

Category of living modified organisms	Contents of Containment Measures
1. GILSP modified microorganisms (which are stipulated by Minister of Finance, Minister of Health, Welfare and Labour, Minister of Agriculture, Forestry and Fisheries, Minister of Economy, Trade and Industry or Minister of the Environment as being usable by taking minimum containment measures because proliferation is limited except	A. In Facilities, a working area (an area in which living modified organisms are used and which is clearly distinguishable from other areas. Hereinafter the same applies) shall be provided. B. In the working area, equipment used for – culture or fermentation for manufacturing products by utilization of a modified microorganism shall be provided. C. In the working area, equipment for washing appliances and containers used in manufacturing or testing/examining or for inactivating modified microorganisms sticking to them shall be provided. D. Equipment for testing/examining biological properties of modified microorganisms shall be provided. E. Equipment capable of storing modified microorganisms separately from others shall be provided. F. Effluent and waste product shall be disposed of only after taking a measure for minimizing the number of

<p>under certain cultural conditions and pathogenicity is not found)</p>	<p>modified microorganisms contained therein.</p> <p>G. When a modified microorganism is taken out of the facilities in production processes, it shall be put in a container of the structure that does not allow it from leaking.</p>
<p>2. Category 1 modified microorganisms (other than those set forth in the preceding subparagraph and those stipulated by Minister of Finance, Minister of Health, Welfare and Labour, Minister of Agriculture, Forestry and Fisheries, Minister of Economy, Trade and Industry or Minister of the Environment as having low possibility of being pathogenic)</p>	<p>A. Matters stipulated in A through E and G of the preceding item.</p> <p>B. Facilities shall physically separate modified microorganisms from the air, water or soil outside them.</p> <p>C. Washing or disinfecting equipments to be used by those who engage in work shall be provided in the working area.</p> <p>D. Ventilation equipment (which shall be able to catch modified microorganism) for minimizing the number of modified microorganisms in the air of a room in the working area shall be provided as occasion demands.</p> <p>E. Equipment used for culture or fermentation and equipment directly connected to the said equipment (hereinafter Culture Equipment) shall be examined for air-tightness or performance at the time when it is set up and periodically.</p> <p>F. In case the leakage preventive portion of Culture Equipment is remodeled or replaced, the air-tightness or performance of the said equipment shall be examined each time when such modification or replacement is made.</p> <p>G. Effluent and waste product shall be inactivated.</p> <p>H. When a germ eliminator is replaced or undergoes periodical examination or the contents of manufacturing work are changed, modified microorganisms sticking to the germ eliminator shall be inactivated.</p> <p>I. When modified microorganisms are put into equipment used for culture or fermentation or taken out of it, the modified microorganisms shall be handled so as not to leak from the facilities and in case a modified microorganism sticks to the outside of the Culture Equipment, it shall be inactivated immediately.</p> <p>K. After the working, the used Culture Equipment shall be washed, or modified microorganisms sticking to</p>

	<p>Culture Equipment shall be inactivated.</p> <p>L. The inside of the working area shall be kept clean and effort shall be made to remove rodents and insects.</p> <p>M. Those other than educated and trained personnel engaging in work shall be restricted from entering the working area. In case anyone other than educated and trained personnel enters the area, he or she shall follow directions of the personnel.</p> <p>N. The sign, "Category 1 Being Handled," shall be posted in an easily visible spot in the working area.</p>
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Form 1 (Related to Article 7)

Application for Confirmation of Containment Measures
for Type 2 Use

Date:

To: The Competent Minister

Applicant: Name

Seal

Address

I wish to obtain your confirmation of containment measures to be taken in the Type 2 Use of living modified organisms (modified microorganisms) and apply as follows under the provisions of Article 13 Paragraph 1 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms.

Name of type of living modified organism			
Place intended for Type 2 Use	Name		
	Location		
Purpose and outline of Type 2 Use			
Properties of Living modified organism	Recipient organism or species to which the recipient organism belongs	Taxonomical position and state of distribution in natural environment	
		History and present state of use	
		Mode of reproduction or proliferation	
		Pathogenicity	
		Other information	
	Donor nucleic Acid	Composition, and origins of component elements	
		Functions of component elements	
	Vector	Name and origin	
		Properties	
	Modified micro-organism	Method for Preparation	
State of existence of nucleic acid transferred in cell and stability of expression			
Difference from recipient organism or the species to which the recipient			

		organism belongs	
Containment measures	Category of use		
	Position of working area		
	Equipments	Arrangement	
		Structure	
		Production Process	
Others			

[Notes]

1. If the applicant is a corporation, give the name of the corporation and the name of its representative for “Name of applicant” and the address of its main office for “Address of applicant.”
2. Instead of providing a name (in the case of a corporation, the name of its representative) and fixing a seal, the applicant him-or herself (in the case of a corporation, its representative) may sign his or her name.
3. For “Name of type of living modified organism,” mention a name which allows the living modified organism to be clearly distinguished from other living modified organisms including such information as the name of the taxonomical species of the recipient organism (that is, a living organism in which nucleic acid, or its replicated product,, obtained by using technology provided in Article 2 Paragraph 2 Subparagraph 1 of the Law is transferred. Hereinafter the same applies) and the properties of the living modified organism. And give the identification designated by the creator or a unique identifier designated uniformly by international organizations when it is designated.
4. For “Purpose and outline of the use of living modified organism,” whether the living modified organism is used as a means of production or it is used as a product by itself shall be mentioned, together with the type of the product and the form of its use.
5. For “taxonomical position and state of distribution in natural environment,”
 - (1) Scientific name (genus and species) and the name of strain;
 - (2) In case it is provided by a public organization for conservation of microorganisms, the name of the organization and the strain No.;
 - (3) In other cases than (2), matters that serve as the grounds for identification (for example, points of identity to and difference from a species of which the scientific name has been officially recognized and the ground thereof, the separation source of the strain and the place to which a standard strain produced from it is deposited and storage No.);
 - (4) In case the recipient organism is obtained by carrying out genetic modification, details of the genetic modification (Mention the progress of genetic modification from the wild strain to the strain of the recipient organism as well as the operation of genetic modification used for inducement (for example, induction of mutation by

means of irradiation of ultraviolet rays, or zygosis)). If the recipient organism is a strain already described in major scientific literature, however, the name of that strain shall be mentioned; and

(5) In case a wild strain is used as a recipient organism, state of distribution in the natural environment

shall be mentioned and related materials shall be attached as occasion demands.

6. For "History and present state of use," in case the strain to be used as the recipient organism has a record of industrial use, its details and the period of the use shall be mentioned and related materials shall be attached as occasion demands.

7. For "Mode of reproduction or proliferation," such properties of the recipient organism or the species to which the recipient organism belongs as the cycle of sexual or asexual reproduction, a temperature range for propagation, the speed of propagation, auxotrophy and drug sensitivity shall be mentioned, and related materials shall be attached as occasion demands.

8. For "Pathogenicity," whether or not the recipient organism or the species to which the recipient organism belongs possesses pathogenicity and its ground and whether or not of the existence of pathogenicity-related virus and plasmid shall be given. In case it is known to be pathogenic, details of the pathogenicity, and preventive and therapeutic methods shall be mentioned and related materials shall be attached as occasion demands.

9. For "Other information," whether or not of the production of a biogenic substance that has harmful effect on the recipient organism or the species to which the recipient organism belongs shall be mentioned. In case the existence of a pertinent substance is known, its name and the intensity of its activity and toxicity shall be mentioned and related materials shall be attached as occasion demands. Further, main physiological properties such as the production of antibiotics shall be mentioned and related materials shall be attached as occasion demands.

10. For "Composition and origins of component elements," target genes, neighboring regions and the composition and origin of a regulatory system shall be given. With respect to the structure, a restriction enzyme map, the number of bases and sequence shall be mentioned as occasion demands.

11. For "Functions of component elements," mention functions which the donor nucleic acid (that is, nucleic acid or replicated product thereof, obtained by using technology provided in Article 2 Paragraph 2 Subparagraph 1 of the Law, excluding vector (that is, nucleic acid and its replicated products which replicate, in the recipient organism transferred, the whole or a part thereof. Hereinafter the same applies). Hereinafter the same applies) possesses in the capacity of genes, and a metabolic pathway assumed in the case of producing or treating a substance.

12. For "Name and origin," the name of the vector and the taxonomic position of the

living organism from which the vector originate shall be given.

13. For "Properties," the infectiousness, pathogenicity, transmissibility and the number of bases of the vector shall be mentioned as far as clearly known. In case a known vector is converted or modified and a new vector is developed, literature concerning the vector before the conversion or modification shall be attached and explanation about what is converted or modified shall be mentioned. Properties of the living organism from which the vector originates shall also be mentioned as occasion demands.

14. For "Method for preparation,"

(1) The composition of nucleic acid to be transferred into a cell (arrangement of target gene, promoter and marker) and the method of inserting the target gene into the vector;

(2) The method of transferring the target gene into the recipient organism;

(3) The progress of rearing the modified microorganism (the method of selecting the modified microorganism and an outline of the subsequent progress of rearing) shall be mentioned, and illustrated as occasion demand.

15. For "State of existence of nucleic acid transferred in cell and stability of expression,"

(1) Whether or not the transferred nucleic acid is integrated in a chromosome of the living modified organism or exists in cytoplasm; and

(2) Stability of expression of target gene in the recipient organism shall be mentioned.

16. For "Difference from recipient organism or the species to which the recipient organism belongs," difference from the recipient organism in matters mentioned for "the mode of reproduction or proliferation," "pathogenicity" and "other information" shall be mentioned and related materials shall be attached as occasion demands. If there is any feature enabling it to be distinguished from the recipient organism, mention it, too.

17. For "Category of use"; categorization shall be made in accordance with the listing below, it shall be mentioned that for an appropriate category of the living modified organism in the left column of the annexed table, corresponding containment measures stipulated in the right column of the annexed table are taken. Those which do not fall in any of the following categories shall be classified as "Others", and detail of the containment measures planned to be taken shall be mentioned on annex.

a. GILSP (recipient organism, donor nucleic acid, vector and modified microorganism meet the following standards):

(1) Recipient organism

(A) Not being pathogenic;

(B) Not containing pathogenic virus and plasmid; and

(C) Either having a record of being used safely for a long period of time or

propagation under special conditions of culture with limitation in propagation under other conditions.

(2) Donor nucleic acid and vector

(A) Properties are sufficiently known and do not contain sequences recognized to be harmful; and

(B) Hardly transmissible and not transmitting a resistant marker gene to living cells that are not known to acquire resistance originally.

(3) Modified microorganism

(A) Not being pathogenic; and

(B) Not having higher prolificity compared to recipient organism;

b. Category 1 (Modified microorganisms which are low in the possibility of having pathogenicity and are not included in GILSP)

18. For "Position of working area," show by a diagram the arrangement of buildings in and outside the place of work and their names and the working area.

19. For "Arrangement," give a plane view which includes the working area, and mention the positions and the names of main installations for handling living modified organisms.

20. For "Structure," about the installations or equipment for handling modified microorganisms, mention the following, and illustrate as occasion demands.

(1) Specification of the equipments;

(2) Drainage system; and

(3) Ventilation equipment (in the case of the "Category 1" Use, the ventilation equipment of the building(s) or the room(s) within the working area for which forced ventilation is carried out).

21. For "Production process," an outline of the processes of production of the modified microorganism or the production of a substance to be carried out by using the modified microorganism shall be shown by a diagram. In the diagram, names of various machines and apparatuses and positions of valves shall be indicated and the name and detailed description of each process shall be mentioned as occasion demands.

22. For "Other," matters concerning the following shall be mentioned as occasion demands.

(1) Knowledge already obtained with regard to the use of living modified microorganisms other than the abovementioned;

(2) Measures to be taken in an emergency such as an accident; and

(3) The management system taken by the business operator

23. Use paper of JIS A4 in size.

Form 2 (Related to Article 7)

Application for Confirmation of Containment Measures
for Type 2 Use

Date:

To: The Competent Minister

Applicant: Name

Address

Seal

I wish to obtain your confirmation of containment measures to be taken in the Type 2 Use of living modified organisms (modified animals) and apply as follows under the provisions of Article 13 Paragraph 1 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms.

Name of type of living modified organism			
Place intended for Type 2 Use	Name		
	Location		
Purpose and outline of Type 2 Use			
Properties of Living modified organism	Recipient organism or species to which the recipient organism belongs	Taxonomical position and state of distribution in natural environment	
		History and present state of use	
		Mode of reproduction	
		Viability and fecundity in natural environment	
		Other information	
	Donor nucleic Acid	Composition and origins of component elements	
		Functions of component elements	
	Vector	Name and origin	
		Properties	
	Modified animal	Method for Preparation	
		State of existence of nucleic acid transferred in cell	

		and stability of expression	
		Difference from recipient organism or the species to which the recipient organism belongs	
Containment measures	Position of working area		
	Equipments	Arrangement	
		Structure	
Others			

[Notes]

1. If the applicant is a corporation, give the name of the corporation and the name of its representative for “Name of applicant” and the address of its main office for “Address of applicant”.
2. Instead of providing a name (in the case of a corporation, the name of its representative) and fixing a seal, the applicant him-or herself (in the case of a corporation, its representative) may sign his or her name.
3. For “Name of type of living modified organism,” mention a name which allows the living organism to be clearly distinguished from other living modified organisms including such information as the name of the taxonomical species of the recipient organism and the properties of the living modified organism. And give the identification designated by the creator or a unique identifier designated uniformly by international organizations when it is designated.
4. For “Purpose and outline of Type 2 Use,” give concrete description of the purpose and an outline of the Type 2 Use of the living modified organism.
5. For “Taxonomic position and state of distribution in natural environment,”
 - (1) Scientific names (genus and species) and the name of the species of the animal (Japanese name or English name) and the name of the variety or the phyletic line if such exist;
 - (2) The contents of genetic modification used to create the variety of the recipient organism (including a genealogical chart from the variety of origin through the variety of the recipient organism intended for use as well as the operation of genetic modification used for creation (for example, subculturing in inbred line); and
 - (3) The state of distribution in the natural environment shall be mentioned and related materials shall be attached as occasion demands.
6. For “History and present state of use,” mention a record of the use of the recipient organism or the species to which the recipient organism belongs, the main form and purpose of the use.
7. For “Mode of reproduction,” mention the period of sexual maturation, breeding season, estrous cycle, pregnant period and litter size in the case of viviparity of

Mammalia; and equivalent information for other modes of reproduction or propagation.

8. For "Viability and fecundity in natural environment," mention assumed points about the viability and fecundity of the variety of the recipient organism by comparing the state in general, free environment with the environment of the main form of the use.
9. For "Other information," mention main physiological properties such as the production of substances, including harmful ones, which affect individuals of other living organisms.
10. For "Composition and origins of component elements," mention information on a target gene, neighboring regions and the composition and the origin of a regulatory system as far as clearly known. Further, on the structure, give a restriction enzyme map, the number of bases and sequence as occasion demands.
11. For "Functions of component elements," the functions donor nucleic acid possesses in the capacity of genes and a change in metabolic pathway shall be mentioned.
12. For "Name and origin," the name of the vector and the taxonomic position of a living organism from which the vector originate shall be mentioned.
13. For "Properties," such properties of the vector as infectiousness, pathogenicity, transmissibility and the number of bases shall be mentioned as far as clearly known. In case a known vector is converted or modified and a new vector is developed, literature concerning the vector before the conversion or modification shall be attached and explanation about what has been converted or modified shall be mentioned. Properties of the living organism from which the vector originate shall also be mentioned as occasion demands.
14. For "Method for preparation,"
 - (1) The composition of and the method of preparing nucleic acid to be transferred in a cell (the entire composition (sequences of target gene, promoter and marker) of nucleic acid to be transferred in a cell and the method of inserting the target gene into the vector);
 - (2) The method of transferring the target gene into the recipient organism (the method of transferring nucleic acid to be transferred in cells into the recipient organism (for example, microinjection, the method using a virus vector or the method using an embryonic stem cell)); and
 - (3) The progress of rearing the modified animal (how the modified animal has been selected and an outline of the subsequent progress of rearing) shall be mentioned. In addition, illustrate essential points as occasion demands.
15. For "State of existence of nucleic acid transferred in cell and stability of expression,"
 - (1) Whether the transferred nucleic acid is integrated in a chromosome of the modified animal or exists in cytoplasm; and

2) Stability of expression of the target gene in the recipient organism (findings on the expression of the target gene obtained as a result of subculturing the modified animal)

shall be mentioned.

16. For “Difference from recipient organism or the species to which the recipient organism belongs,” difference from the properties of recipient organism or the species to which the recipient organism belongs in the mode of reproduction, viability and fecundity in the natural environment, the production of an infectious virus and other information shall be mentioned. If there is any morphological feature enabling it to be distinguished from the recipient organism or the species to which the recipient organism belongs, mention it, too.

17. For “Position of working area,” show by a diagram the arrangement of buildings in and outside the place of work and their names and the working area.

18. For “Arrangement,” show a plane view of a working site which includes the working area. The position and the name of main equipment for handling modified animals, and if deemed necessary the positions of notes to warn outsiders shall be shown in the plane view.

19. For “Structure,” mention the specifications of the equipments for handling modified animals. In case special equipment is provided in a drainage system or the like in order to handle modified animals, the said equipment shall be shown by a diagram.

20. For “Other,” matters concerning the following shall be mentioned as occasion demands.

(1) Knowledge already obtained with regard to the use of modified animals other than the abovementioned;

(2) Measures to be taken in an emergency such as an accident; and

(3) The management system taken by the business operator.

21. Use paper of JIS A4 in size.