

RISK ASSESSMENT OF GENETICALLY MODIFIED MICRO-ORGANISMS: A FORMAT THAT OFFERS ONE POSSIBLE WAY OF ACHIEVING GOOD PRACTICE

1 Regulation 6 of the Genetically Modified Organisms (Contained Use) Regulations 2000, GMO(CU), requires that a suitable and sufficient assessment of the risks to human health and the environment be carried out before any activity involving genetic modification of micro-organisms is commenced. The assessment must take into account the matters in Part I of Schedule 3 and include the steps in Part II of Schedule 3. The ACGM Compendium of Guidance provides example risk assessments for the activities covered in Parts 2A-2C and 2E in the annexes to the Compendium. These, together with the issues raised in the relevant part of the Compendium and Schedule 3 of GMO(CU) should provide a sound basis for risk assessment completion.

2 In the experience of HSE Specialist Inspectors many risk assessment formats are not particularly user-friendly, whilst others are limited to tick-boxes or questions that invite 'yes' or 'no' answers and thereby fail to elicit a full assessment. For these reasons an example risk assessment format, which represents one way of achieving good practice, has been compiled.

3 One problem that can arise as a consequence of designing a risk assessment form to cover all types of work, is that, if care is not taken, proposers of new projects may be required to undertake considerable amounts of paperwork, regardless of the type of work being proposed. The example format, which comes in two parts, shows one way of tackling this problem. Part 1 is a streamlined form that everyone would be expected to complete. If on completion of this form it emerged that the work was clearly class 1, Part 1 might in itself be sufficient for the local Genetic Modification Safety Committee, GMSC, to approve the work. For example, it would seem appropriate to allow the majority of work with disabled bacteria, yeast and cultured mammalian cells to proceed on the basis of a consideration by the safety committee of an abbreviated assessment. On the other hand, if the risk assessment was not straightforward, it would be necessary to complete the much more detailed format in Part 2.

4 Part 2 of the format is designed to assist scientists in undertaking assessments where the issues involved are complex and require detailed consideration. The aim is to take the scientist proposing the work through the process in a logical and systematic way. It is hoped that the structure provided within the format itself will assist the proposers in structuring their thought processes and that it will indicate to them those aspects of specific types of work which need to be given particular attention.

5 The format should not be regarded as suitable for all circumstances. It will almost certainly need to be adapted to meet the needs of individual research establishments. For example, as it stands, the form is designed to aid risk assessments of activities involving genetically modified micro-organisms, GMMs, where the risks to human health are of paramount importance. The form would, therefore, need modification or expansion before it would be suitable to assist in risk assessment of activities where environmental considerations are greatest.

Additional points relating to procedures used for risk assessment of GM work

6 Shortcomings in risk assessments that are frequently observed include:

- One-word answers.

- Lack of justification, explanation and detail
- Failure to adequately describe the nature and biological effects of inserted sequences and how these could alter the nature and biology of the parental organism.
- Failure to consider the risks to the environment. The environment is considered to be land, air and water and any organisms that live in these habitats.

Review of risk assessments

7 Regulation 8 of GMO(CU) states that:

'Where there is reason to suspect that the assessment is no longer valid or there has been a significant change in the activity involving genetic modification, the person undertaking the activity shall ensure that the assessment is reviewed forthwith.'

Obviously some assessments will change more frequently than others. Often the proposed GM activity changes as the work proceeds and results are obtained. This has caused problems as HSE inspectors have found situations where the details of GM activities were changed such that the containment measures in place were no longer suitable for the work underway. It is therefore advisable that risk assessments be reviewed every 1 to 2 years, depending on the class of the activity, to ensure that they reflect the risks of the current activity.

A FORMAT FOR RISK ASSESSMENT OF GENETICALLY MODIFIED MICOORGANISMS

Part 1

(a) Title of project

(b) Scientific goals of project

This information provides a useful background and puts the work in context. This step is not obligatory. The scientific goals need not be disclosed if presenting the information presents problems in relation to intellectual property rights or commercial sensitivity.

(c) An overview of the different types of GMM that will be constructed

This overview should consist of 1 or 2 paragraphs, outlining the scope of the project and setting the boundaries of exactly what work will be done. This overview should be complemented with lists of recipient strains, vectors and inserts that will be used in the project.

(i) List of recipient strain(s)

Cover the name of the strain, the name of the wild-type organism from which it is derived and the extent to which it is disabled.

(ii) List of vector(s)

Cover names and any disabling mutations.

(iii) List of function of inserted gene(s)

In doing this genes should be identified in such a way that an outside reviewer will have a general idea of their function i.e. providing a three-letter name may not be sufficient. Where the function of a gene is unknown, it may help to provide details of any known homologues.

(d) An indication of the most hazardous GMM

Considering both human health and the environment the most hazardous GMM that will be constructed in this work should be identified. This will be the most hazardous combination of recipient strain, vector and inserted material from the lists made under part (c). With some projects it will not be clear that any one GMM will be any more hazardous than any of the others (e.g. if all the work is class 1). If this is the case this should be stated.

(e) Are you confident that for all of the GMMs covered by this assessment there are no harmful properties associated with the recipient strain, the vector, or the inserted material?

If the answer to this question is 'No' or you are in any way unsure, Part 2 of this form should be completed.

(f) Are you confident that none of the final GMMs could be hazardous to humans or the environment?

If the answer to this question is 'No' or you are in any way unsure, Part 2 of this form should be completed.

If the GMM meets BOTH of the above criteria, you may believe that you have sufficient information at this stage to classify the project to **class 1**, as defined in the Contained Use Regulations 2000. In order to do this you should be confident that even in the event of a total breach of containment the genetically modified organism would be of no or negligible risk to human health or the environment.

If you are assigning the work to **class 1** according to the above streamlined procedures, sign the form below and submit it to who will arrange for it to be considered by the local

Genetic Modification Safety Committee. Work should not be commenced until this form has been reviewed by the GMSC.

If you have any uncertainty as to whether the proposal meets the above criteria you should obtain a continuation form from and undertake a more detailed risk assessment.

Signature of Proposer:

Background notes

It is not appropriate to consider non-disabled pathogens of plants, humans, animals or insects as inherently safe recipient micro-organisms. Examples of inherently safe recipient microorganisms which, depending on the nature of the insert, would in most cases be expected to form the basis of extremely safe GMMs are as follows:

(i) *E. coli* K12

(ii) Defective retrovirus produced from packaging line in which the helper genes are located in two separate blocks of DNA (thus eliminating the possibility of a reversion to replication competence by a single recombination event) and which are self-inactivated to prevent insertional activation.

(iii) E1 deleted adenovirus

The types of gene which when cloned into particular recipient microorganisms might give rise to a harmful phenotype can be divided into two types. First the gene might encode a product that could act directly to cause harmful effects e.g. a toxin gene or a cytokine. Second the gene might encode a product that could act alongside the existing characteristics of the recipient microorganism so as to endow the GMM with altered pathogenic properties e.g. a pathogenicity gene or an engineered viral envelope gene with an altered receptor binding capacity.

Part 2 – Continuation Form for Use in Cases Where a Detailed Risk Assessment is Necessary

Projects that have a broad scope will involve the construction of several GMMs. Part 2 is designed for the detailed assessment of a single GMM. In general, as long as the scope of the work has been satisfactorily outlined in Part 1, it is sufficient to complete Part 2 for the most hazardous GMM being constructed. This will be the one identified in Part 1(d). In cases where there are two or more hazardous GMMs, with quite different properties, two or more copies of Part 2 may need to be completed.

In the format shown here, hazards to human health are considered first and used as the basis for assigning provisional containment prior to addressing environmental issues. In cases where environmental issues are of prime concern and there is little possibility of harm to humans e.g. work with plant or animal pathogens, it may be helpful to restructure the form and consider environmental issues first.

(a) Hazards to human health

(i) Hazards associated with the recipient microorganism (e.g. bacterial host or viral vector)

Factors to consider include whether the recipient microorganism is listed in ACDP hazard groups 2, 3 or 4. Other relevant factors may be the micro-organism's mode of transmission, disease symptoms, host range, and tissue tropism as well as an indication as to whether vaccines or chemotherapeutic agents are available. Information should also be provided on any disabling mutations and whether there is any possibility of any disabling mutations being complemented or reverting.

(ii) Hazards arising directly from the inserted gene product (e.g. cloning of a toxin gene or oncogene)

Consideration should be given to whether the inserted DNA encodes a toxin, an oncogenic protein, an allergen, a modulator of growth or differentiation (hormone or cytokine) or any other protein, which may result in potentially harmful biological activity. Where the function of the inserted gene is unknown, it may help to describe the function of any known homologues. Please note that even a normal human gene may be harmful if overexpressed, especially if the overexpression is in tissues that do not normally express the protein.

(iii) Hazards arising from the alteration of existing traits (e.g. alteration of pathogenicity, host range, tissue tropism, mode of transmission or host immune response)

One factor to consider is whether the inserted gene encodes a pathogenicity determinant, such as an adhesin, a penetration factor or a surface component providing resistance to host defence mechanisms. Another important consideration is whether the inserted gene encodes a surface component, envelope protein or capsid protein that might bind to a different receptor to that used by the recipient microorganism. Consideration should also be given to whether the inserted DNA (or the plasmid sequence) encodes resistance to a drug or antibiotic that might be used for the treatment of a laboratory-acquired infection.

(iv) The potential hazards of sequences within the GMM being transferred to related microorganisms

Factors to consider include whether widespread dissemination of the inserted gene as a result, for example, of either gene transfer or recombination of the GMM with a wild-type microorganism, would be a matter of concern. If this is the case an important consideration will be whether, in the event of a breach of containment the GMM could survive in the environment for long enough for such a gene transfer to take place.

(b) Assignment of a provisional containment level that is adequate to protect against hazards to human health

This step will involve considering the containment level necessary to control the risk of the recipient microorganism (i.e. the ACDP Hazard Group of the recipient microorganism) and making a judgment about whether the modification will result in a GMM, which is more hazardous, less hazardous, or about the same.

Sometimes it may help to compare the GMM with the relative hazard presented by other organisms that would fall within the same ACDP Hazard Group as the GMM.

(c) Identification of any hazards to the environment

(i) Hazards associated with the recipient microorganism (e.g. bacterial host or viral vector)

Factors to consider include whether the recipient microorganism is capable of infecting any plants, animals or insects in the environment and whether there is any possibility of any disabling mutations being complemented or reverting. In particular it should be ascertained whether the recipient microorganism is a pathogen that is controlled by DEFRA.

(ii) Hazards arising directly from the inserted gene product

Factors to consider include whether the sequence encodes an insect or animal toxin or a product which can cause silencing of a gene encoding a crucial metabolic enzyme in susceptible hosts.

(iii) Hazards arising from the alteration of existing traits (e.g. alteration of pathogenicity, host range or tissue tropism)

One factor to consider is whether the inserted sequence encodes a pathogenicity determinant, such as an adhesin, a penetration factor or a surface component providing resistance to host defense mechanisms. Another important consideration is whether the inserted gene encodes a surface component, envelope protein or capsid protein that might bind to a different receptor to that used by recipient microorganism.

(iv) The potential hazards of sequences within the GMM being transferred to related microorganisms

Factors to consider include whether widespread dissemination of the inserted gene as a result, for example, of either gene transfer or recombination of the GMM with a wild-type microorganism, would be a matter of concern. If this is the case an important consideration will be whether, in the event of a breach of containment the GMM could survive in the environment for long enough for such a gene transfer to take place.

(d) Consideration of the nature of the work to be undertaken and a detailed review of the control measures

(i) Are any of the work procedures likely to generate aerosols?

If so, should the work be undertaken in a safety cabinet or isolator?

(ii) How will waste materials be disposed of?

Include both solid and liquid laboratory waste and waste from experiments with infected animals.

(iii) Will it be necessary to use sharps?

Does work involve glass Pasteur pipettes?

(iv) If the work involves the experimental infection of animals is it known whether the animal will shed the GMM?

(v) If the work involves the experimental infection of plants what is known about the likely route of transmission of the GMM?

For example, is the microorganism insect-borne or carried in run-off water? This will have important implications for the type of glasshouse used.

(vi) In the case of organisms whose multiplication involves a complex life-cycle will the work involve the propagation of organisms that are in stages in that life-cycle that are particularly hazardous?

Examples include the propagation of the infective stages of parasites or the release of spores from fungi. Consideration should be given to all potential routes of transmission including those that might not be used naturally.

(vii) Have any disinfectants been validated under the actual conditions of use?

For example, if disinfectant is being used for the treatment of virus in tissue culture medium, is it known that the disinfectant is effective in the presence of high levels of protein?

(viii) Does the nature of this work preclude it being undertaken by any workers who have a serious skin condition (e.g. eczema) or other health problems that might make them more susceptible to infection (e.g. some kind of immunological defect)?

(ix) Will workers receive any vaccinations or health surveillance?

(e) Consideration of whether there is a need to assign additional measures over and above the provisional level of containment.

It should be noted that the containment measures set out in Part II of Schedule 8 of the Contained Use Regulations will include some measures that are required where and to the extent that the risk assessment shows they are required

Additional measures may be necessary in any of the following circumstances:

- (i) to take full account of any properties of the GMM that may be hazardous to human health.
- (ii) to protect the environment.
- (iii) to provide additional safeguards for particular work procedures.

Part 3. Final assignment of containment measures and risk class

The following aspects of this project are assigned to class 1.

The following aspects of this project are assigned to class 2.

The following aspects of this project are assigned to class 3.

The following aspects of this project are assigned to class 4.