PART 2
RISK ASSESSMENT OF GENETICALLY MODIFIED ORGANISMS

Introduction

1. The Genetically Modified Organisms (Contained Use) Regulations 2000 - referred to hereafter as the Contained Use Regulations - clearly set out the essential elements of a risk assessment and the basic procedure to be followed. This approach, while new in the regulations, is essentially the same as that described in the previous editions of the Compendium of Guidance, so users who are familiar with the ACGM guidance should encounter little change in the advice that follows.

2. Although the process of risk assessment has been more formally addressed in regulation, those carrying out the assessment still have flexibility in the way it is actually conducted. For example, although the regulations describe the assessment of human health and environmental risks as one process, human health risks could continue to be assessed separately from environmental risks (as was the case in previous editions of this guidance).

3. As well as the general guidance on risk assessments in this section, there is detailed guidance on different GMOs and activities in the following sections:

- **Part 1** for guidance on risk assessments under the COSHH Regulations;
- **Part 2A** on the risk assessment of work with bacteria and cell cultures;
- **Part 2B** on the risk assessment of work with genetically modified human and animal viruses
- **Part 2C** on the risk assessment of work with genetically modified plant viruses;
- **Part 2D** on the risk assessment of work with genetically modified plants (replacing ACGM Note 10);
- **Part 2E** on the risk assessment of work with transgenic animals (replacing ACGM Note 9).

4. A series of worked examples of risk assessments (some of which appeared in ACGM Newsletter 26) are given in the Guide to the

   Genetically Modified Organisms (Contained Use) Regulations 2000. These examples are to illustrate the process of risk assessment set out in the Contained Use Regulations. The format used for the examples in the Guide is probably rather too artificial to be very useful for undertaking actual risk assessments. For this reason the same examples are presented in the Compendium, but in formats which follow the structure of the guidance in the relevant Part. For instance, an example dealing with genetic modification of an adenovirus is annexed to Part 2B and follows the recommended procedure as set out in 2B. Further examples are annexed to Part 2A and Part 2C.

5. One very important point to emphasise is that once performed, risk assessments should not be simply put to one side. They must not only be used to decide the appropriate containment and control measures (taking into account good microbiological practice - GMP - and good occupational safety and hygiene - GOSH\(^1\)), but must also be kept under review. Information derived from the work itself which has a bearing on risk should be fed into the assessment as it becomes available. Equally, new information from the scientific literature needs to be taken into account and the risk assessment re-appraised where necessary. A risk assessment is only as good as the quality of the information which goes into it. It is therefore important to acknowledge uncertainty and to update information where possible.

6. Remember that where new information, which may have significant consequences for the risks of a notified activity, becomes known the competent authorities for the Contained Use Regulations must be informed. (Submit such notifications to HSE, Bootle.)

Risk assessments under the Contained Use Regulations

7. The Contained Use Regulations require that, before commencing any activity involving genetic modification of micro-organisms (GMMs), a

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\(^1\) See Part 3 paragraph 25 for detail of GMP and GOSH.
'suitable and sufficient' assessment is made of the risks to human health and safety and to the environment [regulation 6]. The risk assessment must:

- take into account the matters listed in Part I of Schedule 3 to the regulations; and
- include the steps identified in Part II of Schedule 3.

8. For genetically modified (GM) plants and animals, these regulations also require that, before commencing any activity a 'suitable and sufficient' assessment is made of the risks to human health and safety [regulation 7].

9. Assessment of risk to the environment for GM plants and animals must also be carried out, although this is a requirement of the Environmental Protection Act (EPA) 1990 and associated regulations - the Genetically Modified Organisms (Risk Assessment) (Records and Exemptions) Regulations 1996 (as amended in 1997) (referred to hereafter as the Records and Exemptions Regulations).

10. For GM animals and plants, under the Contained Use Regulations, the assessment of risks to human health and safety must:

- take into account the matters listed in Part I of Schedule 4 to the regulations; and
- include the steps identified in Part II of Schedule 4.

11. There is no equivalent set procedure or list of matters to take into account in the EPA or the Records and Exemptions Regulations to guide assessment of environmental risks. However, it is recommended that a similar approach to that for human health risks from GM plants and animals, as described in the Contained Use Regulations, is used (see para 29-30).

"Harm" to the environment and "risk"

12. "Harm to the environment" is difficult to define or to quantify precisely. Section 107(6) of the EPA is useful as guidance, especially as the Act does impinge on the Contained Use Regulations. The EPA defines harm as follows:

"harm means harm to the health of humans or other living organisms or other interference with the ecological systems of which they form part and, in the case of man, includes offence caused to any of his senses or harm to his property".

13. For example, following an escape from containment, for instance of pollen from a glasshouse, or of transgenic animals, the unintentional transfer of genes to a farmer's crops or livestock is a potential hazard and could constitute harm if realised. Toxic or allergenic effects arising from the expression of genes in pollen is a potential hazard to human health. Possible displacement of "natural" populations by GMOs would also constitute a potential hazard as would the potential for other ecological damage.

14. The environment is defined as "land, air or water" and harm would result if an organism affected any or all of these components of the environment directly, or in such a way that in turn, deleterious effects were produced on other organisms ("knock-on" effects). Components of the environment are here taken to mean organisms and systems of which these form part.

15. Risk is defined as the probability that a particular adverse event (or "harm") occurs during a stated period of time or results from a particular challenge. In the context of the contained use of GMOs, therefore, the objective of an environmental risk assessment is to determine the probability of harm to the environment, including ecological damage, arising as a result of the escape of organisms from the containment facility. This assessment must include escape to the environment by means of waste streams/waste disposal etc.

16. Risk assessment has to take into account an assessment of the degree of potential harm, severity of consequence, and the likelihood, or frequency, of that harm occurring.

Level of detail required

17. The level of detail to be considered in a risk assessment will depend on circumstances. It has to be "suitable and sufficient" [regulations 6(1) and 7(1)]. However, this does not mean it has to be very detailed; it may be short, for example, where it is immediately obvious that the risks are low or that the proposed control measures are clearly adequate. For a simple operation involving a low hazard, well known and well understood organism

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2 Risk: Analysis, Perception and Management: The Royal Society, London 1992

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it may be possible to declare the result of the assessment almost at first glance. For a complex operation involving more hazardous organisms about which there is a lot of uncertainty, the assessment will have to be extensive and may involve the acquisition of new data.

18. There is no need to include every detail or to spell out in detail what is in the text books or HSE/ACGM guidance, etc. But the logic of the argument should be clear and enough detail should be included for the assessment to be reviewed without needing to request additional information. Care should be taken to justify statements - this may be by providing references to the scientific literature. Note also that under regulation 14(2) and (4) any delays caused by the need to request additional information will not be counted as part of the time period for review of a notification and, in addition, work may not commence until HSE has given its approval.

**Review of assessment**

19. A risk assessment should be reviewed if there is any reason to suspect that the initial assessment is no longer valid because of a significant change in the activity [regulation 8(1)]. Examples of such changes might include:

- change of scale of operation;
- change of containment measures;
- change in waste treatment procedures; or
- the availability of new information concerning the organism.

20. Records of risk assessments should be kept for at least 10 years from the date that the work covered by the risk assessments finished.

**Risk assessment of activities involving genetic modification of micro-organisms**

21. Parts I and II of Schedule 3 to the regulations set out the things to consider and the steps to be included in the risk assessment. This must cover both human health and safety and environmental risks.

22. The risk assessment requires the identification of hazards (harmful effects) associated with the host (recipient) micro-organism, and where appropriate, the donor micro-organism. In many cases, the characteristics of the host organism will be more relevant to a risk assessment than those of the donor organism. As a general guide, if a donor organism is merely used as a source of well characterised DNA for a selectable phenotype (e.g. kanamycin resistance or β-galactosidase activity) or a promoter or other control sequence, the characteristics of the donor will not need to be considered. If, however, the insert contains genes encoding biologically active molecules, toxins or virulence factors, then relevant information from the donor organism should be considered.

23. When constructing cDNA or genomic libraries it will be necessary to consider the range of the possible hazards associated with the donor organism. This should be commensurate with the level of hazard and the likely abundance of hazardous sequences.

24. Consideration of the hazards associated with the organism and its constituent parts and the severity of any possible harmful effects will result in the identification of a provisional containment level for the GMM. This identification can also be informed by taking into account relevant classification schemes for micro-organisms such as the Approved List of Biological Agents or the MAFF classifications of animal and plant pathogens. In effect, a judgement is being made about the containment necessary to control the risk of the host and whether the modification affects the risk; i.e. does it increase, decrease or stay the same.

25. This provisional containment level is then adjusted in light of other information such as:

- the nature of the work (e.g. scale);
- any non routine procedures or other procedures which might significantly affect the risk associated with the GMM, e.g. procedures which give rise to aerosols; and
- the characteristics of the environment (see below) likely to be exposed to the GMM.

26. This stage will include an estimation of the likelihood that the hazard(s) will be realised. It is helpful to refer back to the provisional containment level that has been allocated when making this assessment of likelihood. As a result of these considerations, it may be apparent that different containment measures from those indicated by the hazard of the GMM and would be needed. The

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3 Second supplement to: Categorisation of biological agents according to hazard and categories (fourth edition, 1995). Available from HSE Books (C40 02/00 MISC208). The list is also reproduced on HSE's Internet web site.

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provisional containment, therefore, would need to be adjusted to ensure that all hazards are properly controlled by the proposed final containment.

27. The containment measures selected ultimately determine the class of the activity. The Contained Use Regulations now link notification with this classification - this is a significant change from the previous regulations where notification was triggered by classification of the GMM (Group I/II) and a categorisation of the activity (Type A/B). For further detail on containment requirements see the relevant sections of Part 3. Guidance on the notification process itself can be found in Guide to the Regulations and Part 1 of the Compendium.

**Assessing environmental risks**

28. For the large majority of GM work, containment measures selected to protect human health will also be sufficient to protect the environment. Nevertheless, assessing environmental risks is required to ensure that such containment also reduces all of the identified environmental risks to an acceptable level.

29. If the environmental risk assessment indicates that the level of containment set for human health and safety is not sufficient, then additional controls will be required to ensure that all risks are controlled to low or effectively zero.

   For example, risk assessment of work with a MAFF group 2 animal pathogen, exotic to the UK, which has been modified such that it can infect indigenous species may show that laboratory containment level 2 is still sufficient to protect human health but that filtration of extract air through HEPA filter (a feature of CL3) would be required in order to protect the environment.

**Risk assessment of activities involving organisms other than micro-organisms**

30. The Contained Use Regulations require an assessment of risks to human health from GM animals or plants. It is recognised that the risks from such organisms are likely to be low or that the modified organism will present no greater risk than the unmodified organism. Therefore, assessment should concentrate more on the possible additional hazards to human health which result from the genetic modification itself, e.g. does modification make the plant more allergenic/toxic? Does the modification change the behaviour of animal such that it presents a greater risk that the parental animal? Schedule 4 to the Contained Use Regulations sets steps to be included in the assessment of risks to human health and safety together with a number of factors that should be considered during the assessment.

31. As has already been indicated, assessment of environmental risks for work with GM animals and plants is not required under the Contained Use Regulations - it is however still a regulatory requirement (see para 9). Although there is no equivalent of Schedule 4 in the regulations made under the Environmental Protection Act, it is recommended that a similar procedure to that used to assess human health risks is used to assess environmental risks.

32. By using Schedule 4 as a basis but with the inclusion of other appropriate potentially harmful effects and taking into account relevant factors in Part I of Schedule 3 (see Box 1), the environmental assessment can be carried out in much the same format as that for human health.

**Box 1 - Hazards to take into account when assessing environmental risks of GM work with non-micro-organisms**

- disease to plants or animals;
- acting as an animal or plant disease or vector;
- adverse effects arising from the inability to treat animal or plant disease or offer effective prophylaxis;
- ability to survive, establish or disseminate in the environment and cause adverse effects; and
- adverse effects arising from natural transfer of inserted genetic material to other organisms

33. In all other respects, the process of assessment is very similar to that for micro-organisms. However, the idea of levels of risk (and so containment level) will obviously not apply to GM animals and plants. The provisional level of risk (associated with the inherent hazard of the GMO itself) and the final level of risk (adjusted to take account of the characteristics of the activity) could still be expressed in terms of modifications to the standard containment measures that would be applied to the

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non-modified parental organism, but the concept of specific containment levels does not apply.

34. For GM animals and plants classification into Class 1 - 4 does not apply. Instead, notification is triggered by a consideration of whether the GMO is more hazardous than the parental organism - this assessment is made on the basis of risk to human health only.

35. Further details of risk assessment of transgenic plants and animals is given in Parts 2D and 2E respectively.