The SACGM Compendium of guidance

Part 5: Genetic modification of animals

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5.1 Genetic modification of animals

Overview

1. The Genetically Modified Organisms (Contained Use) Regulations 2000, Environmental Protection Act 1990 (EPA) and associated regulations require that suitable and sufficient risk assessments be carried out for activities involving the genetic modification of organisms. The Contained Use Regulations cover hazards to human health and the EPA those to the environment. The primary role of the risk assessment is to determine the appropriate control measures that are needed to afford maximum protection to both human health and the environment. This, in turn, will determine if there are any notification requirements for the proposed work.

2. For many activities involving the genetic modification of animals, the risks to human health will be outweighed by the potential for harm to the environment. It is acknowledged that in many cases, genetically modified (GM) animals will be no more likely to cause environmental harm than the species from which they are derived. Taken together, both the Contained Use Regulations and the EPA require that appropriate measures be taken to ensure that GM animals do not cause harm to either human health or the environment. By following the advice and measures set out in this guidance, you will be doing everything that is reasonably practicable to comply with the legislation covering activities involving the genetic modification of animals in **containment**.

3. The Genetically Modified Organisms (Deliberate Release) Regulations 2002 and the Environmental Protection Act regulate activities where a genetically modified organism (GMO) is intentionally released from someone's control into the environment. A GMO is considered 'released' if someone deliberately allows it to pass from their control into the environment without specific measures to minimise contact or harm to the general population and the environment. Under the Deliberate Release Regulations, an application for consent must be submitted to the Department for the Environment, Food and Rural Affairs (Defra). Any GMO must be authorised before it can be released into the environment or marketed within the European Union. For further information on the Deliberate Release regime and the application procedure, contact the GM Policy and Regulation Unit, 3/F6 Ashdown House, 123 Victoria Street, London SWE1 6DE (Tel: 08459 33 55 77; e-mail: gm@defra.gsi.gov.uk).

Animal welfare legislation

4.   The Animals (Scientific Procedures) Act 1986 regulates any experimental or other scientific procedure applied to a 'protected animal' that may have the effect of causing that animal pain, suffering, distress or lasting harm. Codes of Practice relating to care and housing of laboratory animals, including breeding and humane killing, are available from the Home Office.

5.   The Act defines a 'protected animal' as any living vertebrate (other than man) and the invertebrate species *Octopus vulgaris*. This protection extends to certain immature forms from the following stages of development:

   • mammals, birds and reptiles from halfway through the gestation or incubation period;
   • fish, amphibians and *Octopus vulgaris* from the time at which they become capable of independent feeding.

6.   Protection is also provided when animals are at an earlier stage of development if the animal is to be allowed to live, or the procedure may result in pain, suffering, distress or lasting harm beyond this stage of development.

7.   In the context of GM animal work, section 2(3) of the Act is of prime importance. This section states that anything done for the purpose of, or liable to result in, the birth or hatching of a protected animal that may as a result of the procedure experience pain, suffering, distress or lasting harm is a regulated procedure. Therefore, the following procedures are regulated if the intention is to maintain the animals produced beyond midway through gestation or incubation:

   • the breeding of animals with harmful genetic defects;
   • the manipulation of germ cells or embryos to alter the genetic constitution of the resulting animal;
   • the subsequent breeding of such genetically modified animals.

8.   Many of the procedures necessary for the production and identification of the GM animal are covered by the Act. Breeding of GM animals is also regulated. If GM animals can be demonstrated not to be prone to pain, suffering, distress or lasting harm, they may be discharged from the controls of the 1986 Act, providing the Secretary of State for the Home Office is satisfied that this condition is met.

Home Office licensing

9. A **project licence** that specifies the programme of work must be obtained before any procedures can be carried out. Applications for project licences are considered on a case-by-case basis and will only be authorised if there are no suitable alternatives that *replace* animal use, **reduce** the number of animals needed or **refine** the procedures used to cause less suffering. In addition, the likely benefits (to humans, other animals or the environment) must be weighed against the likely welfare costs to the animals involved.

10. Each person who undertakes the work must hold a **personal licence**. This lists the techniques and species they might use and the establishments where they work. The places where scientific procedures are carried out must be licensed under a **Certificate of Designation** unless the nature of the work requires that it be carried out in other places, such as farms or fields. Certain types of animal will need to be obtained from designated breeding or supplying establishments.

11. GM animals are not considered any differently from any other laboratory or domestic species, and are subject to the same regulations and Codes of Practice as any other animal in a similar situation. Likewise, when GM animals are subsequently discharged from the need for a project licence, they remain subject to the same controls as other animals.

12. Guidance and application forms for obtaining licences and certificates can be obtained from the Home Office.

Other legislation

13. The welfare of domestic species is subject to the Protection of Animals (Amendment) Act 2000, which makes it an offence to cause unnecessary suffering to any animals. Furthermore, the Agriculture (Miscellaneous Provisions) Act 2003 makes it an offence to cause unnecessary pain or distress to livestock on agricultural land. Detailed advice on the application of the relevant Code in individual circumstances is available through the official advisory services. The Welfare of Animals (Transport) Order 1997 is concerned with the welfare of all vertebrate animals in transit. If a GM animal is fit to travel and is transported in accordance with the provisions of this legislation, then no action would be taken. However, if the animal's condition, through being GM, were to render it unfit in any way, then its movement could constitute an offence. Codes of Practice for the welfare of most species of farm livestock (cattle, sheep, pigs, poultry, etc) are published by Defra. Further information can be obtained from the Defra animal health and welfare web pages (www.defra.gov.uk).

Consumption of GM animals

14. It is recommended that the secretariat to the Advisory Committee on Novel Foods and Processes (ACNFP) be consulted at an early stage if it is intended to work on any GM animals that might be used for food. Similarly, the Animal Feeds Committee of Defra should be consulted about the potential use of any GM animals in feed.

Scope

15. The following guidance is intended for users wishing to undertake the risk assessment of activities involving the genetic modification of animals. It covers:

    • the risk assessment of activities with GM animals;
    • the assignment and implementation of containment and control measures.

16. GM animals are defined as those where their genetic material has been altered using a method that does not occur naturally. Methods that will result in genetic modification include incorporation of recombinant nucleic acid into the animal in a relatively stable form, but exclude chemical or physical mutagenesis. The modification does not have to involve alteration of the germ line. Even if only some of the animal's cells contain the modification (ie mosaics), the animal will be considered to be GM. Techniques such as the direct injection of naked DNA to elicit an immune response would not normally be considered to constitute genetic modification. This is because the effect will be very short lived, despite constituting a transient change to the animal's genome.

17. The majority of GM animals generated or handled in the UK are knockout mutants. Although these animals may not contain foreign DNA sequences, their genetic material has been altered by a means that does not occur naturally and are therefore covered by the Contained Use Regulations. Furthermore, the Regulations also cover the propagation of a GM animal line. Even if a GM animal is crossed with a non-GM animal, the progeny are considered to be GM. The only exception to this would be where tests demonstrate that no modified genetic material has been passed to the progeny.

18. The general requirements of regulation 17 and the application of any relevant principles outlined in Schedule 7 are required for **all activities in any setting**. In some cases, GM animals may be exempt from control under the Contained Use Regulations, except for regulation 17. This includes GM animals produced by cell fusion (including protoplast fusion) between any eukaryotic species, provided that no recombinant nucleic acid or other GMOs are involved.

19. Activities involving the handling of genetically modified microorganisms (GMMs) in animal facilities are not covered here. Users wishing to undertake animal studies with GMMs are directed to Part 2. Where activities involve both GM animals and GMMs, users are required to consider both the risks from the GMMs *and* the risks from the GM animals to ensure that all aspects are appropriately controlled.

Definitions

20. For the purposes of this guidance, the term 'animal' is used in its broadest sense, and includes vertebrates, invertebrates and complex, free-living multicellular organisms such as nematodes. Users will need to take account of the characteristics of the species on a case-by-case basis. Clearly, containment measures for mammals are going to be very different to those for insects or nematodes.

21. Legal requirements will be stated clearly as such, with the use of the words 'regulatory requirement', 'required' or 'must'. In cases where the word 'should' is used, the guidance highlights approaches that can otherwise be used to achieve the appropriate standards. These approaches are only illustrative and users may adopt other approaches so long as the standards set by the Regulations are met.

22. The following terms do not have legal definitions and the explanations below are intended to aid understanding:

- **Animal unit:** A building, or separate area within a building, that contains an animal facility and includes other areas such as changing rooms, showers, autoclaves and food storage.
- **Animal facility:** A facility that is normally used to house stock, breeding or experimental animals or one that is used for the performance of minor surgical procedures on animals.
- **Isolator:** A transparent box used to contain small animals either within or outside a cage, or isolated rooms for larger animals.
- **Required where and to extent the risk assessment shows it is required:** This indicates that the need for a particular measure is determined by the risk assessment. If the risk assessment specifies that a measure is needed for human health or environmental protection, its use is mandatory.
- **Competent authority:** The body with enforcing jurisdiction over the Contained Use Regulations. In England and Wales the competent authority includes the Health and Safety Executive (HSE), the Secretary of State and the Department for Environment,

Food and Rural Affairs (Defra). In Scotland the competent authority includes HSE, the Scottish Executive Environment and Rural Affairs Department (SEERAD) and the Scottish Ministers. Northern Ireland has its own separate competent authority. When seeking approval from the competent authority for particular actions, users should contact HSE in the first instance.

Risk assessments

23. Schedule 4 of the Contained Use Regulations sets out the steps to be included and the matters to be taken into account for the assessment of the risks posed to human health by GMOs other than microorganisms (in this case, GM animals). The EPA requires that risks to the environment be assessed but does not set out specific matters to be considered. This guidance is fully compatible with the Schedule 4 requirements and proposes that a similar procedure also be applied to environmental risk assessment.

Risk assessment procedure

24. The following procedure represents a recommended model for GM risk assessments and for the assignment of containment and control measures. The procedure is reflected in the structure of the guidance. This suggested format includes the steps required for risk assessment under the Regulations, although it is not intended to be prescriptive:

- **Risk assessment for the environment.** The identification of potential mechanisms by which the GM animal might pose a hazard to the environment. Consideration of the potential severity, likelihood of occurrence and considerations of uncertainty. Assignment of control measures needed to safeguard the environment.
- **Risk assessment for human health.** Identification of any potential risks to human health. Consideration of the potential severity and likelihood of occurrence. Assignment of control measures needed to safeguard human health (if appropriate).
- **Review of Procedures and control measures.** Consideration of the nature of the work and implementation of any additional control measures necessary to safeguard both the environment and human health.
- **Determination of notification requirements.** Work with GM animals that pose an increased risk to human health compared to the wild type will need to be notified to the competent authority. In practice very few activities with GM animals will require notification.

25. It is a regulatory requirement to thoroughly assess the risks posed by GM animals. However, in practice, activities with GM animals are unlikely to pose a risk to human

health and the main consideration will be in regard to preventing the animal escaping into the environment. Therefore, activities should be assessed in a way that is commensurate with the actual hazards posed. There is a need is for an informed and pragmatic approach, rather than an overcomplicated assessment and unwarranted control measures.

Level of detail required

26. Much of the guidance has been prepared to aid the risk assessment of activities where uncertainty as to the nature of the intended GMO necessitates more in-depth consideration. The level of detail required will vary from case to case and will depend upon the nature of the hazards and the degree of uncertainty. Where a potential for harm is identified, a more detailed consideration of the risks associated with the activity should be undertaken. Equally, less detail will be required for less hazardous work, such as work with GM animals that cannot reproduce or could not survive in the UK.

27. Much of the work on GM animals in the UK involves the generation or handling of knock-in or knockout mutants. In some cases, this will involve many different GM animal lines and the handling of large numbers of individual animals. In most cases, these animals will represent minimal risk and so the procedure can be streamlined, for example, by adopting a generic approach to risk assessment.

28. Arguments must be clear, but needn't be exhaustive. The final risk assessment must contain enough background information and detail to ensure that a reviewer with a limited understanding of the precise nature of the work will not require further information to comprehend the nature of any hazards. Supplementary information could take the form of references to the scientific literature and reports, for example, in reference to the likelihood of the animal surviving in the environment.

29. All GM risk assessments should be reviewed regularly and be updated in the light of new scientific knowledge or where there has been a change in the nature of the activity (including a change in scale or any new procedures and containment measures). Therefore, the initial risk assessment should consider the purpose of the work and consider any changes that are likely. Documentation is important for GM work and all data should be recorded and used to supplement the risk assessment where appropriate. Records pertaining to environmental risk assessments should be kept for ten years after work has ceased.

30. For the majority of activities involving the genetic modification of animals, the primary consideration will be the potential for harm to the environment. Therefore, the risk

assessment should determine whether or not a GM animal, or its descendants, could cause adverse effects in the event of an escape. Thus, in most cases, containment and control measures will be implemented primarily to prevent release of the GM animal into the environment, or to limit the impact of environmental harm. However, containment and control measures must be assigned on the basis of both environmental and human health protection. Whether or not those measures implemented for environmental protection are also sufficient to protect human health should be carefully evaluated and will be dependent upon the nature of the GM animal itself.

Activities likely to raise safety issues

31. There are some types of work where particular caution should be exercised. These cases will generally involve work with GM animals that are able to persist or become established in the environment. Particular attention should be given to:

- GM animal species likely to disturb natural ecosystems, especially derivatives of naturally-occurring species that may have a selective advantage;
- GM derivatives of non-indigenous species that are able to become established and might prey upon native species or compete for the niche they currently occupy;
- GM derivatives of non-indigenous species that might consume indigenous plant life and disrupt the ecology;
- GM animals that express potentially harmful biologically active products, especially if they are likely to be preyed upon.

32. Also, careful consideration must be given to procedures that require the handling of GM animals in circumstances where 'standard' containment and control practices used in a laboratory or animal facility may not be possible or applicable. Particular attention should be given to large-scale propagation of GM animals, especially where this occurs in specialised facilities, for example, the breeding of GM fish in ponds or lakes.

Notification requirements

33. Regulation 9 of the Contained Use Regulations stipulates that the competent authority (HSE) be notified of the intention to begin any GM work on the premises. If no previous GM work has taken place at the site, then a premises notification must be submitted to HSE. If appropriate, this can accompany an individual activity notification.

34. The risk assessment will determine the containment and control measures needed as well as the notification requirements for individual activities. Risk assessments for activities with GM animals are carried out under regulation 7 and the associated Schedule

4. **Only activities generating a GMO with a greater potential to cause harm to human health compared to the unmodified organism require notification.** Further information regarding notifications can be found in Part 1 of the Compendium.

5.2 Risk assessment of work with genetically modified animals

Overview

1. For most activities involving the genetic modification of animals, the primary considerations of the risk assessment will be given to the effects the GMO may have on the environment in the event of an escape. This is likely to be the case for GM activities using non-indigenous species that could become established in the UK, or indigenous species with altered survival characteristics, as the potential ramifications for human health will be negligible. However, human health implications will require greater emphasis where activities involve the expression in animals of biologically active products, or products that may be toxic or allergenic. Therefore, while the potential environmental impact of any GM animal will require careful assessment and control, it is important not to overlook the possible effects on workers who may be exposed to any allergens or toxins not normally associated with them.

2. The Environmental Protection Act and the Contained Use Regulations require that risk assessments for both environmental and human health protection be carried out respectively. Each part of the risk assessment will involve the following steps:

    *   hazard identification;
    *   assessment of the likelihood of hazards being realised;
    *   assessment of the consequences of hazards being realised;
    *   determination of the risk that hazards will be realised;
    *   assign containment level or control measures to reduce the risks to 'effectively zero'.

3. The risk assessment process should also include a consideration of the nature of the work and a review of the procedures, with additional control measures implemented, if necessary. From this, the minimum containment requirements will be evident and any notification requirements can be determined.

Risk assessment for the environment

4. It is acknowledged that GM animals are more likely to pose a risk of damage to the environment than they are to human health. The Environmental Protection Act defines damage very broadly as being caused by the presence of GMOs that have escaped from containment and are capable of causing harm to any living organisms supported by the

environment. Therefore, the primary objective of this section of the risk assessment is to determine the likelihood and the possible consequences of an accidental release of a GM animal from containment into the environment. In a properly maintained and managed facility with the correct containment measures in place, the likelihood of such a release will be low. However, it is important to identify all possible hazards and consider any routes by which a GM animal could escape.

5.   Clearly, the concern is for GM animals that could feasibly cause harm to the environment, particularly those that could impact upon any environmental ecosystem (including indigenous plant and animal populations). While it is important to consider the intrinsic characteristics of the animal species being modified, the focus of the risk assessment should be on the genetic modification itself and whether this will increase or decrease the risk. However, in some cases the hazards arising directly from the modification may interact directly with characteristics of the recipient species.

Mechanisms by which the GMO might pose a hazard to the environment

6.   During the hazard identification process, the factors to consider will include:

- the capacity of the GM animal to survive, become established and disseminate. This includes its ability to compete with other animals and any other adverse effects on animal and plant populations;
- hazards associated with the inserted gene/element. This will be particularly relevant if the insert encodes a toxic product and could have adverse effects due to its biological activity;
- potential for transfer of genetic material between the GM animal and other organisms;
- phenotypic and genetic stability.

7.   Therefore, consideration should be given to whether any of the above factors represent hazards associated with the GM animal when taking into account the characteristics of the recipient organism, the insert and the final GMO. The assessment should evaluate whether or not the gene could be passed on to another organism (for example, a sexually compatible species) and the potential consequences of this. Synergistic and cumulative effects should also be considered.

Capacity to survive, establish and disseminate

8.   The ability of a GM animal to survive will be a key attribute and may affect whether or not other potential risk factors will come into play. If the animal cannot survive outside of containment, it is unlikely to cause environmental harm. For example, *Tilapia* is a

freshwater fish native to Africa and unlikely to survive in UK waters, as it requires ambient temperatures of above 27 °C. It is, therefore, effectively under innate biological control.

9. Some animals may be able to survive for a short period when conditions are favourable, even if they are unlikely to persist in the longer term. For example, some insects may not be able to overwinter in the UK, but could potentially survive through the summer months. In these cases there would be a short-term possibility of some of the other identified hazards being realised and these must be considered, even if the organism is unlikely to become established.

10. For GM animals that could survive, it is important to consider how they might interact with the environment. GM animals may cause harm simply due to their presence in the environment. If they are adapted to the climate and environment, they may out compete and displace other populations of animals or prey upon native populations. Effects on plant species should also be considered, as the establishment of significant populations of an escaped GM animal might lead to overgrazing and serious ecological impacts. Loss of biodiversity in plant species could, in turn, adversely affect the ability of the environment to support native fauna. Particular attention should be paid to non-indigenous species. There have been documented escapes by non-indigenous animals (eg non-GM mink) that have had ecological ramifications such as population growth, competition with native species and physical damage to the environment. Although they were non-GM animals, these incidents may serve as useful models for escape scenarios.

11. It is acknowledged that in many cases, GM animals will be no more likely to cause environmental harm than the species from which they are derived. However, it is possible that the genetic modification itself could give the GM animal a competitive advantage. Similarly, modified environmental tolerances could increase an animal's survivability and range. For example, salmon have been modified to express an anti-freezing protein from the Atlantic Pout, thus potentially allowing them to colonise colder waters. Increased fecundity might lead to rapid population growth and displacement of non-GM relatives in the wild. Conversely, many modifications will lead to decreased fitness and impaired competitive potential. It may be possible, and in some cases prudent, to engineer such characteristics into an organism for biological control purposes. For example, a strategy based upon the GM animal being infertile or dependent on a specific nutrient supplement could be employed.

12. Another factor that may affect survival and dissemination in the environment is the ease with which it is possible to recover escaped animals. For large animals such as sheep or pigs, it should be feasible to retrieve escapees. However, fish, insects and small mammals may be extremely difficult, or even impossible, to recover. In particular, the

small size and short reproductive cycles of many of these animals may mean that the GMO could become disseminated very rapidly. Furthermore, the complex life cycle of many invertebrates may expose additional pathways for escape and dissemination. Tracking and recovering them may be extremely difficult.

Hazards associated with the inserted gene/element

13. It is likely that animals modified to produce biologically active substances will be used to express molecules of pharmacological use, for example blood clotting factors or hormones such as insulin. The possible harmful effects of these biologically active substances on other organisms should be considered, although it is acknowledged that they are relatively unlikely to pose a serious hazard.

14. The possibility that the inserted gene could cause harm to other animals should be considered. For example, an animal modified to express biologically active products may be allergenic, immunogenic or toxic to exposed animal populations. This may be due to exposure to animal secretions contaminated with the product or as a result of the GM animal being consumed by a predator.

15. Consideration should be given to the possibility of the GM animals acting as novel animal disease vectors or reservoirs. For example, if an animal was modified to express a receptor for a particular virus, those animals may be able to act as a reservoir for it. Similarly, it should be considered that species modified to become susceptible to UK pathogens could disseminate disease.

Transfer of harmful sequences between organisms

16. Consideration should be given to the possibility that the inserted genetic material could be transferred to other organisms that may be present in the receiving environment. It is likely that this will be dependent upon the presence of species that are sexually compatible. Clearly, if the GM animal is infertile, then it is impossible that the inserted genes will be passed on via the germ line, unless a genetic reversion event results in restoration of fertility (see *Phenotypic and genetic stability*). Similarly, if only female animals are handled, then in the event of an escape the chances of gene transfer into the wider population will be greatly reduced, provided they can be recovered before they reproduce.

17. The nature of the hazard arising from a gene transfer event should also be considered. If the modification has negative effects on the health or longevity of the animal then there will be a strong deleterious selection pressure. For example, if the modification resulted in

a high incidence of tumour formation then there would be a strong selection pressure against that phenotype and the longer-term ecological impact may be diminished. However, the short-term effects may include a decrease in natural population numbers and associated ecological ramifications.

Phenotypic and genetic stability

18. Given that genetic instability is most likely to result in loss of the introduced gene and any associated traits, it will rarely be a source of potential harm. However, if the purpose of a modification was for biological containment of the GM animal, and those restricted characteristics could revert to wild type, then genetic stability should be considered. For instance, one of the aspects of control may be a modification that results in infertility. If this were to revert, the level of control would be lost or diminished. Therefore, the genetic stability of a modification may be inextricably linked to phenotypic stability, where it restricts the GM animal's ability to survive and to spread.

19. An organism with a restricted capacity to survive will be under stress in the environment and there will be a strong selection pressure in favour of reversion. The possibility that the genotype of a modified animal will be unstable in the environment should be taken into account and consideration given to any detrimental effects this might cause.

Likelihood that the GMO will be a risk to the environment

20. The initial stages in the risk assessment process thus far involve identifying those features of the GM animal that have the potential to cause harm and the mechanisms by which these hazards could be realised. While it may be possible to draw up theoretical scenarios whereby the GM animal may be hazardous to the environment, the chances of them being realised should be evaluated and understood.

21. Estimating the likelihood of a harmful consequence being realised will be difficult where there is no firm data on which to base a judgement. In general, the weight given to information used in these considerations should reflect the quality of the supporting data. Where the likelihood of harm is poorly understood, a precautionary approach should be adopted until evidence to the contrary has been obtained.

Assessment of likelihood

22. It is often possible to assign a frequency to a given event. Often, this can take the form of a precise numerical frequency (eg the frequency of reversion of a genetic modification or phenotype over several generations or back-crosses) obtained in-house or through

published data. However, in many cases this will not be possible and an approximate, semi-quantitative or descriptive assessment of the frequency, based upon experience and scientific knowledge, may be more applicable. In these cases, a cautious approach is advised and it should not be assumed that failure to observe an event is evidence that it does not or will not occur. For the purposes of using the risk determination matrix Table 5.2.1, likelihood can be expressed as 'high', 'medium', 'low' or 'negligible'.

23. When estimating the likelihood of harm occurring to the environment, a significant factor is that the GM animals are contained, so their access to the environment is limited. The basic level of containment that is appropriate to the species being used should be applied. This might include fish tanks, insect cages, animal houses, fenced fields, barns etc. (See also Part 3 Section 3.4 for further information on containment.) This basic containment can be subsequently revised if necessary to reduce any risks to 'low' or 'effectively zero'.

24. In the event that a GM animal does escape, a key factor in whether or not a hazard will be realised is the environment into which the GM animal would be released. Therefore, it is important to consider the nature of the organism in relation to the receiving environment. Even if the GM animal could conceivably survive and disseminate in the environment, it may be that the environment itself would not be able to support it or allow dissemination over the longer term.

25. Therefore, there may be characteristics of the local environment that will contribute to the likelihood of the hazard being manifested. These may be climatic or geographical conditions that might affect the ability of the organism to survive. For example, GM salmon released near a UK watercourse would have a high probability of establishing novel populations if they escape. Conversely, GM *Tilapia* would not be expected to survive, as they are tropical freshwater fish.

26. In addition, the nature of indigenous organisms should be considered, including the presence of sexually compatible species. The ability of the GM animal to disrupt populations of natural fauna and flora should also be considered. For instance, the GM animal may occupy the same ecological niche as another organism and hence have greater potential for competition.

Assessment of consequence

27. After the likelihood of all hazards is assessed, the consequences of each identified hazard being realised should be estimated in terms of severity. Again, the consequence will depend to a very large extent on the potential receiving environment. In particular, the presence of sexually compatible relatives or species with which the GM animal may be

able to compete will be important considerations. The reversibility of the effects should also be considered. If the GM animals and their offspring (if appropriate) can be traced and recovered, then the severity of the consequences will be diminished.

28. Evaluation of the magnitude of a potential consequence is difficult since there is inevitably a degree of judgement involved, although a qualitative appraisal of the impact on other species or ecosystems should be possible. For the purposes of using the risk determination matrix Table 5.2.1, consequences could be described as being 'severe', 'modest', 'minor', or 'negligible'.

29. The following descriptions may help:

- **Severe consequence**: A major change in the numbers in the populations of one or more species. The interpretation of 'major' will be dependent on the species affected. For example, harm caused to a single individual of a protected species could be interpreted as a major event. Conversely, quite large changes in numbers of a ubiquitous and rapidly reproducing species (eg certain small mammals and insects) may be relatively insignificant, unless the population fluctuation goes beyond the limits that would occur naturally. Severe consequences might also be where there is a measurable disruption to the functioning of an ecosystem. Severe consequences are unlikely to be easily reversible.
- **Negligible consequence**: No measurable change in any population of animal, plant or microbial species, or in any ecosystem function. This should not preclude some fluctuation in indigenous populations as long as this is within the range of that which could be expected to occur naturally.

30. It should be emphasised that the degree of severity must be estimated under the assumption that the GM animals have escaped and entered the environment. Even if it is highly unlikely that an escape will occur, considerations of the severity of the consequence should be made independently and based upon the assumption that harm will occur.

31. It should be borne in mind that even if the consequences of a hazard being realised are deemed 'severe', if the probability of the hazard being manifested at all was 'negligible' then there is 'effectively zero' risk of harm. Likewise, if the consequence of a hazard was 'negligible' or 'minor', then even if the probability of its manifestation was 'high' the risk of harm would still be 'low' (see Table 5.2.1). However, a precautionary approach to risk determination is advised. In situations where the probability of the hazard being manifested was 'negligible', should there be a 'severe' consequence to the identified hazard, then more stringent containment than would otherwise be appropriate for an

'effectively zero' risk of harm might be prudent. Therefore, a balanced view of the risks is required.

Determination of risk

32. The risk determination matrix Table 5.2.1 can be used to estimate the level of risk. This matrix is provided as a tool and is not intended to be a definitive measure of risk.

		Likelihood of hazard			
		High	**Medium**	**Low**	**Negligible**
Consequence of hazard	**Severe**	High	High	Medium	Effectively zero
	Modest	High	Medium	Medium/low	Effectively zero
	Minor	Medium/low	Low	Low	Effectively zero
	Negligible	Effectively zero	Effectively zero	Effectively zero	Effectively zero

Table 5.2.1 Risk determination matrix

33. It may be necessary to evaluate whether any specific control measures are required to adequately protect the environment. Containment measures should be applied until the risk of harm is 'effectively zero'. Further guidance on containment measures to protect both the environment and human health can be found below.

Containment measures needed to sufficiently protect against harm to the environment

34. It is recommended that the minimum containment measures that are necessary to protect the environment be set at this stage. The containment measures required will be solely for the purpose of preventing release of the GM animal, or to minimise the likelihood that it will become a threat to the environment.

35. A judgement should be made about whether the GM animal will be a risk to the environment. If all risks are deemed to be 'low' or 'effectively zero' then no specific measures will be required. However, if any risk exceeds this level then control measures should be implemented such that the risk of harm to the environment is reduced to 'low' or 'effectively zero'.

Risk assessment for human health

36. There is a requirement under the Contained Use Regulations to consider risks to human health posed by the GM activity. The objective is to identify all plausible hazards to human health and then to assess the likelihood and potential severity of the consequences, should the hazards be realised. It is recognised that many activities with GM animals pose no additional risk to workers over those that would be expected from the unmodified animal. The intrinsic hazards will include such things as scratches, bites, allergenicity and zoonotic infections (users are directed to the HSE publication *Working safely with research animals: Management of infection risks* ISBN 978 0 7176 1377 9). However, these potential hazards are, of course, common to all animals and the GM risk assessment should focus on any additional hazards to human health arising directly from the genetic modification. Hazards to humans might arise due to modifications that affect allergenicity or toxicity.

Mechanisms by which the GMO could be a risk to human health

37. As for the environmental risk assessment, the hazard identification process must include considerations of potentially harmful or adverse effects to human health that would be mediated by the organism in relation to the products of inserted genes or characteristics of the final GMO.

38. For example, if an animal line was produced which was modified to contain a receptor for a human virus, these animals may act as a novel reservoir for human disease. Although the possibility of such additional hazards to humans must always be considered, it is recognised that, in most cases, the activities will not pose any extra hazards to humans.

39. Any additional risks to humans will most likely arise due to modifications that alter allergenic or toxic properties. Such hazards might include:

- novel or increased allergenicity;
- possible toxic effects due to production of toxins or other biologically active proteins;
- adverse effects due to altered behaviour (for example, enhanced aggression).

Likelihood that the GMO will be a risk to human health

40. For each hazard identified, you should consider the likelihood of the hazard being realised and the severity of the potential harmful effect. An approach similar to that for assessment of environmental risks is recommended. It might be necessary to adjust the

proposed containment if any of the risks to humans are not controlled by the containment assigned to protect the environment.

Control measures needed to sufficiently protect human health

41. It may be necessary to evaluate whether any specific control measures are required to adequately protect human health. If necessary, containment measures should be applied until the risk of harm is 'effectively zero'. It is a requirement of the Contained Use Regulations that all measures deemed by the risk assessment as necessary for the protection of human health be implemented.

42. In many cases, the principles of good occupational safety and hygiene will be sufficient to protect human health. These principles are detailed in Part 3, Section 3.1 for work in laboratories and animal facilities. Furthermore, some of the measures implemented for environmental protection may be adequate to minimise or prevent exposure. However, only risks to human health will have a bearing on the notification requirements for the work (see below).

Review of procedures and control measures

43. The ultimate aim of the risk assessment is to determine the appropriate containment and control measures to prevent harm occurring. These measures will vary with the level of risk and are dependent upon the nature of the animal being controlled. For instance, the containment methods for an insect will be very different to those for small mammals, which in turn will be different from those needed for larger animals such as sheep. Control can be provided using a mixture of physical (eg cages and enclosures), chemical (eg oil traps for insects), biological (eg reproductive sterility) and procedural measures.

44. The containment measures must be sufficient to control all the potential harmful properties of a GM animal and offer adequate protection for both the environment and human health. The containment and control measures identified thus far for environmental and human health protection only broadly define those needed as a function of the properties of the GM animal itself.

45. The nature of the activity will also affect the level of risk. Therefore, it is important to take into account the nature of the work or any non-standard operations that might increase the likelihood of release or risk of exposure. For example:

- large-scale propagation of a GM animal, for example to generate stocks of an insect for biological control trials. This will often mean that large numbers of the GMO will be handled, resulting in increased likelihood of release and exposure;

- the use of specialised facilities. This could be any facility that differs from the usual 'animal house' style facilities. For example, this might include the propagation of GM fish in ponds. The control measures needed to prevent accidental release may well differ for these facilities.

46. If any such operations or activities are likely to generate risks that are not accounted for in the minimum containment measures already applied in reaction to individual risk assessments for the environment and human health, then additional control measures should be applied. Equally, it may be that as a result of the activity, the nature of a risk that is inherent to the GMO itself is diminished. For example, if aquatic GM animals are contained within in a system that is totally sealed from any drainage or external water supply, then a release might be less likely and certain control measures may not be needed.

47. Guidance on containment and control strategies that are relevant to animal facilities can be found in Part 3, Section 3.4.

Assignment of final containment measures

48. There is no regulatory requirement to set a formal containment level (ie Containment Level 1, 2, 3 or 4) for work with GM animals. A number of containment measures and procedures that can be used to reach the required standards can be found in Section 5.3. **It is important to remember that the Environmental Protection Act requires the containment measures used to be sufficient to safeguard the environment.**

5.3 Containment and control measures for activities involving genetically modified animals

Overview

1. The following procedures and containment measures are recommended as minimum standards of good practice and will need to be adapted or supplemented with measures appropriate for specific animal types. Users will note that all references to 'Containment A' and 'Containment B' have been removed. This differentiation had no regulatory basis. Furthermore, most activities with GM animals in the UK do not clearly fall under the requirements of either of these levels of containment. Therefore, this terminology is no longer considered helpful and has been replaced by a series of measures that can be adopted as far as they are appropriate to the activity.

2. The general principles of containment will be consistent irrespective of the species or size of the animals. Appropriate physical barriers will usually be required to prevent the animals from escaping into the wider environment. Chemical barriers are not usually appropriate, beyond the use of chemical moats to aid containment of GM invertebrates. Biological barriers (such as reproductive incapacitation) might be suitable for work with GM animals.

3. Rigorous procedural and management control is also important, especially in animal houses where escapes may be possible or security against theft or vandalism is a concern. **All measures must be chosen in accordance with the risk assessment.** The principles of good microbiological practice and good occupational safety and health (GOSH) (see Part 3, Section 3.1) must also be applied to the containment of GM animals, where they are relevant.

4. For GM animals that are incapable of surviving in the environment in the UK, have limited ability to transfer genetic material to UK animal species or where the genetic modification does not increase the level of risk to human health or the environment above that of the unmodified organism, it is anticipated that minimal containment measures will be necessary.

5. For GM animals that (i) could become established outside of the containment facility; (ii) have a genetic modification that increases the level of risk to human health or the environment above that of the unmodified organism; or (iii) could cause harm to humans or the environment if they escaped from the containment facility **and** have the ability to

transfer novel genetic material to UK animal species, then more rigorous containment measures might be required and should be applied.

Animal containment measures

6. Animals should be kept in appropriate cages or enclosures. Large animals should be kept in appropriate pens or fenced areas (double fencing may be appropriate, dependent on the level of risk). Aquatic animals, including viable fertilised eggs, should be kept in appropriate tanks fitted with filters that are sufficient to retain the smallest organism or egg likely to be present. Appropriate vessels should be used to house invertebrates. The containment area should conform to Home Office requirements for animal welfare, where appropriate.

7. All potential routes of escape should be identified and appropriate measures put in place to prevent it. Floor drains and low-level ventilation ducts should be made escape-proof using a mesh or similar physical barrier. The mesh size should be suitable to prevent the smallest animals escaping. Fencing used to confine larger animals should go down to a sufficient depth to prevent escape via burrowing. Fencing should also be of sufficient height and mesh size to prevent escape. Secondary filters may also be required when handling aquatic animals, the number of which will be dependent upon the risk. Secondary containment measures may be required when handling GM invertebrates, for example, muslin 'tents' should be considered if indicated by the risk assessment.

8. Measures should be taken to enable escaped animals to be detected and recaptured or destroyed. If appropriate, animal traps should be used. Outlet pipes from a facility handling aquatic animals may need a filter barrier, especially where discharge is directly into a river or the sea. An electrical kill system typical of the kind used in the aquaculture industry may also provide a suitable final barrier before final discharge. Ticks and mites should be kept over trays of oil and flying or crawling arthropods handled on white trays to facilitate the detection of escape. The use of an electric insect control unit should be considered. Chilling can reduce arthropod activity and can be used to reduce the risk of escape. Furthermore, maintaining corridors that surround the containment areas at low ambient temperature can help avert a release.

9. Barriers should be placed on exits from animal units and facilities to prevent escape of animals into corridor areas. This is particularly important when rooms, cages or tanks are being cleaned. Where aquatic animals are handled, the containment area may need to be bunded to prevent overflow to outside (this need will be determined by the risk assessment and geographical considerations, such as proximity to watercourses or sea).

Consideration should also be given to the use of alarms to detect flooding or the use of a 'soak away' outside the facility should be considered if the facility is close to a river or the sea. Such an area may consist of a gravelled area that allows water to soak through while retaining any escaped fish on the surface.

10. All experimental procedures, such as the administration of drugs and the bleeding of animals should be carried out in a way that minimises chance of escape.

11. The containment area should be kept locked and access to the containment facility should be restricted. For higher risk activities, security measures should be taken to prevent theft or vandalism. For example, external or remote locations should be regularly patrolled and/or monitored (for instance, with the aid of closed-circuit television).

12. Animals should be transported to and from the facility in appropriate animal containers. The nature of the container should take into account the need to prevent escape, animal welfare requirements and ease of transport.

13. For work with vertebrates, a written record should be maintained of the birth, death, experimental use and disposal of each animal or group of animals. Records required to be kept as part of a Home Office licence should be sufficient for this purpose. The permanent marking of GM animals may be appropriate but in any case, cages or enclosures should be clearly labelled and documented.

14. For animals or invertebrates that pose a risk to human health or the environment, written records of any accidents or escapes from cages or primary containment should be kept. Any accident or escape that could present a hazard to human health must be notified to the competent authority.

15. Staff should be given appropriate training and instruction on the procedures to be carried out. A set of local rules and standard operating procedures should be drawn-up, which should be read by all staff using the facility. Where there is a greater risk to human health, written record of staff training will be required.

16. The disposal of carcasses from research facilities should be treated as clinical waste, and handled accordingly. Waste material such as bedding, faeces and urine are not considered to be GM waste and will not require inactivation prior to disposal. However, bedding, faeces and urine may contain pathogens or other hazardous materials that would necessitate specific measures for handling and disposal. Milk from GM cattle, goats and sheep does not contain viable GM material.

Further information

This document contains notes on good practice which are not compulsory but which you may find helpful in considering what you need to do.

This document is available web only at: www.hse.gov.uk/biosafety/gmo/acgm/acgmcomp