

Guidance on the contained use of eukaryotic viral vectors in genetic modification / Advisory Committee on Genetic Modification.

Contributors

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ADVISORY COMMITTEE ON GENETIC MODIFICATION
GUIDANCE ON THE CONTAINED USE OF EUKARYOTIC VIRAL
VECTORS IN GENETIC MODIFICATION

BACKGROUND

1 The following guidance and recommendations have been prepared by an ACGM Working Group and endorsed by the main committee of ACGM. This guidance should be brought to the attention of the genetic modification safety committee who should also consider any local factors which may lead them to require more stringent biological or physical containment. This guidance updates and replaces that issued in 1986.

2 This guidance is designed to facilitate compliance with the risk assessment requirements of both the current Genetic Manipulation Regulations 1989 and the forthcoming Genetically Modified Organisms (Contained Use) Regulations, which will replace the 1989 Regulations. The guidance is designed to help centres address the parameters to be taken into account in risk assessment of work involving the use of eukaryotic viral vectors.

RECOMMENDATIONS

3 The genetic modification safety committee must contain sufficient expertise in the viral vectors under consideration to undertake review of risk assessment. It may be necessary to consult appropriate experts from outside the centre.

4 Host cells capable of colonising workers, for example the operator's own cells, or those from other laboratory staff having access to the laboratory must not be used.

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5.1 The system of risk assessment outlined in ACGM/HSE Note 7 calls for the assignment of numerical factors under the headings of Access, Expression and Damage. This is not felt to be applicable for viral vectors. It is difficult to generalise concerning the potential hazard to the operator or to the environment from the insertion of genes into eukaryotic host vector systems which produce infective virus. However, when assessing such experiments, the considerations in paras 6, 7 and 8 should be taken into account.

5.2 The Control of Substances Hazardous to Health (COSHH) Regulations, 1988 include micro-organisms which "create a hazard to the health of any person" in the definitions of substances hazardous to health. The Regulations place a duty on employers not to carry out work liable to expose employees to such substances unless a suitable and sufficient assessment of the risks created by that work has been undertaken and appropriate control measures taken. It may be necessary to read this guidance note in conjunction with the HSE publication 'COSHH Assessments'.¹ COSHH risk assessments must also address any allergenic or toxic hazard which may be posed by recombinant proteins.

RISK ASSESSMENT CONSIDERATIONS FOR EUKARYOTIC VIRAL VECTORS

General Considerations

6.1 Genetic modification work with eukaryotic viruses should utilise disabled viral vectors. The origin of these must be known, as must the mechanism of their attenuation and the stability of the features concerned. Whenever practicable the presence of such features should be confirmed to be present in the virus, before and after modification is carried out. Where such vectors are used, only deletion mutants are to be employed. Vectors with a probability of reversion, eg point mutations, conditional lethal mutants etc, must not be used without specific guidance being sought from ACGM/HSE.

6.2 The replication competence of the modified viral vector should be considered. This may be especially important in transgenic animals, gene therapy or long term use of modified cell lines. If this cannot be confirmed then the initial risk assessment may need to be reviewed.

1 COSHH Assessments HMSO 1988 ISBN 0 11 885470 4.

2.1 The system of risk assessment outlined in this document is designed to be used for the assignment of potential hazards under the headings of Acute, Subacute and Chronic. This is not to be applied to the other types of hazard, such as the hazard to general health resulting from the potential hazard to the environment from the location of genes from antibiotic resistant genes which produce antibiotic resistance. However, when assessing such exposures, the considerations in parts 2, 3 and 4 should be taken into account.

2.2 The Control of Substances Hazardous to Health (COSHH) Regulations, 1988 include substances which "create a hazard to the health of any person" in the definition of substances hazardous to health. The Regulations place a duty on employers not to carry out work which is likely to expose employees to such substances unless a suitable and sufficient assessment of the risks involved by that work has been undertaken and appropriate control measures taken. It may be necessary to read this guidance note in conjunction with the HSE publication COSHH Assessment. COSHH risk assessments must also address any alternative or other hazards which may be posed by occupational practices.

RISK ASSESSMENT CONSIDERATIONS FOR BIOMATERIALS VIAL VECTORS

General Considerations

4.1 Genetic modifications such as antibiotic resistance should utilize defined viral vectors. The origin of these must be known, as must the mechanism of their transmission and the stability of the inserted construct. However, essentially the presence of such features should be confined to be present in the virus, before and after modification is carried out. Where such vectors are used, only defined extracts are to be employed. Vectors with a propensity for reversion, eg point mutations, conditional lethal mutants etc, must not be used without specific guidance being sought from ACOG/98.

4.2 The restriction component of the modified viral vector should be considered. This may be especially important in transgenic animals. Genes they are likely to be modified will insert. It may be necessary to ensure that the initial risk assessment may need to be reviewed.

6.3 It may be necessary to review the risk assessment as new information is available. The points set out in the sections below should not be dealt with in isolation one from another.

Human Health and Safety

6.4 Particular care must be given to the assessment of vectors with an actual or potential ability to infect humans or human cells in vitro. The Advisory Committee on Dangerous Pathogens (ACDP) classification of viruses pathogenic to humans is at Annex I. This illustrates the minimum level of containment to be used when working with these agents. When in doubt the advice of HSE/ACGM should be sought.

6.5 The nature of the inserted gene(s) and the properties of the final genetically modified organism must be considered with particular attention to any potential for harm, viz:

6.5.1 does the insert code for a protein(s) with known or suspected pharmacological or physiological effect? Consideration should be given to possible effects other than those being sought in the construction.

6.5.2 is there reason to suspect that the tissue tropism or the host range of the recombinant virus will be different from that of the unmodified virus?

6.5.3 is there reason to suspect that the modified virus may have altered interactions with host defence mechanisms? Will normal immune status be compromised by the modified virus? Will vaccination protect against the modified virus? Is the recombinant likely to have enhanced effects upon an immuno-compromised host, beyond those normally expected with the parent virus?

6.5.4 will viral susceptibility to anti-viral drugs (where these are available) be affected by genetic modification?

6.5.5 are all the potential routes of transmission of the virus known, eg those that might occur in a laboratory accident? If so, will the routes of transmission bring the virus or its product(s) to tissue in which they may be biologically active.

6.5.6 particular attention should be paid to the insertion of oncogenes, and potentially oncogenic sequences into viruses capable of infecting human cells. When insertion of oncogenes or of genes encoding highly toxic proteins into the genome of a virus capable of infecting humans is proposed, it will be necessary to raise the level of containment above that recommended in Annex I. Attention is also drawn to ACGM/HSE Note 1 which sets out requirements for handling DNA containing oncogenes and related sequences.

Environmental Protection

6.6 When considering experiments using viruses that affect organisms other than man, the major consideration is whether damage might result from any escape from containment. Knowledge or suspicion of a host range extending beyond humans will also need to be taken into account. Consideration must be taken of the effect of a virus on other vertebrates, invertebrates, plants or other organisms. As well as notification or consent required by the current or forthcoming regulations (see paragraph 2) work with such viruses may require a licence from the Ministry of Agriculture, Fisheries and Food (Annex II). Advice should be sought from appropriate government departments (eg MAFF, SOAFD, etc).

6.7 The nature of the inserted gene(s) and the final genetically modified organism must be considered with particular attention to any potential for harm, viz:

6.7.1 does the insert code for a protein(s) with known or suspected inhibitory, detrimental or other physiologically active effect on other organisms? Consideration should be given to possible effects other than those being sought in the construction.

6.7.2 is there reason to suspect that the tissue tropism of the recombinant virus in host organisms will be different from that of the unmodified virus?

6.7.3 is there reason to suspect that the modified virus might have altered infectivity or interactions with host defence mechanisms? Will the normal status of host defence systems be compromised by the modified virus? Is the recombinant likely to have enhanced effects on a weakened host, or host lacking normal vigour, beyond those normally expected with the parent virus?

6.7.4 will virus susceptibility to control agents (where these are available) be affected by genetic modification?

6.7.5 are all potential routes of transmission or escape to the environment of the virus that might occur, eg in a laboratory accident, known? If so, will such routes allow the modified virus and/or its products access to the organisms in which effects may be manifested?

6.7.6 will the insert cause changes in the host range of the virus?

6.7.7 is there reason to suspect that the modification carried out to the virus may result in altered survivability in the environment? Special attention should be given to effects on UV tolerance, temperature and resistance to desiccation.

6.8 There may be a need to pay particular attention to the disposal of infected material to minimise risks of accidental spread of virus beyond the laboratory.

USE OF ACGM LEVEL 1 CONTAINMENT

7.1 Experiments using viral vectors that do not normally infect human cells in culture and for which there is no evidence of human infection are considered to represent a minimal risk to the operator and can be conducted at ACGM Level 1 containment, unless a higher standard of containment is indicated as a result of a potential for harm to other species. The requirements of MAFF, SOAFD etc must also be taken into account. Care must be taken however where expression of potentially allergenic proteins may take place. (See para 5.2 above).

7.2 Experiments which involve DNA (or RNA) vectors derived from viruses and cells in culture as hosts (even if the cells contain viral sequences) and in which no infective virus is involved or can be produced, are considered to represent minimal hazard and can be carried out under ACGM level 1 containment. Particular attention should be paid to experimental procedures that might activate an endogenous or latent virus capable of acting as a helper.

GUIDANCE ON COMMONLY USED VIRAL VECTORS

8.1 Baculoviruses: The most commonly used Baculovirus vector utilises the highly expressed and regulated Autographa californica nuclear polyhedrosis virus polyhedrin promoter modified for the insertion of foreign genes. One of the major advantages of this invertebrate virus vector is the very abundant expression of recombinant proteins.

Baculoviruses are pathogens of a range of insect hosts and as such may, in certain circumstances, pose a potential threat to such species in the natural environment. In particular the use of such viruses and organisms such as susceptible caterpillars must be given particular attention to ensure release to the environment do not occur. MAFF/SOAFD advice should be sought on the requirements pertaining to insect pests.

Baculovirus expression systems should not automatically be assigned to ACGM Level 1 containment but the risk assessment should take the above into consideration before determining the appropriate containment.

The Baculoviruses are not capable of infecting vertebrate or plant cells and as such do not pose any inherent hazard to workers. However the high level of expression of recombinant proteins possible with such vectors may cause workers to be exposed to pharmacologically or physiologically active products. The potential for such exposure must be examined in the COSHH risk assessment for each piece of work.

8.2 Vaccinia: Certain aspects of the biology of vaccinia virus make it a useful tool for the molecular biologist facilitating the introduction of large gene inserts and subsequent high levels of expression. Vaccinia virus is categorised as a ACDP hazard group 2 pathogen and as such requires careful handling. The vaccine strain can be a cause of severe infection in humans.

The use of the thymidine kinase (TK) gene as an insertion site, creating a Tk-minus phenotype, is believed to reduce the virulence of the virus in mice but this should not be taken to imply lower virulence in man, nor to a downgrading of categorisation.

Particular attention must be given during the risk assessment to the insertion of genes that code for proteins that may have adverse physiological or pharmacological effects in vivo. Such work may warrant additional containment.

Those working with vaccinia virus should be familiar with the ACGM/ACDP guidance on vaccination² issued in 1990.

8.3 Retroviruses: Work employing non-primate retroviruses in an ecotropic envelope (ie. not capable of infecting human cells) may be carried out in ACGM Level 1 containment provided that there is no harm from accidental spread of virus to other host species beyond the laboratory. Such experiments should employ packaging cell lines in which the helper functions are encoded by at least two separate segments of DNA, in order to minimise the chances of generating a replication competent helper virus by recombination.

Work employing non-primate retroviruses that have an amphotropic coat, ie one capable of infecting human cells in culture, should use vectors rendered defective by deletion mutations. Consideration should be given to the probability of, and possible route of, recombination leading to reversion. If replication competent vectors are used, then ACGM Level 2 containment must be used as a minimum. The helper functions in the packaging cell line should again be encoded by at least two separate segments of DNA. In all such cases the nature of the gene insert is of importance and reference must be made to the risk assessment factors set out in paragraphs 6.5 and 6.7.

Work employing primate retroviruses (ACDP Hazard Group 3 agents) or with any system which includes envelope genes derived from primate retroviruses are subject to prior notification to DOE/HSE.

(V/HPDA3/J03C/2.11.92/BH)

2 Vaccination of laboratory workers handling vaccinia and related poxviruses infectious for humans. (ACGM/ACDP joint guidance). HMSO 1990 ISBN 0 11 885450 X.

VIRUSES PATHOGENIC TO HUMANS - ADVISORY COMMITTEE ON DANGEROUS PATHOGENS

Hazard Group 4

Arenaviridae

Junin virus
Lassa fever virus

Machupo virus
Mopeia virus

Bunyaviridae

Nairoviruses
Congo/Crimean haemorrhagic
fever

Togaviridae

Flaviviruses
Tick-borne viruses
Absettarov V
Hanzalova V
Hypr V
Kyasanur Forest V
Omsk V
Russian spring-summer
encephalitis V

Filoviridae

Ebola virus
Marburg virus

Poxviridae

Variola (major & minor)
virus¹ V
('whitepox' virus)²

Hazard Group 3

Arenaviridae

Lymphocytic choriomeningitis
virus (LCM)

Rhabdoviridae

Rabies virus V

Bunyaviridae

Bunyamwera supergroup
Oropouche virus
Phleboviruses
Rift Valley fever
Hantaviruses
Hantaan (Korean haemorrhagic fever)
Other hantaviruses

Togaviridae

Alphaviruses
Eastern equine
encephalomyelitis
Venezuelan equine
encephalomyelitis v
Western equine
encephalomyelitis
Flaviviruses
Japanese B encephalitis
Kumlinge
Louping ill v
Murray Valley encephalitis
(Australia encephalitis)
Powassan
Rocio
St Louis encephalitis
Tick-borne encephalitis v
Yellow fever V

Hepadnaviridae

Hepatitis B virus V
Hepatitis B virus + Delta V

Herpesviridae

Herpesvirus simiae (B virus)

Poxviridae

Monkeypox virus V

Retroviridae³

Human immunodeficiency viruses
(HIV)
Human T-cell lymphotropic
viruses (HTLV) types 1 and 2

1 Work with these viruses must not be carried out in the United Kingdom.

2 So called 'whitepox' virus is now acknowledged to be a cell culture contaminant derived from smallpox material. All strains of 'whitepox' virus are therefore subject to the same restriction as that now applied to variola virus (see 1 above).

3. At present there is no evidence of infection of man with either simian immunodeficiency viruses (SIV) or simian T-cell lymphotropic viruses (STLV). For this reason they are not allocated to a hazard group but in the present state of uncertainty attention is drawn to them here as a precautionary measure. Containment Level 3 is recommended for work with them.

Hazard Group 2

Adenoviridae	Echoviruses	
	Hepatitis A virus (human enterovirus type 72)	
Arenaviridae	Polioviruses	V
other arenaviruses		
Rhinoviruses		
Astroviridae		
	Poxviridae	
Bunyaviridae	Coxsackie virus	G
Hazara virus	Molluscum contagiosum virus	
other bunyaviruses	Orf virus	G
	Vaccinia virus	
Caliciviridae		
	Reoviridae	
Coronaviridae	Human rotaviruses	
	Orbiviruses	
Herpesviridae	Reoviruses	
Cytomegalovirus		
Epstein-Barr virus	Rhabdoviridae	
Herpes simplex viruses types 1 & 2	Vesicular stomatitis virus	S
Herpesvirus varicella-zoster		
Human B-lymphotropic virus (HBLV - human herpesvirus type 6)		
	Togaviridae	
Orthomyxoviridae	Other alphaviruses	
Influenza viruses types A, B & C	Other flaviviruses	
Influenza virus type A-recent isolates	Rubivirus (rubella)	v
	S Unclassified viruses	
Paramyxoviridae	Hepatitis non-A non-B viruses	
Measles virus	Norwalk-like group of small round structured viruses	v
Mumps virus	Small round viruses (SRV - associated with gastroenteritis)	E
Newcastle disease virus		
Parainfluenza viruses types 1 to 4	Unconventional agents associated with	
Respiratory syncytial virus	Creutzfeldt-Jakob disease	EG
	Gerstmann-Straussler-Scheinker syndrome	EG
Papovaviridae	Kuru	EG
BK and JC viruses		
Human papillomaviruses		
Parvoviridae		
Human parvovirus (B19)		
Picornaviridae		
Acute haemorrhagic conjunctivitis virus (AHC)		
Coxsackieviruses		

E - eye protective equipment must be used

G - gloves must be used

S - a microbiological safety cabinet must be used

V - vaccination essential

v - vaccination recommended

VIRUSES CONTROLLED BY THE AGRICULTURE AND FISHERIES DEPARTMENTS

Pathogens of animals and poultry

1 The Importation of Animals Pathogens Order 1980 prohibits the importation into Great Britain of any pathogen that may cause disease in agricultural animals or birds, or any material in which a pathogen might be carried, except under the authority of a licence in writing issued by the appropriate Minister and in accordance with the conditions of that licence. The 'appropriate Minister' in the application of this Order to England means the Minister of Agriculture, Fisheries and Food; to Scotland, the Secretary of State for Scotland; and to Wales, the Secretary of State for Wales.

2 The pathogens of most concern to the Agriculture Departments are listed below. Those shown in capital letters may cause diseases that are notifiable or otherwise subject to statutory control by Orders made under the Animal Health Act 1981.

Bunyaviridae

Bunyaviruses
 Akabane
 Nairoviruses
 Nairobi sheep disease
 Ganjam

Caliciviridae

Vesicular exanthema

Herpesviridae

AUJESZKY'S DISEASE (PSEUDORABIES)
 Duck virus enteritis (duck plague)
 Equine rhinopneumonitis
 Malignant catarrhal fever

Iridoviridae

AFRICAN SWINE FEVER

Orthomyxoviridae

AVIAN INFLUENZA (FOWL PLAGUE) and other influenzas

Paramyxoviridae

Morbilliviruses
 RINDERPEST (CATTLE PLAGUE)
 Peste des petits ruminants
 Paramyxoviruses
 NEWCASTLE DISEASE

Picornaviridae

Enteroviruses

SWINE VESICULAR DISEASE
TESCHEN

Rhinoviruses

FOOT AND MOUTH DISEASE

Poxviridae

Camel, goat and horse poxes

Lumpy skin disease
SHEEP POX

Reoviridae

Orbiviruses

AFRICAN HORSE SICKNESS
Bluetongue
Epizootic haemorrhagic disease of deer
Ibaraki

Retroviridae

Lentiviruses

Maedi/visna

Oncoviruses

ENZOOTIC BOVINE LEUCOSIS

Unclassified

Borna

EQUINE INFECTIOUS ANAEMIA

Rhabdoviridae

Bovine ephemeral fever

RABIES

Vesicular stomatitis

Togaviridae

Alphaviruses

EQUINE ENCEPHALOMYELITIS

Arteriviruses

Equine arteritis

Flaviruses

Japanese B encephalitis

Wesselbron disease

Pestiviruses

SWINE FEVER (HOG CHOLERA)

Unconventional agents

BOVINE SPONGIFORM ENCEPHALOPATHY (BSE)

3 Details of the requirements for the importation or handling of pathogens of animals or poultry may be obtained from:

Ministry of Agriculture, Fisheries and Food
Veterinary Investigation Section
Hook Rise South
Tolworth KT6 7NF
(Tel: 081-330 4411)

The Scottish Office Agriculture and Fisheries Department
Pentland House
47 Robbs Loan
Edinburgh EH14 1TW
(Tel: 031-556 8400)

Welsh Office Agriculture Department
Crown Buildings
Cathays Park
Cardiff CF1 3NQ
(Tel: 0222 693131)

Pathogens of other animals

4 The following virus of rabbits is controlled by an Order made under the Pests Act 1954:

Poxviridae
Leporipoxviruses
Myxoma

5 Details of the requirements may be obtained from:

Ministry of Agriculture, Fisheries and Food
Worplesdon Laboratory
Tangle Place
Worplesdon GU8 3LQ
(Tel: 0483 232581)

6 The following pathogens of fish cause diseases that are currently notifiable and controlled by Orders made under the Diseases of Fish Acts 1937 and 1983.

Birnaviridae
Infectious pancreatic necrosis

Rhabdoviridae

Infectious haematopoietic necrosis
Spring viraemia of carp
Viral haemorrhagic septicaemia

7 Details of the requirements may be obtained from:

Ministry of Agriculture, Fisheries and Food
Fish Disease Laboratory
The Nothe
Weymouth DT4 8UB
(Tel: 03057 72137)

Pathogens of plants

8 The Plant Health (Great Britain) Order 1987, as amended by the Plant Health (Great Britain) (Amendment) Order 1989, prohibits the importation into Great Britain and the keeping of any plant pathogen or plant pest not established in Great Britain and of other plant pathogens and plant pests considered to be of quarantine significance and controlled by the above Order, except under the authority of a licence in writing issued by the appropriate Minister and in accordance with the conditions of that licence. Any activity that involves the genetic modification of a plant pathogen or pest or which is likely to result in the production of a plant pathogen or pest is also covered by the 1987 Order. In addition, the Plant Health (Great Britain) Order 1989 prohibits the landing in Great Britain of certain specified tree pests and also of any non-indigenous tree pests.

9 The following pathogens and pests of plants and trees are specifically controlled by the 1987 and 1989 Orders or will be controlled by amendments to bring the Orders into line with the EC Plant Health Directive.

Viruses and virus-like pathogens

Harmful viruses and virus-like pathogens of the genera Cydonia, Fragaria, Malus, Prunus, Pyrus, Ribes and Rubus:

Apple Proliferation Disease mycoplasma
Apricot Chlorotic Leaf Roll Disease mycoplasma
Black Raspberry Latent virus (Rubus strains)
Cherry Leaf Roll virus (Rubus strains)
Cherry Rasp Leaf virus (American)
Little Cherry pathogen (non-European strains)
Peach Mosaic virus (American)
Peach Phony Rickettsia
Peach Rosette Disease mycoplasma
Peach Yellowing Disease mycoplasma
Pear Decline Disease mycoplasma
Plum Line Pattern virus (American)
Plum Pox (Sharka) virus
Prunus Necrotic Ring Spot virus (Rubus strains)
Raspberry Leaf Curl viruses (American)
Strawberry Latent C virus
Strawberry Vein Banding virus
Strawberry Witches' Broom Disease mycoplasma
X Disease mycoplasma

Other harmful viruses and virus-like pathogens of the genera Cydonia, Fragaria, Malus, Prunus, Pyrus, Ribes and Rubus that are not known to occur within EC Member States.

Harmful viruses and virus-like pathogens of potato:

Potato Yellow Dwarf virus
Potato Yellow Vein virus
Tomato Spotted Wilt virus (potato strains)
Other harmful viruses and virus-like pathogens of potato that are not known to occur within EC Member States.

Beet Curly Top virus
Beet Leaf Curl virus
Elm Phloem Necrosis mycoplasma
Potato Spindle Tuber viroid
Stolbur Disease mycoplasma
Tomato Ring Spot virus
Beet Necrotic Yellow Vein virus - Beet Rhizomania Disease

10 Details of the requirements of the Order and for the importation and keeping of plant pathogens may be obtained from:

Ministry of Agriculture, Fisheries and Food
Plant Health Division
Nobel House (Room 504)
17 Smith Square
London SW1P 3HX
(Tel: 071-2386483)

and for technical enquiries from:

Ministry of Agriculture, Fisheries and Food
Agricultural Development and Advisory Service
Harpenden Central Science Laboratory
Hatching Green
Harpenden
Herts AL5 2BD
(Tel: 0582-715241)

and for Scotland from:

The Scottish Office Agriculture and Fisheries Department
Plant Health Branch
Pentland House
47 Robbs Loan
Edinburgh EH14 1TW
(Tel: 031 - 556 8400)

and for technical enquiries:

The Scottish Office Agriculture and Fisheries Department
Agricultural Science Services
Plant Health Branch
East Craigs
Edinburgh EH12 8NJ
(Tel: 031 - 556 8400)

and for pests of trees, wood and bark:

Forestry Commission
Plant Health Branch
231 Corstorphine Road
Edinburgh EH12 7AT
(Tel: 031 - 334 0303)

11 In certain cases, licences may also be required to import alien isolates or strains of plant pathogens or pests which occur here but which are likely to be of differing pathogenicity or host range from those occurring naturally within Great Britain.

12 It is the responsibility of the user to determine whether or not the organism to be used is a plant pathogen or pest, whether or not it is established in Great Britain, and to apply to MAFF/SOAFD for a licence as appropriate. In such cases, the user will be helped to select lower risk organisms where possible.

