HSE

Health and Safety Executive

Biological agents

The principles, design and operation of Containment Level 4 facilities

Advisory Committee on Dangerous Pathogens

Contents

Preface

In the UK, the principles and standards for working with high-hazard pathogens were originally laid down in the Advisory Committee on Dangerous Pathogens (ACDP) publication *Categorisation of biological agents* (1984; revised in 1990 and 1995).[1] This publication set new practical standards for safe working with such agents. It had the status of guidance supporting the Health and Safety at Work etc Act 1974[2] (HSW Act) and the Control of Substances Hazardous to Health Regulations 1988 (COSHH, now amended).

The fourth edition (1995) of *Categorisation of biological agents* reflected the need to implement two new European Community Directives: the Biological Agents Directive (90/679/EEC),[3] which was implemented by new COSHH regulations in 1994 (revised in 2000 and 2002);[4] and the second Directive, 93/88/EEC (now replaced by 2000/54/EC)[3] which contained a European Community classification of biological agents capable of causing infection. This classification was implemented by means of an approved list of biological agents and has legal status under COSHH.

The ACDP has been working to revise and update the 1995 *Categorisation of biological agents* guidance over the last five years. The 1995 guidance has now been replaced by three separate documents:

- *The management, design and operation of microbiological containment laboratories* HSE Books 2001,[5] which is aimed at those responsible for the management and operation of Containment Level 2 and 3 (CL2 and CL3) laboratories;
- *Biological agents: Managing the risks in laboratories and healthcare premises* HSE 2005,[6] which is aimed at the healthcare sector; and
- *Biological agents: The principles, design and operation of Containment Level 4 facilities* – this document, which is aimed at high-hazard containment facilities.

This ACDP guidance is aimed mainly at laboratories handling pathogens that present a risk to human health under COSHH. However, genetically modified pathogens and zoonotic pathogens will also pose a potential risk to workers. Some of these are covered by other regulatory schemes (eg the Genetically Modified Organisms (Contained Use) Regulations 2000[7] (GMO(CU)) and the Specified Animal Pathogens Order 1998[8] (SAPO)) that are discussed here only as far as they relate to human health. Further specific guidance on these is provided elsewhere.[9-10]

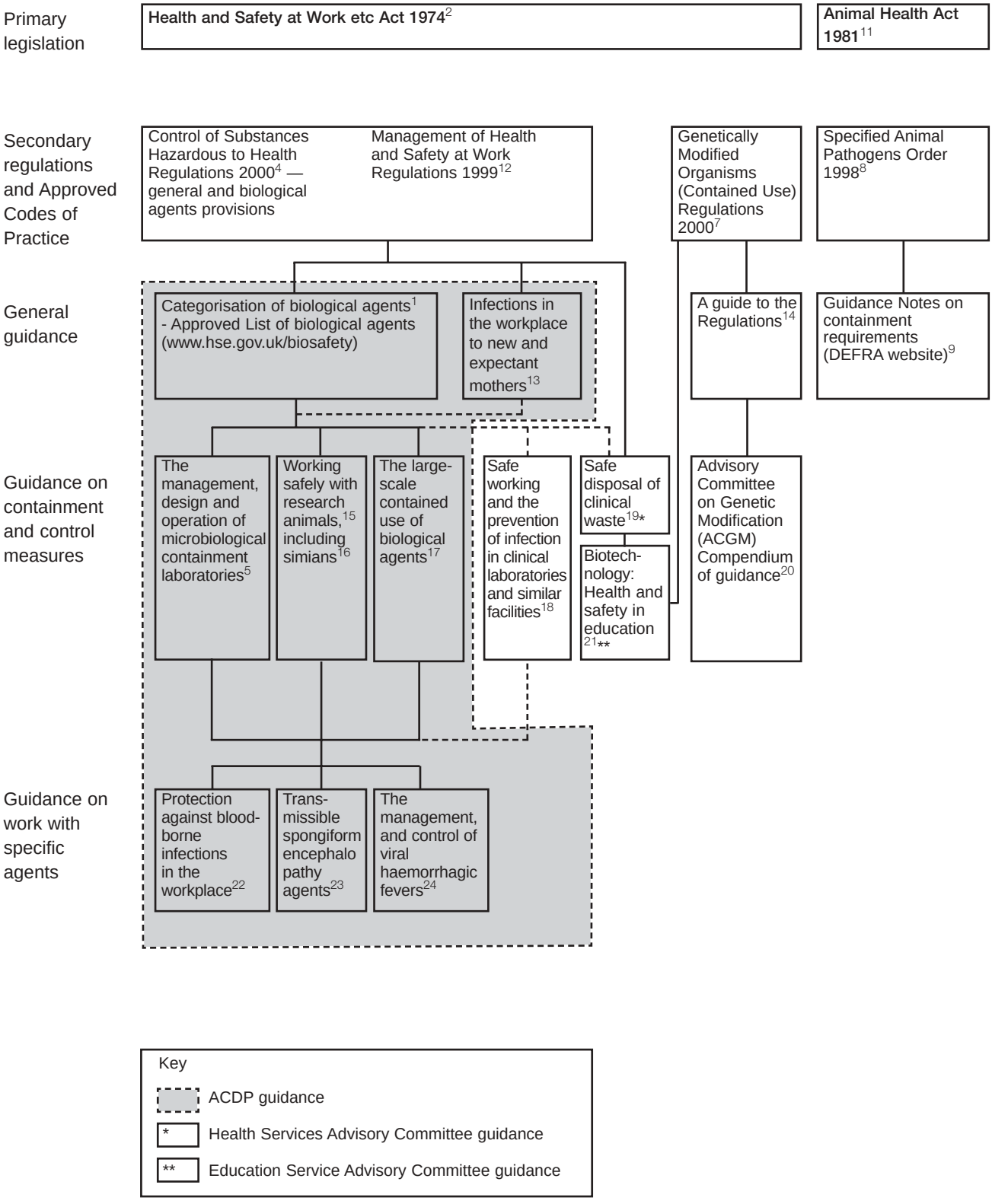
The term **'high-hazard pathogen'**, for the purpose of this document, will include those organisms categorised by:

- EC Directive 2000/54/EC – the Community classification of biological agents, implemented in the UK by means of an Approved List and known widely as ACDP Hazard Group 4 (HG4) agents;
- the Department for Environment, Food and Rural Affairs (DEFRA), for administering licensing under the Specified Animal Pathogens Order 1998

(SAPO), for the purpose of protecting animal health from escape of organisms from laboratories. SAPO is administered by the Scottish Executive Environment and Rural Affairs Department (SEERAD) in Scotland and by the Office of the Chief Veterinary Officer at the Welsh Assembly Government in Wales. High-hazard pathogens under this scheme are those that require bio-containment at DEFRA Containment Level 4 (CL4); and

- the Genetically Modified Organisms (Contained Use) Regulations 2000 (as amended) (GMO(CU)). A suitable and sufficient risk assessment under these Regulations may result in a genetically modified micro-organism (GMM) being allocated appropriate containment and control measures at GM (genetically modified) Activity Class 4.

Figure 1: An overview of the relevant health and safety legislation and other guidance that should be consulted when working with biological agents in any type of microbiological containment laboratory



List of abbreviations

ACDP	Advisory Committee on Dangerous Pathogens
ACGM	Advisory Committee on Genetic Modification
ASPA	Animals (Scientific Procedures) Act 1986
ATCSA	Anti-terrorism, Crime and Security Act 2001
BMS	building management system
BSA	biological safety advisor – or other competent person appointed under the Management Regulations
CCHF	Crimean/Congo haemorrhagic fever
CCTV	closed-circuit television
CDM	Construction (Design and Management) Regulations 1994
CHIP	Chemicals (Hazard Information and Packaging for Supply) Regulations 1994
CL	Containment Level
COSHH	Control of Substances Hazardous to Health Regulations 2000 (as amended)
DEFRA	Department for Environment, Food and Rural Affairs
FDA	Food and Drugs Administration (USA)
FFI	flexible-film isolator (animals)
FMEA	failure modes and effects analysis
GM	genetically modified
GMO(CU)	Genetically Modified Organisms (Contained Use) Regulations 2000 (as amended)
GMM	genetically modified micro-organism
GMO	genetically modified organism
HEPA	high efficiency particulate air
HG4	Hazard Group 4
HSE	Health and Safety Executive
HSW Act	Health and Safety at Work etc Act 1974
HVAC	heating, ventilation and air conditioning
LEV	local exhaust ventilation
Management Regulations	Management of Health and Safety at Work Regulations 1999
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
NaCTSO	National Counter-Terrorism Security Office
PPC	pollution prevention control
PPE	personal protective equipment
RIDDOR	Reporting of Injuries, Diseases and Dangerous Occurrences Regulations 1995
RPE	respiratory protective equipment
SAPO	Specified Animal Pathogens Order 1998
SEERAD	Scottish Executive Environment and Rural Affairs Department
SIV	simian immunodeficiency virus
SOP	standard operating procedure
UKAS	United Kingdom Accreditation Service
ULPA	ultra low penetration air filters
VHF	viral haemorrhagic fever
VHFV	viral haemorrhagic fever viruses
WEL	workplace exposure limit
WHO	World Health Organisation

Aims of this guidance

1 This guidance aims to expand and explain the legal requirements for working with high-hazard pathogens, with a particular focus on the way in which these requirements influence the design, construction and operation of CL4 facilities. This guidance is intended for all laboratories in which high-hazard pathogens may be handled. Additional guidance covering the clinical care of patients suspected of being infected with such pathogens can be found in other ACDP guidance.[1, 5, 6]

2 In addition to providing practical guidance on how to meet the requirements of specific legislation, this document also provides advice on good practice in related aspects of design, operation and management of such facilities.

3 Details of some DEFRA CL4 containment and operating requirements for work with specified animal pathogens under SAPO licences are included throughout this guidance for comparative purposes, but the full range of DEFRA CL4 requirements are not covered. For further details of these please refer to DEFRA's website (www.defra.gov.uk).

Scope of this guidance

4 This guidance covers work in all types of laboratories where **high-hazard pathogens** are handled, such as in diagnostic laboratories and research facilities. It covers both deliberate propagation/concentration of the agents and work with material that contains or is likely to contain agents for which **Containment Level 4** (CL4) is required. The scope of this guidance does not include work with large animals at CL4 – additional guidance on this area will follow in due course.

5 For the purposes of this guidance, the following definitions apply:

- a **laboratory** is the room in which biological agents are handled;
- the **laboratory suite** is one or more laboratories, not necessarily of the same discipline or containment level, and ancillary rooms within a section or department with shared use of equipment and facilities such as media preparation, autoclaves and centrifuges; and
- a **laboratory unit** is a separate building or self-contained suite within a building containing one or more laboratories and with ancillary rooms such as airlocks, changing rooms, showers or autoclave rooms.

6 CL4 laboratories are highly specialised and those considering the design and construction of such facilities should consult widely from the outset. It would be advantageous to consult with others who have experience of such facilities including:

- the Health and Safety Executive (HSE);
- the Department for Environment Food and Rural Affairs (DEFRA);
- the Environment Agency;
- the Home Office; and
- the National Counter-Terrorism Security Office (NaCTSO).

7 In some respects the management, design and operational requirements of CL4 laboratories are outwardly similar to those of laboratories at CL2 and CL3. However, because the agents being handled at CL4 are more hazardous, the standards that must be achieved are considerably higher. There is, therefore, a hierarchy of control, which increases in complexity from CL2 through to CL4. An example of this hierarchy is the requirement to HEPA (high efficiency particulate air) filter input and extract air to and from the workplace; CL2 laboratories, for example, do not require any air filtration, CL3 laboratories require only the extract air to be filtered and for CL4 laboratories, both input and extract air must be filtered, with the extract air passing through two filters. Apart from the numerous differences in physical containment, a further major distinction between such laboratories is the way in which they are managed. At **all** types of CL4 there has to be a much more rigorous and controlled approach to management, with a correspondingly high level of work supervision.

8 It should be remembered that, at any containment level, the risk from work with biological agents is dependent on the severity of infection, the means of transmission, quantity of agents being handled and the nature and

location of the work. This needs to be addressed in local risk assessments (under COSHH and GMO(CU)). If necessary, specific control measures, in addition to the minimum required under relevant legislation, should be put in place to ensure that the work is carried out safely.

9 Table 1 illustrates the number of laboratory-acquired HG4 infections reported worldwide during the past 30 years or so. The table clearly shows that laboratory-acquired infections do occur despite stringent laboratory controls. The figures given are based on documented cases of severe and frequently fatal naturally occurring human infections and aerosol-transmitted laboratory infections. It should be noted, however, that these viruses can cause severe human disease that can spread to the community and there is no effective prophylaxis or treatment available. Although naturally occurring outbreaks of these viruses are rare, they can have a devastating effect. The recent Marburg outbreak in Angola (2005) had a 90% fatality rate in the 252 people infected.

Table 1: An illustration of the number of cases of laboratory-acquired infection with HG4 agents worldwide over the past 30 years

Laboratory or laboratory animal associated human infections			
Virus	**Cases**	**Fatalities**	**Source(s) and route of infection**
Lassa	2	1	Aerosol – processing infected rodent tissue
Junin	21	1	Aerosol – processing infected rodent tissue
Sabia	3	1	Aerosol – centrifuging infected tissue culture
Crimean/Congo haemorrhagic fever	8	1	Aerosol – processing infected rodent tissue
Machupo	1	1	Aerosol – processing infected rodent tissue
Marburg	15	1	Direct contact with infected monkey tissue
Ebola	1	0	Direct through needle stick
Herpesvirus B	~50	29	Direct contact with monkeys

Liaison with other government bodies

10 In addition to the health and safety requirements covered in this guidance, a number of other agencies have mandatory requirements, which will influence the design process. These may include the agencies listed in paragraphs 11-23.

Department for Environment, Food and Rural Affairs (DEFRA)

11 In England and Wales, DEFRA forms part of the joint Competent Authority (with HSE and the Secretary of State) to oversee the GMO(CU) Regulations. DEFRA also administers the Specified Animal Pathogens Order in England. DEFRA should be consulted throughout the design stage to ensure compliance with any mandatory control measures under these regulations. The Specified Animal Pathogens Order is discussed in further detail in paragraphs 29-31.

Health and Safety Executive (HSE)

12 HSE forms part of the Competent Authority for England and Wales (along with DEFRA and the Secretary of State) to oversee the GMO(CU) Regulations. These Regulations specify mandatory containment controls for high-hazard laboratories and HSE provides a key regulatory function through notifications, interventions and inspections.

Scottish Executive Environment and Rural Affairs Department (SEERAD)

13 In Scotland, the Specified Animals Pathogens Order is administered by the Scottish Executive Environment and Rural Affairs Department (SEERAD). SEERAD aims to promote rural development and ensure that the needs and interests of rural Scotland are reflected in all of the Executive's policies and priorities.

14 SEERAD is responsible for advising ministers on policy relating to agriculture, rural development, food, the environment and fisheries, and for ensuring the implementation of those policies in Scotland.

National Assembly for Wales

15 In Wales, the Office of the Chief Veterinary Officer at the Welsh Assembly Government is responsible for administering SAPO.

The Home Office

16 If living animals are to be tested and experimented upon, then the Animals (Scientific Procedures) Division and the Animals (Scientific Procedures) Inspectorate will need to be involved in discussions. The Inspectorate has the responsibility for inspecting those facilities where work with animals is carried out and will be seeking to ensure that facilities conform to the code of practice for the housing and care of animals used in scientific procedures. Consequently, designers of the premises will need to ensure that animal facilities conform to defined standards for animal welfare. For example:

- the animal house should be designed, sited and constructed to provide a suitable environment, including any special requirement for exercise or social contact for the species to be housed;
- temperatures in animal rooms will need to be carefully controlled and continuously monitored. The equipment, insulation and design of the building should be such as to ensure that the correct temperature can be maintained in both winter and summer;
- extreme variations in relative humidity can have adverse effects on the well-being of animals. Prolonged periods below 40% or above 70% should be avoided;
- design should take into account the fact that building maintenance may disturb animals and disrupt experiments;
- services should be installed to be accessible from outside and with fittings that can be removed by staff for maintenance and repair;
- the air distribution system should deliver as even a proportion of air to each cage or animal as possible while avoiding draughts. This is an area of particular importance, especially as differential air pressures will be used throughout the facility. The number of air changes per hour required by Home Office regulations is different for various animal species. Please refer to Home Office guidance (see paragraph 17) for further details.

17 Much of the information relating to animal welfare is provided in the Home Office document *Code of Practice for the housing and care of animals used in scientific procedures*.[25]

The Environment Agency

18 The Environment Agency has responsibility for enforcing the laws covering the risks to the environment from hazardous waste. It is important to inform the agency that plans are being progressed to build a CL4 facility, the most appropriate way of doing this will be via the local area office.

19 The special waste regulations are currently being superseded by the Hazardous Waste Regulations 2005.[26] Under the new Regulations, any waste requiring specialist treatment or disposal (including incineration) due to the infection risk posed, irrespective of the level and type of infection, will be considered 'hazardous infectious waste'.

20 In summary, the new Regulations require producers to:

- register with the Environment Agency;
- segregate more categories of hazardous waste from non-hazardous waste;
- increase the amount of information provided for consignment;
- keep consignment notes (and any associated paperwork) for three years.

21 The Environment Agency has produced *Technical Guidance WM2*[27] on the Hazardous Waste Regulations 2005. This guidance is available from the Environment Agency's website (www.environment-agency.gov.uk).

Local authorities

22 The main consideration for the local authority relates to provision of adequate planning and public consent. The design team may want to consider the merits of local public consultation. A remit of this committee would be to seek out and provide accurate information to the community to foster a greater understanding of the activities that will be undertaken in the building.

Fire authorities

23 Pertinent information can be obtained from the local fire brigade and the British Fire Service.[28] The planning team would need to ensure that the design process identified what was required to prevent fire in the workplace. Furthermore, sufficient information about the layout of the building and what the building was used for would have to be provided to firefighters to enable them to carry out their duties safely. In the event of a fire at a high-hazard facility, it is highly unlikely that fire service personnel would readily enter the building without first being appraised of the situation and the hazards involved. Careful consideration should be given in the design of these facilities for the inclusion of appropriate fire control/suppression systems (automatic shut-down systems, inert suppression systems) or detailed thought into the best policy to adopt, such as a 'burn-down' policy, should be taken in consultation with the fire service and local authority.

Principles of containment

24 The term 'containment' describes the way in which high-hazard pathogens are managed in the laboratory environment to prevent exposure of laboratory workers, other workers and people and animals in the outside environment to the agent(s) in question. This can be achieved in a number of ways:

- **primary containment**: ie protection of the worker and the immediate environment can be achieved through a combination of good microbiological practices or techniques and the use of appropriate primary containment devices, eg Class III microbiological safety cabinets;
- **secondary containment**: ie protection of people and the environment outside the laboratory can be achieved by a combination of laboratory design and operating procedures, eg access restriction, air handling and safe disposal of waste.

25 In addition to the more general means of preventing or controlling exposure to high-hazard agents, there is also a requirement for the use of certain minimum containment measures for laboratories handling particular groups of biological agents. CL4 must be used if an assessment indicates to an employer that such a containment level is necessary, even if there is no intention to deliberately propagate and concentrate high-hazard agents.

Control of Substances Hazardous to Health Regulations 2002 (COSHH) (as amended)[4]

26 The ACDP classification of biological agents was revised in 1994 as a result of the implementation of European Directive 2000/54/EC, which changed the status of the classification list into law, now being an Approved List made under the Health and Safety at Work etc Act 1974. COSHH was revised in 2002 to move the general requirements for work with biological agents into the main body of the COSHH Regulations.

27 COSHH classifies biological agents into four hazard groups based on their ability to infect and cause harm to humans. COSHH does not consider environmental risks.

28 If employers cannot prevent exposure to a biological agent they should take steps to ensure that it is adequately controlled. A risk assessment should be performed and appropriate control measures selected to adequately control the risks. For Hazard Group 4 (HG4) agents, the controls from Part II of Schedule 3 should be applied as a minimum.

Specified Animal Pathogens Order 1998 (SAPO)[8]

29 The Specified Animal Pathogens Order 1998 prohibits any person from having in their possession any specified animal pathogen listed in Part I of the Schedule to

the Order, or any carrier in which they know such a pathogen is present, except under licence. It also prohibits the introduction into any animal or bird of any pathogen listed in the Schedule to the Order (Parts I and II) except under licence.

30 The purpose of SAPO is to prevent the introduction and spread of animal pathogens that cause serious exotic diseases in livestock and poultry and economic loss to the British livestock and poultry industries. Containment and operating requirements imposed under SAPO are therefore concerned with preventing the escape of pathogens from the laboratory and not with the protection of laboratory workers or other people. The possession of a licence under SAPO does not in any way limit the obligations placed upon employers and employees by the Health and Safety at Work etc Act 1974 or specific legislation made under the Act. Where work with specified animal pathogens is being undertaken, both DEFRA requirements and the relevant requirements of health and safety legislation apply.

31 Specified animal pathogens are classified into three main categories by DEFRA: DEFRA Group 2, DEFRA Group 3 and DEFRA Group 4 – Group 4 requiring the highest level of containment. This guidance is also intended for laboratories working with Group 4 specified animal pathogens that can cause harm to humans, for which the relevant COSHH and DEFRA containment requirements will both apply.

Genetically Modified Organisms (Contained Use) Regulations 2000 (GMO(CU)) (as amended)[7]

32 Contained use is where control measures are used to limit contact between GMO's and humans and the environment, to provide a high level of safety. In practice, this involves work in laboratories, animal houses, plant growth facilities (including growth rooms in buildings and suitable glasshouses) and large-scale production facilities on industrial sites.

33 The primary piece of legislation that applies to the use of genetically modified organisms in the workplace is the Genetically Modified Organisms (Contained Use) Regulations 2000 (GMO(CU)), as amended in 2002 and 2005.

34 The GMO(CU) Regulations provide for human health and safety and environmental protection from genetically modified micro-organisms in contained use. The key requirement of the GMO(CU) Regulations is to assess the risks of all activities and to classify each activity based on the control and containment measures required.

35 The main requirement of GMO(CU) is to assess all activities for the risk to human health and the environment. Containment is based on a risk assessment and selection of appropriate control measures from Part II, Schedule 3 of COSHH. All Class 4 activities require notification of premises and consent from the Competent Authority before work can begin.

Anti-terrorism, Crime and Security Act 2001 (ATCSA)[29]

36 Part 7 of the Anti-terrorism, Crime and Security Act 2001 contains further legal requirements to ensure that the storage and use of dangerous pathogens and toxins listed in Schedule 5 of the Act is as secure as practicable. This is achieved by effective levels of physical security and by limiting access to those authorised to work with Schedule 5 agents.

37 All facilities handling or storing Schedule 5 agents must satisfy Home Office requirements, whether they are being developed as part of a refurbishment or a complete 'new-build'. All current CL4 premises must comply with these requirements. Organisations considering new or upgraded CL4 premises should contact the National Counter-Terrorism Security Office (NACTSO) at the earliest stage possible for specialist advice on how to comply with current legislation (Tel: 020 7931 7142; or in writing to NACTSO, PO Box 849, London SW1P 1XD).

38 The security of each individual site will need to be approached according to its own unique features. It is strongly recommended that advice is sought at the earliest possible stage from NaCTSO, who will assess security measures in consultation with the site owners/managers and their own experts. To facilitate this process, the project manager should contact NaCTSO with the following information before the design of the facility:

- name and contact details of the project manager/point of contact;
- full location details of the proposed site;
- nature of the build (new facility or refurbishment);
- proposed timescales for the project.

39 The level of physical security required for CL4 facilities includes a robust perimeter fence (or equivalent), 24-hour manned security and multiple layers of access control. Further details on physical security requirements can be found in the Home Office publications *Security standards for laboratories*[30] and *Personnel security measures for laboratories*,[31] which are available on request from NaCTSO (Tel: 020 7931 7142).

Animals (Scientific Procedures) Act 1986 (ASPA)[32]

40 The Animals (Scientific Procedures) Act 1986, administered by the Home Office, imposes clear responsibilities on people with specific roles in relation to the care and use of animals in laboratories. (These are elaborated further in *Guidance on the operation of the Animals (Scientific Procedures) Act 1986.*)[33] All animal-handling procedures should only be carried out under the authority of a Project Licence and a Personal Licence issued by the Home Office.

41 Table 2 sets out the **minimum** containment requirements of the COSHH, SAPO and GMO(CU) Regulations for work in CL4 laboratories. (Under GMO(CU), an assessment may indicate that not all of the containment controls need to be applied. Consent from the Competent Authority is required before making any changes to the requirements in this table.)

Table 2: Containment measures for CL4 laboratories under appropriate legislation

Containment measures	COSHH	SAPO	GMO(CU)*
The workplace is to be separated from any other activities in the same building	Yes	Yes	Yes
Input air and extract air to the workplace are to be filtered using HEPA or equivalent	Yes, on input and double on extract air	Yes, single on input and double on extract air	Yes, extra requirements for viruses
Access is to be restricted to authorised people only	Yes, via airlock key procedure	Yes, restricted and entry through an airlock, clean/ dirty area. Shower on exit	Yes, via airlock key
The workplace is to be sealable to permit disinfection	Yes	Yes	Yes, sealable for fumigation
Specified disinfection procedure	Yes	Yes	Yes
The workplace is to be maintained at air pressure negative to atmosphere	Yes	Yes, pressure to be maintained at not less than -75 Pa	Yes
Efficient vector control, eg rodents and insects	Yes	Yes, and proofed against entry or exit of animals and insects	Yes
Surfaces impervious to water and easy to clean	Yes, for bench, floor, walls and ceiling	Yes, for working surfaces, walls and ceiling	Yes, for bench, floor, walls and ceiling
Surfaces resistant to acids, alkalis, solvents, disinfectants	Yes, for bench, floor, walls and ceiling	Yes, for working surfaces, walls and ceiling	Yes, for bench, floor, walls and ceiling
Safe storage of a biological agent	Yes, secure storage	Yes, secure storage in the laboratory suite. Inventory to be maintained	Yes, secure storage
An observation window, or alternative, is to be present, so that occupants can be seen	Yes	Yes	Yes
A laboratory is to contain its own equipment	Yes	Yes	Yes
Infected material, including any animal, is to be handled in a safety cabinet or isolator or other suitable containment	Yes	Yes	Class III cabinet required
Incinerator for the disposal of animal carcasses	Yes, on site	Yes, or some other validated means of pathogen inactivation and safe carcass disposal	Yes, on site

Table 2: Containment measures for CL4 laboratories under appropriate legislation (continued)

Containment measures	COSHH	SAPO	GMO(CU)*
Treatment of liquid and solid wastes	All waste should be made safe or safe to handle before leaving the laboratory	All wastes to be sterilised by a procedure known to inactivate the pathogen(s). For solids this requires autoclaving followed by incineration	Inactivation by validated means
Laboratory security		Laboratory and animal rooms to be kept secure and locked. Intruder alarm system to be fitted	

* GMO(CU) Regulations specify additional control measures for work with genetically modified micro-organisms in animal units, plant growth facilities and for large-scale work.

Part 1: Hazard Group 4 pathogens

42 This section covers both ACDP Hazard Group 4 agents and DEFRA Group 4 zoonotic pathogens.

43 The Advisory Committee on Dangerous Pathogens has specified that CL4 must be used for all work involving the 18 agents listed in Table 3. These agents are all viruses and can cause severe, life-threatening disease. Most of these viruses are endemic in many parts of the world, notably Africa, South America and some rural parts of the Middle East.

44 The UK does not contain natural reservoirs of these viruses and environmental conditions are unlikely to support an epidemic spread of these agents. It is more likely that infections with these agents will be acquired abroad, from a laboratory infection or from an imported animal.

Table 3: Hazard Group 4 viruses

1 Haemorrhagic fever viruses					
	Virus	**Country first recognised**	**Date**	**Natural host**	**Mortality rate (humans)**
Arenaviridae Old World Arenaviruses	Lassa virus	Nigeria	1969	Rodent	15%
	Guanarito	Venezuela	1989	Rodent	25%
	Junin	Argentina	1957	Rodent	15-30%
	Machupo	Bolivia	1962	Rodent	25%
	Sabia	Brazil	1990	Rodent	33%
Bunyaviridae Nairovirus	Crimean/Congo haemorrhagic fever	Crimea Democratic Republic of Congo	1944 1969	Hyalomma ticks	10-50%
Filoviridae Ebola virus	Ebola Reston	USA	1989	Unknown	Sub-clinical
	Ebola Sienna	Italy	1992	Unknown	Non-infectious?
	Ebola Sudan	Sudan	1976	Unknown	50%
	Ebola Zaire	Democratic Republic of Congo	1976	Unknown	90%
Marburg	Marburg	Germany and Yugoslavia	1967	Unknown	23-25%

Table 3: Hazard Group 4 viruses (continued)

2 Other viruses					
	Virus	**Country first recognised**	**Date**	**Natural host**	**Mortality rate (humans)**
Herpesviridae	Herpes simiae (B virus)	Worldwide	1932	Primate	80%
Paramyxoviridae	Nipah	Malaysia	1999	Fruit bat	2 out of 3
	Hendra	Australia	1994	Fruit bat	60%
Poxviridae	Variola (major and minor)	Worldwide – now eradicated, last natural case Somalia 1977		Humans	30% (major), 1% (minor)
Flaviviridae	Kyasanur Forest Disease	India	1957	Tick	10%
	Omsk	Russia	1990	Muskrats	Variable
	Russian Spring Summer Encephalitis	Russia	1937	Tick	50%

Viral haemorrhagic fever viruses (VHFVs)

45 Viral haemorrhagic fevers (VHFs) are a group of illnesses caused by several distinct families of viruses. The term is used to describe a severe, multi-organ syndrome in which the overall vascular system is damaged and the body's ability to regulate itself is impaired. These symptoms are often accompanied by bleeding. While some types of VHFV can cause relatively mild illness, many of these viruses cause severe, life-threatening disease.

46 Humans are not the natural reservoir for any of these viruses. Humans become infected when they come into contact with infected hosts. The main reservoirs of these viruses are rodents and insects. However, the host for some of these viruses is still unknown. Humans can transmit the viruses to other humans under specific circumstances (person-to-person transmission).

47 Viruses associated with haemorrhagic fever are RNA viruses from four distinct virus families: arenaviruses, filoviruses, bunyaviruses and flaviviruses. They all have a RNA genome, are enveloped and are transmitted via animal or insect hosts. Viral survival is dependent on the availability of their natural host and as such they are restricted to where their host species live.

48 There is a risk of secondary infection with these diseases, particularly among hospital and laboratory staff, due to possible inoculation or contamination of broken skin or mucous membranes by infected blood or body fluids. Between 1997 and 2001, there were only eight notified cases of suspected VHF (only three of which were confirmed) in England and Wales. When cases of VHF do occur in the UK, they tend to involve personnel involved in patient care, such as general practitioners, community nurses, accident and emergency staff, diagnostic staff, ambulance workers, nurses, mortuary staff and funeral workers. Further guidance for these workers can be found in ACDP publication *The management and control of viral haemorrhagic fevers*.[24]

Arenaviruses

49 Arenaviruses are generally associated with rodent-transmitted disease in humans and a number of arenaviruses can cause haemorrhagic disease. The first of these to be isolated and identified was Junin virus, isolated in 1958. This virus caused Argentine haemorrhagic fever in a limited agricultural area of the pampas in Argentina. Several years later, in 1963, in the remote savannahs of the Beni province of Bolivia, Machupo virus was isolated. Lassa virus was the next member associated with an outbreak of human illness in Africa in 1969. This virus has proven to be endemic in West Africa, where there have been many epidemics of varying size. More recently, two further viruses have been isolated: Guanarito virus (responsible for 15 cases of haemorrhagic fever in the central plains of Venezuela in 1989) and Sabia virus (isolated in Brazil in 1990).

Filoviruses

50 Filoviruses can cause severe haemorrhagic fever in humans and non-human primates. So far, only two members of this virus family have been identified: Marburg virus and Ebola virus. Marburg was first recognised in 1967 when a number of laboratory workers in Germany and Yugoslavia, handling tissue from green monkeys, developed an acute haemorrhagic fever. A recent outbreak of Marburg virus in Angola (2005) killed over 200 people. The second member of the filovirus genus, Ebola, was first discovered during a simultaneous outbreak of a haemorrhagic infection in the Democratic Republic of Congo (DRC, formerly Zaire) and the Sudan (1976).

51 In 1989 a new Ebola subtype was identified from imported cynomolgus macaques during an outbreak in a primate quarantine facility in the USA in 1989.

52 There have been a number of sporadic Ebola-related outbreaks of VHF in the Gabon, Cote d'Ivoire, Sudan and DRC from 1976–2001. Four distinct species of Ebola virus are now known: Ivory Coast, Sudan, Zaire and Reston. Ebola Reston is the only filovirus that does not cause disease in humans.

Bunyaviruses

53 Crimean/Congo haemorrhagic fever virus (CCHF) is a tick-borne virus first discovered in the Crimea in 1944. The virus was more recently recognised and isolated following an outbreak in the DRC in 1969. CCHF is carried by the Hyalomma tick, which is widespread throughout Africa, Asia, the Middle East and southern/eastern Europe.

Mode of transmission

54 All HG4 VHF viruses are transmitted through direct contact with virus-infected body fluids such as blood, saliva, vomit, stools and possibly sweat. Person-to-person transmission of arenaviruses is very rare, although there have been reports of Lassa fever being transmitted this way. Cross infection with partially sterilised needles is associated with a high infection risk and a high fatality rate.

55 There is no evidence of VHFVs being transmitted through close personal contact with non-febrile, non-symptomatic, infected individuals during either incubation or convalescence periods. Previous epidemics in Africa have resulted largely from secondary transmission to healthcare workers and close family contacts caring for infected individuals. The reuse of needles and syringes, inadequate barrier techniques, and unhygienic practices are the major sources of hospital-acquired infections among staff and patients. Close contact with the body or body fluids of the dead in customary preparation for burial is also a recognised source of infection.

56 These viruses are not airborne, but they may be transmitted by aerosols of body fluids from infected patients if these aerosols come into contact with mucous membranes.

57 Most CCHF infections occur through tick bites, but airborne infections have occurred in both hospital and laboratory environments, and in the livestock industry (agricultural workers, slaughterhouse workers and veterinarians).

Infectious dose

58 The infectious dose of all VHF infections is unknown.

Incubation period

59 The incubation period varies between 1 and 21 days. The infectivity period depends on viral type and the mode of infection.

Period of communicability

60 Patients with clinical symptoms are considered to be infectious. There are reports of late transmission events (92 days for Marburg). Lassa fever virus can be shed in urine for several weeks following infection and carried in semen for several months after the illness has resolved.

Reservoirs of infection

61 Arenaviruses are divided into two groups: the New World or Tacaribe complex and the Old World or Lassa complex. Lassa-complex viruses are associated with the Old World rats and mice (family *Muridae*, subfamily *Murinae*, especially in West Africa (*Mastomys coucha* and *M. natalensis*)). The Tarcaribe-complex viruses are generally associated with the New World rats and mice (family *Muridae*, subfamily *Sigmodontinae*).

62 All of the rodent reservoirs experience silent, lifelong viraemia with high titre viruria, which is the primary source of environmental contamination with these viruses.

63 Non-human primates were associated with the initial outbreaks of Marburg disease *(Cercopithecus spp.)* and more recently filoviruses related to Ebola were associated with *Macaca spp.* and chimpanzees.

64 CCHF has been recognised in a wide range of domestic and wild animals. Ostriches, for example, are extremely susceptible and show high prevalence of infection in endemic areas.

65 A number of tick species are capable of becoming infected with CCHF virus, the most efficient being members of the Hyalomma genus where transmission from female to offspring via eggs has been demonstrated.

66 The most important source for the acquisition of the CCHF virus is believed to infect small vertebrates on which the immature Hyalomma ticks feed. Tick transmissions to large vertebrates such as domestic livestock (cattle, sheep and goats) are very common.

Laboratory hazards

67 Work with or exposure to rodents, non-human primates or vectors naturally or experimentally infected with these agents represents a potential source of human infection.

68 The infectious agents may be present in the blood, urine, respiratory and throat secretions, semen and tissue from human and animal hosts and in rodents and non-human primates.

69 Health workers in endemic and non-endemic areas should be particularly aware of the illnesses, since there may be a high risk of hospital-acquired infection.

Hendra and Nipah viruses

70 **Hendra** (formerly called *equine morbillivirus*) and **Nipah** viruses are newly recognised zoonotic viruses that have caused disease in animals, and via contact with infectious animals, in humans.

71 Both viruses are members of the *Paramyxoviridae* family and named after the locations where they were first isolated, in Australia and Malaysia respectively.

Epidemiology

72 Human cases of Hendra virus infection have been associated with one Australian outbreak to date. Hendra virus was first isolated from horses during an outbreak of respiratory and neuralgic disease in Hendra, a suburb of Brisbane, Australia, in September 1994. Of the 21 horses suffering from severe respiratory disease, 13 died. Two people looking after the index case also developed the disease and died. In 1995, a third human case of Hendra disease was recorded, believed to be associated with the previous outbreak. These three human cases are the only known occurrences of Hendra virus infection in humans.

73 The last fatal animal case of Hendra virus in one horse was recorded in January 1999 in Cairns, North Queensland.

74 Nipah virus was discovered in 1999, during an outbreak of viral encephalitis in Malaysia between September 1998 and April 1999. The total number of suspected cases was 265, of which 108 were fatal. Those mainly affected were pig farmers, due to their close contact with infected and sick pigs.

75 During March 1999, 11 abattoir workers in Singapore developed a febrile illness with one fatality caused by Nipah virus, following close contact with urine from pigs imported from Malaysia. No new cases have been recorded following restrictions on pig importation; however, there have been other Nipah outbreaks in central Bangladesh in 2004 and northern Bangladesh in 2005.

Reservoirs of infection

76 The exact geographical distribution of both Hendra and Nipah virus has not been defined, although Australia and south-east Asia are considered as endemic areas due to previous notifications. These areas are also known to be consistent with the distribution of the fruit bat (*Pteropus*), which is suspected of being the natural host of both Hendra and Nipah viruses. The fruit bat is found in north, east and southeast areas of Australia, Indonesia, Malaysia, Philippines and some of the Pacific Islands. Fruit bats infected with Hendra virus have also been reported in Papua New Guinea.

Transmission

77 Hendra and Nipah viruses are not easily transmitted. There are no reports of person-to-person transmission and the risk of transmission of the viruses from horse to human or pig to human is believed to be very low. The exact mode of transmission from animal to animal and from animal to human is uncertain but seems to require close contact with contaminated tissue or body fluids of infected horses (Hendra virus) or pigs (Nipah virus). Experimental studies with both viruses have shown that the risk of aerosol transmission is considered to be very low.

Laboratory hazards

78 The risk to laboratory workers is unknown.

79 Accidental release of these viruses into the wider environment is likely to have a considerable impact on indigenous livestock.

Herpesvirus simiae (B virus)

80 B Virus or alpha herpesvirus *cercopithecine herpesvirus 1* is an infectious agent commonly found in macaque monkeys. The virus was formerly known as herpes simiae and is closely related to herpes simplex virus. Although B virus is classified as a HG3 agent under the EC Directive, ACDP has classified this agent as HG4 in the UK.

Epidemiology

81 B virus is enzootic among Old World *Macaca* monkeys. Monkeys infected with the virus usually have very mild symptoms – or show no symptoms at all. B-virus infection in humans is very rare but it can lead to fatal encephalomyelitis. There have been at least 50 instances of human infection reported, with 29 fatal cases. This represents a fatality rate of 58%.

82 An estimated 80% of untreated patients die of complications associated with infection.

83 B virus can remain latent within its hosts and may reactivate spontaneously or in times of stress, resulting in shedding of the virus in saliva and/or genital secretions. Sexually mature macaques are more likely to have been exposed to the virus and more likely than immature animals to be shedding virus at any given time.

Laboratory hazards

84 B virus presents a potential hazard to any laboratory workers, veterinarians and others who have close contact with Old World monkeys or monkey cell cultures. Human infection is often the result of bites, scratches, or exposure to the tissues or secretions of macaques.

85 Respiratory exposure to infectious aerosols, mucous membrane exposure to infectious droplets, and accidental parental inoculation are the primary hazards to laboratory and animal care personnel.

86 The stability of the virus on surfaces, cages etc is not known, so caution in handling cages used to house macaques is strongly recommended.

Variola (smallpox)

87 Smallpox is a serious, contagious and sometimes fatal disease for which there is no specific treatment. There are two main forms of smallpox: Variola major and Variola minor. Variola major is the severe and most common form of smallpox. The disease follows a milder course in Variola minor, which has a case-fatality rate of <1%. The fatality rate of Variola major is around 30%.

88 There are two very rare forms of smallpox: haemorrhagic and malignant. In the haemorrhagic form, a rash is accompanied by haemorrhage into the mucous membranes and the skin. This form of the disease is often fatal. Malignant smallpox is characterised by lesions that do not develop to the pustule stage but remain soft and flat. It, too, is almost always fatal.

Transmission

89 There is no animal reservoir and insects play no role in the transmission of smallpox. The main route of exposure is from person to person by infected aerosols and air droplets spread in direct face-to-face contact with an infected person after fever has begun, especially if symptoms include coughing. Contaminated clothes and bedding can also transmit the disease, though the risk

of infection from this source is much lower. In the absence of immunity induced by vaccination, humans appear to be universally susceptible to infection with the smallpox virus.

90 The spread of smallpox infection was limited to contacts in close vicinity. Variola minor, however, was so mild that patients infected with this form frequently remained ambulatory during the infectious phase of their illness and so spread the virus far more widely.

91 Outbreak studies caused by importation of cases into industrialised countries in temperate areas showed that, in a closed environment, airborne virus could sometimes spread within buildings via the ventilation system and infect people in other rooms or on other floors in distant and apparently unconnected spaces.

Infectiousness

92 People carrying the virus during the incubation period cannot infect anyone else. The frequency of infection is highest after face-to-face contact with a patient once fever has begun and during the first week of rash, when the virus is released via the respiratory tract.

93 Although patients remain infectious until the scabs fall off, the large amounts of virus shed from the skin are not highly infectious. Exposure to patients in the late stages of the disease is much less likely to produce infection in susceptible contacts. As a precaution, the World Health Organisation (WHO) isolation policy during the eradication campaigns required that patients remain in isolation, in hospital or at home, until the last scab had separated.

Incubation period

94 The incubation period of smallpox is usually 12-14 days (range 7-17) during which there is no evidence of viral shedding.

95 The incubation period is followed by the sudden onset of influenza-like symptoms including fever, malaise, headache, prostration, severe back pain and, less often, abdominal pain and vomiting. Two to three days later, temperature falls causing patients to feel better, at which time the characteristic rash appears, first on the face, hands and forearms and then, after a few days, progressing to the trunk. Lesions can also develop in the mucous membranes of the nose and mouth, and ulcerate very soon after their formation, releasing large amounts of virus into the mouth and throat.

Part 2: Health and safety management in Containment Level 4 facilities

96 This section covers health and safety requirements in CL4 facilities.

Management responsibilities

97 Employers have general duties under health and safety legislation to protect both employees and non-employees (eg visiting workers, service engineers and members of the public) from risks to their health and safety arising from work activities.

98 Accountability for occupational health and safety management procedures rests with senior management. It is recommended that an appointee from senior management should have particular responsibility for ensuring that any occupational health and safety management system is properly implemented.

99 Under the HSW Act, employers must prepare a statement of their health and safety policy. There is a similar provision in the Management of Health and Safety at Work Regulations 1999 (the Management Regulations)[12] and where there are five or more employees, these health and safety arrangements must be recorded and the health and safety policy brought to the notice of all employees. Details of the management structure, individual responsibilities and employee involvement and responsibilities should all be included in the policy. In view of the potential risks associated with high-hazard agents, it is essential that there is a clear and effective health and safety policy in place for the organisation to follow.

100 In practice, to ensure that adequate precautions are in place, specific functions, such as carrying out risk assessments, may be delegated down the management chain but it should be remembered that **responsibility** for health and safety management cannot be delegated.

101 If an individual is responsible for directing, controlling or supervising the work of others, eg researchers, clinical scientists or biomedical scientists, then they should be regarded as 'managers' for the purposes of identifying who is responsible for health and safety management. For instance, while the head of department will have a key role in health and safety management, they may designate a laboratory supervisor/manager to assist in overseeing and implementing health and safety arrangements. The recruitment of a biological safety advisor (BSA) is pivotal in ensuring management are provided with sufficient information and advice to ensure risks related to biological agents are either controlled or prevented.

102 For the purposes of this document the competent person appointed under the Management Regulations will be termed the biological safety advisor (BSA), although a range of other titles can be used. The BSA must have sufficient relevant CL3 or CL4 training, experience, and knowledge of high-hazard work to enable them to properly assist management in meeting statutory provisions.

103 As well as advising on the containment and training aspects of CL4 work, the BSA will be expected to advise on risk assessments and co-ordinate notification procedures. In larger institutions more than one person may undertake this role.

104 Any BSA appointed under regulation 6 of the Management Regulations must be allocated sufficient time and resources to do the job. Appropriate training and technical assistance should be provided as necessary and deputising arrangements made.

Risk assessment

105 It is a legal requirement that all employers and self-employed people assess the risks to their employees and others who may be affected by their work activity. More specific legislation (COSHH, GMO(CU)) requires an assessment of the risks of work with hazardous organisms: COSHH requires an assessment of the risk to human health only; GMO(CU) requires an assessment of the risk to human health and of environmental harm. Although the main focus of this guidance is to help control microbiological risk, other risk factors should be considered, including things such as radiation, noise, ergonomic factors and the design of laboratory furniture. These topics are covered in greater detail elsewhere (see Appendix 4).

106 A risk assessment should be 'suitable and sufficient' and reflect the nature of the work being assessed. Risk assessments for work involving high-hazard organisms should be based on specialist advice, identify foreseeable risks and specify how long the assessment is likely to remain valid. In addition to those directly involved in the work, the risk assessment should also consider those not directly involved in the work but who may also be affected, such as engineers and visitors.

107 The risk assessment for high-hazard organisms should consider:

- the nature (host range, physiochemical properties) of the agents that are to be handled and, if clinical material is being handled, whether additional (adventitious) high-hazard agents may be present;
- the form in which agents may be present;
- the disease caused and how it can be transmitted;
- likelihood of exposure and consequent disease (those who may be more susceptible to disease, eg the immuno-compromised or pregnant workers, should be identified);
- the activities being carried out (both in terms of the number of people exposed and the quantity of the agent that will be used);
- control measures to be applied and how exposure will be controlled;
- environmental protection under GMO(CU).

Review of risk assessments

108 It is important to review the risk assessment. This should be done periodically but particularly following any change to the original activity. The review should confirm that all of the hazards associated with the work have been identified and that the measures put in place to prevent or control exposure are suitable and sufficient. All staff should be made aware that the reviewer(s) (eg the local safety advisor/biological safety advisor or the local safety committee/genetic modification safety committee) have the full support and approval of senior management. The review team should also know that their part in the process might be monitored and that the process is not perceived as a paper exercise. Robust systems should be in place to ensure no experimental work is performed until all documentation relating to the process has been approved and signed off.

Local safety policies and codes of practice

109 Specific information on the arrangements for safe day-to-day working can best be set out in local codes of practice. Employers have a responsibility to make the policy and codes freely accessible either by putting them on display or by individual issue. All staff must be made aware of them. A guide to the main areas that should be covered in a CL4 laboratory is given in Information box 1.

110 The local health and safety policy sets out, in general terms, how management intends to develop and maintain a safe working environment. It should also make reference to ways in which the safe day-to-day working of the laboratory will be achieved and managed. Much of this information should also be contained in the local codes of practice.

111 Another route for conveying health and safety information to employees is through the use of documented procedures. Many procedures within the laboratory will be carried out using a standard operating procedure (SOP). They are often used to meet external (and internal) quality standards, but by integrating the health and safety arrangements into the SOPs, employers can ensure that they also meet acceptable standards of health and safety. The SOP should be developed in consultation with staff to ensure commitment to safe working procedures.

Information box 1 Suggested topics to be covered in a local code

Introduction
This could state the reasons for having such a code and refer to other relevant health and safety documents. Staff could be made aware of the nature and range of agents to which they might be exposed, the possible source of infection and the containment (physical and procedural) measures to be used. Staff could be made aware of the training and supervision arrangements for working in the laboratory.

General procedures
These could specify which staff (or grade of staff) are authorised to carry out particular procedures, there could also be appropriate guidance for ancillary and maintenance staff, contractors and visitors (see also Information box 4).

Operation of unit
This could detail start-up procedures, how the ventilation system works, operation of cabinet lines, procedures for operating equipment (eg centrifuges) and use of personal/respiratory protective equipment (PPE/RPE), cleaning procedures.

Local rules
These could cover such issues as arrangements for lone working, the maximum number of people allowed in the laboratory and entry/exit procedures.

Waste
This could detail the waste disposal and disinfection policy (both routine and emergency, eg spills and fumigation).

Staff health
This could include the immunisation policy and arrangements for reporting injuries/infections (see paragraphs 127-128), including occupational-health requirements, contact details and the name of the person to whom incidents should be reported.

Information box 1 Suggested topics to be covered in a local code (continued)

Testing and maintenance
This could cover the maintenance and test procedures for engineering controls, such as Class III microbiological safety cabinets.

Emergency procedures
This could cover procedures for dealing with accidents involving biological agents, including the name of the person to whom accidents should be reported (see paragraphs 131-135).

112 Once the arrangements for safe working are in place, management need to monitor them to ensure that the systems and controls are effective and that they remain so. Monitoring should be both active and reactive:

- **Proactive monitoring** means that employers need to make arrangements for supervising work and checking that health and safety measures remain effective and that operating standards by all staff are well maintained.
- **Reactive monitoring** ensures the implementation of procedures to investigate injuries, cases of ill health, equipment damage and near misses and to learn from such incidents.

Staff selection, training and supervision

Selection

113 Working at CL4 is an experience that is both rigorous and demanding, requiring a high level of expertise. The appropriate knowledge, skill and ability to perform the duties of the job will be emphasised during training. However, it is essential that the selection stage adopts a mechanism for ensuring the suitability of people chosen to work in these high-hazard areas; suitability may depend on factors other than academic or technical ability. To ensure good practice in recruitment and selection it is essential that employers make full use of all available techniques, eg structured interviews, simulations or ‘dry runs’ etc.

Competence

114 Previous experience of laboratory work should not automatically be taken as a demonstration of someone’s competence to work in a CL4 laboratory. The term ‘competent’ has a very loose meaning; however, in health and safety law it has a specific and legal meaning that has come about through both statute and case law.

115 Managers of CL4 facilities should ensure that appropriate, named personnel are available with experience and competence in the following areas:

- drawing up local rules for the safety of personnel;
- training laboratory workers in appropriate microbiological practices within the containment strategies being used;
- investigating accidents and incidents;
- ensuring records of safe storage are kept;
- participation in locally organised inspections;
- ensuring the laboratories are appropriately disinfected at the end of experimental procedures, or before maintenance personnel enter;
- ensuring that control measures and equipment are tested and maintained at appropriate intervals (eg safety cabinets);
- ensuring that all statutory notifications are in place;
- physical security of the laboratory.

116 If there is a lack of appropriate personnel to advise in these areas, the employer should appoint other suitably qualified people, eg by using outside contractors to test and maintain the containment environment being used.

117 It is also important that individuals are competent and able to do their jobs safely, although there may be degrees of ability/experience (so that people can be ranked) associated with degrees of responsibility within the team. Competency may be seen as a combination of experience and formal training. A detailed, written training programme would be essential at CL4. Laboratory managers and safety advisors should be clear about the competency level expected for critical areas. In addition, remember that competency gained at one containment level should not necessarily mean that an individual is competent to work at **any** containment level.

Training for CL4 laboratory staff

118 Employers have defined responsibilities under the HSW Act and the Management Regulations to provide suitable and sufficient information, instruction and training for their employees. COSHH also contains specific requirements to provide information, instruction and training for those who may be exposed to substances hazardous to health, including biological agents. All employees must have a clear understanding of any identifiable risks to their health arising from work and the actions to be taken in dealing with situations in which exposure may occur.

119 Before working with the most hazardous organisms, workers should also gain an appropriate amount of practical experience at lower containment levels and become proficient in the techniques and procedures required here, particularly that of CL3. Once suitably experienced at lower containment levels, training for work at CL4 should ideally include an initial period of 'dry runs', handling dummy samples free of hazardous pathogens, until competence and confidence can be demonstrated within the CL4 environment.

120 Individual workers may wish to consider keeping a personal training portfolio, endorsed by their employer, to provide a useful indicator of continuing professional development and competence. An experienced worker may well have trained under a number of previous employers.

Training for other workers involved in CL4 work

121 Training should not be limited to those working within the high containment environment; laboratory managers, supervisors and safety advisors should also be trained to ensure that they are competent to perform their duties in connection with the CL4 facility. They should maintain their professional competence by refresher training or other means. It is also necessary for other workers (eg maintenance staff, external contractors and administrative staff) to receive sufficient and appropriate information, instruction and training about the hazards they may encounter when their work involves a CL4 laboratory. There should be rigorous procedures in place to ensure the safety of these workers.

Training for emergency planning and response

122 More detailed information is provided in Appendix 3. General training should address emergency situations and everyone should know:

- what to expect if there is an emergency; and
- what to do and what not to do in the event of an emergency.

123 Additional training for the individuals who deal with emergency responses should also be arranged. Employers should ensure that any on-site emergency procedures are tested regularly and those individuals with duties under the plans receive initial and refresher training. To complement the training, exercises should be arranged to test each part of the emergency plan. It may be possible to use

'table-top' exercises to test emergency plans, however, such exercises are theoretical and should be complemented by 'control-post' exercises. Additional information on emergency planning can be found in *A guide to the Radiation (Emergency Preparedness and Public Information) Regulations 2001*.[34]

124 Employees have a duty to report defects and deficiencies in arrangements and to co-operate with their employer, eg by applying agreed local rules and procedures. It is also necessary to report any accident or incident that resulted, or could have resulted, in the release or escape of a high-hazard biological agent.

125 Section 3 of the HSW Act makes provision for the duties of employers and the self-employed to people who are not their employees. This means that employers and the self-employed are required to carry out their work in such a way as to ensure that they do not expose people who are not their employees to risks to their health and safety. This duty extends to, for example, risks to the public outside the workplace from the release of harmful substances into the atmosphere. If people working under the control and direction of others are treated as self-employed for tax and national insurance purposes, they are nevertheless treated as their employees for health and safety purposes. It may therefore be necessary to take appropriate action to protect them. Any doubt that exists about who is responsible for the health and safety of a worker should be clarified and included in the terms of a contract. A legal duty under Section 3 of the HSW Act cannot, however, be passed on by means of a contract. If such workers are employed on the basis that they are responsible for their own health and safety, legal advice should be sought before doing so.

Temporary or visiting workers

126 If temporary workers, eg those on short-term contract or visiting from other research establishments, are allowed access to the site, the 'host' employer will be responsible for providing appropriate instruction and information to the guest worker. Host employers should satisfy themselves that any visiting worker has the necessary qualifications or skills to carry out the work safely and that any appropriate health surveillance controls required for the work are provided to the guest employee. All security measures and procedures should be explained in detail (further information on additional security aspects of temporary workers can be found in the Home Office publication *Personnel security measures for laboratories*).[31]

Health surveillance

127 A suitable occupational-health programme for laboratory workers should include clinical examinations and written records. It is important to include visiting researchers in these checks as well as permanent staff.

128 More detailed guidance on occupational health (vaccinations, pre-employment screening, baseline serum samples etc) can be found in the ACDP publication *Biological agents: Managing the risks in laboratories and healthcare premises*.[6]

Record keeping

129 Health records are only required if you are carrying out health surveillance as defined by COSHH. The elements of a health record are given in the Appendix to COSHH and include:

- personal details of the individual;

- the type of work the employee does;
- records of accidents and incidents involving exposure to the biological agents concerned;
- historical exposure record (it may be sensible to combine this with a list of workers exposed to a HG4 biological agent);
- dates and a record of any immunisations and the conclusions of any checks on immunity. The conclusions should be about the individual's fitness for work or any specific precautions that should be taken. It should **not** include any confidential clinical data.

130 Further details on keeping health records are given in the ACDP publication *Biological agents: Managing the risks in laboratories and healthcare premises*.[6]

Information box 2 The Data Protection Act[35]

If records (computerised or manual) are kept about individuals (such as employees) in connection with health and safety legislation, eg health or medical surveillance records, the requirements of the Data Protection Act 1998 may apply. These requirements may include informing people that certain information is held on them and granting them access to that information, should they request it. Guidance on the Act can be requested from the Office of the Data Protection Commissioner, Wycliffe House, Water Lane, Wilmslow, Cheshire SK9 5AF (Tel: 01625 545745).

Emergency procedures and contingency planning

131 There are requirements under COSHH, GMO(CU) and DEFRA's licensing regime under SAPO for employers to prepare plans for dealing with accidents and emergencies, in addition to the general requirements of the Management Regulations.

132 Employers should draw up plans for dealing with accidents involving hazardous substances, including high-hazard organisms.

133 Under COSHH there must be written instructions, displayed as notices if necessary, about the procedures to be followed if there is a significant accident or incident when working with biological agents, eg in the event of a significant spill. Emergency procedures for the laboratory should be documented (either in the local code or as a stand-alone document) and practiced to ensure that all employees are familiar with steps and actions to take during emergencies.

134 The Management Regulations require procedures to be in place for responding to serious and imminent danger, eg fire or flooding. However, the risk assessment should identify all the readily foreseeable incidents to be covered by the procedures. The procedures should also cover:

- roles and responsibilities of individuals during an emergency: this should include a first point of contact;
- training requirements: all new staff should be trained in emergency procedures. Such arrangements can be tested by regular drills;
- arrangements for the investigation of accidents/incidents;
- first-aid arrangements: including the availability of post-exposure prophylaxis if appropriate; and
- procedures for reporting incidents/accidents involving individuals other than employees (eg visitors).

135 Employers should consult widely with those bodies likely to respond in emergency situations so that they are aware of their arrangements. The local fire service should be contacted and a copy of the emergency procedures should be made available. If an accident could have serious repercussions on the environment, the employer should also consider providing information to the local office of the Environment Agency.

Emergency contingency plans

136 A written emergency plan should be provided to deal with any significant uncontrolled release that is likely to affect the health and safety of any people **outside** the facility or likely to cause harm to the environment.

137 An emergency plan should be kept up to date to reflect changes in risk procedures or personnel. Anyone on site who may be affected by the plan should be aware of its relevant provisions. This will include visitors and contractors and anyone who may require evacuation under the plan. The plan should be drawn up in consultation with appropriate organisations including the emergency services, the local authority planning officer, the Environmental Health Department, the Environment Agency and relevant parts of the health service network.

138 Emergency plans should provide a sufficient level of detail to address issues such as:

- the types of foreseeable incidents to people and the environment and the immediate steps to be taken;
- organisations involved, including key personnel, their responsibilities and liaison arrangements between them;
- communication links;
- key information about the site;
- evacuation arrangements.

139 Further information on emergency planning is given in Appendix 3.

140 Employees (or their representatives) must be informed of such accidents/incidents, their cause and the action taken to rectify the situation. The employer should also ensure that:

- any important lessons learned from the incident are passed onto employees and/or their appointed safety representative; and
- the information is used in any subsequent review of the risk assessment for the process or activity concerned.

Incident reporting

141 The accidental release of, or infection with, an ACDP HG4 pathogen must be reported to HSE under the Reporting of Injuries, Diseases and Dangerous Occurrences Regulations 1995[36] (RIDDOR). The same is true for zoonotic Category 4 specified animal pathogens and genetically modified organisms. An official local record should be made of all accidents and occurrences with infectious or potentially infectious material involving the exposure of individuals (including near misses). This will include a wider range of incidents than would be covered by statutory schemes, and will help those responsible for laboratory safety check the effectiveness of existing safety precautions and make any necessary changes.

142 There is a requirement in RIDDOR for employers to report any infection readily attributable to work with live or dead humans or animals, exposure to blood or body fluids or any potentially infected material derived from any of the above. Accidents or incidents that result in, or could result in, the release or escape of a HG4 agent must also be reported under RIDDOR as a dangerous occurrence. However, under DEFRA requirements and GMO(CU), there is an additional requirement to notify DEFRA and the Competent Authority respectively, in writing, of any such incidents.

143 Premises holding pathogens or toxins listed in Schedule 5 of the Anti-terrorism, Crime and Security Act 2001 should report any incident (theft, loss of sample in transport, missing cultures etc) to the local police command centre (ie by dialling 999).

Part 3: General principles of design and operation of Containment Level 4 facilities

Introduction

144 The following section sets out the main principles that should be followed in the initial phases of the construction, upgrading or conversion of a CL4 laboratory. While the scale and purpose of CL4 laboratory work may vary (eg processing clinical specimens for diagnostic purposes, to high-titre viral cultures for research purposes), the basic principles will remain the same and this guidance details the key elements that need to be addressed.

145 The design and construction of the laboratory must meet the specific requirements laid out in the relevant legislation.

146 For any new building, the Construction (Design and Management) Regulations 1994[37] (CDM) require that health and safety is taken into account and managed throughout all stages of a project, from conception, design and planning through to site work and subsequent maintenance and repair of the structure. These Regulations apply to most common building, civil engineering and engineering construction work (including demolition, dismantling and refurbishment).

147 There are a number of publications that provide more detailed information on the design and construction of laboratories (both general and microbiological). Details of these can be found elsewhere.[38-39] However, it must be remembered that each CL4 laboratory will be unique and that the number of publications and people (eg architects, designers and engineers) with experience of building a CL4 facility will be limited. Consequently, extensive liaison and consultation between all parties, including regulators, at a very early stage is highly recommended for a successful build (ie eliminating problems at the design stage is much easier and more cost effective than rectifying problems once the facility is built).

General principles of design

148 The decision to build a new high-containment laboratory is not to be taken lightly because they are expensive to build and annual maintenance or running costs can be very high. However, there is a general increase in the construction of these facilities worldwide resulting in increased experience and appreciation of the problems encountered during such projects. It is critically important that the expectations of the end-user are clearly defined at the conceptual stages. This will help in setting realistic goals and standards during the design, construction and commissioning stages of the project and should help ensure that the final facility will be 'fit for purpose' and function as intended.

149 The experiences of CL4 users and institutions that have been through the design and build process can be invaluable in highlighting problems that are likely to be encountered and these views should be sought. The use of contractors and subcontractors with knowledge of the principles of containment and previous experience in the construction of high-hazard facilities is often cited as a major

benefit in any new build. Considerable benefit can be derived by discussing the project with people who have been through a similar process elsewhere.

150 Experience suggests that a key factor for the success of any new build is strong project management, with close liaison between all involved in the design, planning, construction, commissioning, use and regulation of these facilities. The appointment of a project sponsor, project board and a full-time project manager at an early stage is highly recommended. The project manager must be an experienced individual with knowledge of the building industry, planning issues, design and commissioning. The project sponsor would ideally be a technical person from the end-user institution with appropriate time and resources allocated to this function; the project board may include key management representatives from the end-user institution, maintenance engineers, users and all other interested parties. Liaison with other interested parties, such as key regulators, is explored further in paragraphs 10-23.

151 There may be other regulatory requirements that should be considered for high-containment facilities, eg the USA Food and Drugs Administration (FDA), the Medicines and Healthcare Products Regulatory Agency (MHRA), as well as *Good microbiological practice* or *Good manufacturing practice* guidelines. Compliance with such schemes may be an important business need and this may highlight some important differences: ie the different HVAC (heating, ventilation and air-conditioning) standards between America and Europe, for example. Compliance should be consolidated with other regulations, such as FDA/good microbiological practice, which will be of particular importance in the commissioning and validation stages and appropriate documentation would be needed to support this.

Detail design and planning

152 The first stage in the process is the preparation of a specification based on the broad requirements of the client. A series of briefing meetings are required to establish these requirements. The purpose and function of the laboratory should be clearly identified and the principles of containment fully established. It cannot be over-emphasised that these meetings are a vital part of the project and time spent at this stage is never wasted. An adequate budget should be set to ensure proper and adequate consultation can take place with specialists and local planning authorities so that the scope of the project can be defined as early as possible. The final specification should be agreed and if possible, a pre-build testing stage for materials should be included to ensure that the basic build materials are suitable. This is particularly important for unusual designs or for proposed refurbishment of existing laboratories to ensure compatible materials are used. Planning should also take into account the various stages for inclusion of control systems and utilities.

153 Safety measures (such as operating procedures, mechanical barriers, alarms) should all work together so that the risk is reduced ‘so far as is reasonably practicable’.

154 The specification should provide as much detail as possible on each required component, including operating parameters, replacement or maintenance requirements, emergency provisions, commissioning protocols and security measures.

155 Design and risk management issues should be dealt with as far as practicable at the pre-contract stage. The project manager and sponsor should decide at the earliest stage possible whether the build is to be procured through a single or two-stage tendering process. This in turn will dictate the degree of design detail

required before the contract is let. If a firm-price contract is being sought, the client needs to ensure the indicative cost model derived during the planning process includes all predicted expenditure and that the client's contingency is sufficient to cover any additional costs once construction has started. The client also has to ensure that the construction company clearly understands their requirements as to the retention of specialist subcontractors.

156 When deciding on the location of the laboratory there are a number of points to consider which will influence the positioning (the list is not exhaustive and there may be other physical constraints on the final position of the laboratory). Similar points should also be considered when designing a new building:

- **Headroom**: will this be adequate for the installation of ductwork and utilities and will this be sufficient to allow the movement of large equipment into and out of the laboratory?
- **Access**: good access to a staircase and/or service lift may be required for transport of materials, including waste. Has sufficient consideration been given to the possible movement of materials through communal areas? Has laboratory traffic been sufficiently separated from 'public' areas wherever possible? Careful consideration should also be given to the general security aspects of the laboratory.
- **Daylight and visibility**: ideally, access to natural light should be provided. Consider the positioning and location of windows and doors etc, for security reasons.
- **Utilities**: these should be of sufficient capacity to support the laboratory but space may be required to install additional capacity should the requirements of the laboratory change;
- **Air handling and ventilation**: the location of the air inlet and air extract for the building should be considered to avoid cross contamination. The location of existing inlets/extraction points (including windows, as other rooms in the building may be naturally ventilated) should also be considered. Air-handling systems for containment laboratories should not share ductwork etc with non-containment rooms that may be within the suite.
- **Other facilities**: office areas should be sited outside the laboratory containment zone.

157 All the hazards inherent in carrying out the construction work should be identified and, where possible, designed out of the construction phase. If the construction hazards cannot be removed from the design, the risks will need to be controlled.

158 Hazard analysis is an essential part of the overall risk assessment procedure as failure to identify a hazard at the start of the design process may mean associated risks will not be assessed. To be effective the hazard analysis will involve a number of practical considerations. It will be important to distinguish between continuing hazards (ie those inherent in the work activity, eg propagation of a highly pathogenic virus), and those hazards that can result from failures/errors (ie hardware/software failures, eg failure to maintain the laboratory at negative pressure as well as foreseeable human error). There are several qualitative approaches to hazard identification, which provide a more formalised and structured procedure. Selection of the appropriate procedure will depend on the type of equipment/process used and the hazards involved.

159 Procedures may range from simple checklists to more open-ended approaches. Checklists may be used to identify continuing hazards as well as to ensure compliance with relevant regulations such as COSHH and associated maintenance, testing and examination requirements (eg HEPA filter testing). More open-ended techniques may be needed to identify and analyse failures and errors.

Hazards resulting from equipment failure and human error require:

- a detailed hazard identification to be carried out for all stages of the equipment's lifecycle, eg the cabinet line; and
- analysis of systems of work and established procedures to identify who might be exposed to a hazard and when, eg the research scientist under normal operating conditions and the engineer performing a maintenance task.

160 Structured and systematic techniques that would assist in the identification of these hazards might include:

- hazard and operability study (HAZOP)[40] – a qualitative technique to identify hazards resulting from hardware failures and human error;
- failure modes and effects analysis (FMEA)[41] – an inductive quantitative technique to identify and analyse hardware failures;
- task analysis.

Commissioning and validation

161 Commissioning and validation will vary from laboratory to laboratory but the basic principles will be the same. The commissioning stage should ensure that the laboratory meets the regulatory requirements and provides the required degree of personal and environmental protection. This requirement for testing and commissioning components must be built into the building contract and should be fully documented and certified by experienced engineers. Commissioning usually comprises two stages: testing and validation.

162 It is essential to test individual component systems to ensure that design specifications have been met and that control systems can operate and function safely within their required ranges.

163 Validation can be defined as a documented procedure for obtaining, recording and interpreting the data required to show that a process/equipment/activity will consistently comply with predetermined specifications.

164 The laboratory (together with its equipment and procedures) should be tested to ensure that it meets the specifications of the original design and construction brief.

165 Independent specialist contractors are often used for the validation and commissioning stages. This provides an additional level of confidence in the laboratory's ability to provide suitable operator protection. Validation testing may involve the use of benign or attenuated biological agents as indicator organisms. The validation stage should include testing of all key control measures, such as physical containment systems, procedural systems, waste treatment control and emergency protocols, etc. For example:

- Physical containment systems may include:
  - effluent treatment facilities;
  - double-ended autoclaves;
  - ventilation systems;
  - fumigation systems;
  - cabinet lines/suits;
  - building management systems etc.
- Procedural systems may include:
  - risk assessments;
  - fumigation procedures;

  - decontamination procedures;
  - autoclave procedures etc.
- Emergency protocols may involve:
  - accidents;
  - spills;
  - egress procedures from the laboratory (suits); and
  - emergency aid protocols.

166 There will be a number of general items that should also be tested and performance-verified before work begins in the laboratory. For example:

- the laboratory itself must be sealable to permit disinfection, usually by gaseous formaldehyde fumigation (the process of fumigation should be validated – see Appendix 1) and should able to withstand the loading characteristics imposed by negative air pressure when the laboratory is in operation;
- all seals (eg around pipe work) should be checked visually and smoke tested under different pressure regimes, ie at higher and lower pressures compared to the normal operating pressure;
- it is recommended that all air supply and exhaust ductwork is checked in situ for leak-tightness, eg using bubble testing. The air supply and exhaust should be checked to ensure that there is a means of preventing reverse airflows;
- all HEPA filters should be tested to ensure that they meet the required specification after installation and all HEPA filter housings should be leak-tight. HEPA filters should meet the performance criteria of a class H14 filter as defined in BS EN 1822-1: 1998 *High efficiency air filters (HEPA and ULPA). Classification, performance testing, marking.*[42]

167 Microbiological safety cabinets, positive pressure suits, autoclaves and other equipment should be tested against the appropriate standards where these exist, or else against recommendations/guidance produced by such bodies as ACDP or relevant professional organisations. All alarm systems (eg for air systems failure, electrical failure or fire) should be checked to ensure proper functioning.

Other issues

Envelope integrity

168 All ductwork, pipe work, cables etc into the laboratory should be carefully sealed, inspected and tested during construction.

169 Laboratory integrity should be monitored at regular intervals. This is particularly important for older facilities due to natural movements in the general fabric of the building over time. The use of ‘smoke pencils’ is a relatively quick and convenient way to check for minor leaks around fixtures, conduits, filter housings, plumbing etc. When using smoke pencils in this way, the HVAC system should be operating at the working flow rate and pressure differential.

170 Validation of all the key items should be repeated on a regular basis and whenever there is a significant modification to the laboratory. Validation may also be required when there is obvious wear and tear noted (this may be localised, eg around pipe work). The process of validation should be documented; the initial validation records will serve as a baseline performance measure for subsequent tests. Further details on regular maintenance and testing can be found in Appendix 2.

Electrical systems

171 Safety-related electrical and electronic systems must achieve a suitable level of risk control, and this can be best demonstrated by the application of good-practice guidelines or a suitable standard such as BS EN (IEC) 61508: 2002 *Functional safety of electrical/electronic/programmable electronic safety-related systems.*[43] BS EN 61508 requires that safety-related systems are designed and built according to a safety life cycle that reduces the probability of an oversight causing a failure that could lead to harm. BS EN 61508 is a goal-setting standard, requiring that the risks posed by the activity be controlled by appropriate techniques and measures.

172 BS EN 61508 is an international standard that provides guidance on how electrical, electronic and programmable electronic safety-related systems should be designed, built, operated and maintained. It is used by HSE as a benchmark for assessing the suitability of electrical and electronic system design and implementation for a safety-related application.

173 There are a number of issues that arise specifically from the use of complex electrical and electronic safety-related systems. These have not been explicitly described in previous ACDP or Advisory Committee on Genetic Modification (ACGM) guidance, but may be important when assessing the suitability of electronic safety-related systems:

- employers should understand the basis of operation of any electrical and electronic system that is safety related, and should be able to correctly operate controls and respond to alarms;
- employers should be able to identify and diagnose faults and take action within an adequate time to reduce the risk of a loss of containment;
- the standard operating procedures should ensure that there is not an excessive demand being placed upon any safety-related system;
- any unanticipated challenges and failures to the safety-related system should be recorded and investigated so that the effectiveness of the safety-related systems can be continuously assessed, and action taken;
- an impact analysis should be performed before any modifications are carried out on any safety-related system, including software changes. There should be procedures indicating how this is to be done;
- there should be maintenance procedures for every item of safety-related equipment, particularly where the item is programmable;
- particular care should be exercised regarding the connectivity of electronic systems. Any connection between a safety-related and non-safety-related system has the potential for the safety-related system to be adversely affected. The potential challenges to a safety-related system arising from this should have been assessed and measures taken to reduce their impact;
- where a safety-related electronic system is being used to provide safety measures for more than one facility, possible interactions arising from different operating modes of those facilities should be identified and assessed. The effect of a single failure on more than one facility should be assessed.

Heating, ventilation and air-conditioning (HVAC) systems

174 In terms of ensuring both operator safety and comfort, the air handling system is one of the most critical systems in the CL4 laboratory.

175 Early planning for such systems is essential, eg in ensuring the provision of sufficient space for the HVAC ducting. This is particularly important if the CL4 laboratory is a conversion or renovation of an existing room where ducting location will be influenced by existing building structures.

176 It is important to ensure that sufficient safeguards are designed into the system (eg the supply and exhaust systems should be interlocked to prevent the supply fan from running if the exhaust fans fail). There should be at least one supply fan and two exhaust fans. Under normal conditions, the supply fan and one of the exhaust fans operate continuously. In the event of an exhaust fan failure, to prevent potential loss of negative pressure, the second exhaust fan would start automatically. Alternatively, both exhaust fans could be run at 50% capacity with an automatic increase in speed should one of the fans fail. A standby generator is strongly recommended.

177 The mechanical ventilation system should be capable of isolation, eg by the use of manual or electrically operated mechanical dampers, to ensure that the room can be closed and sealed for fumigation.

178 Ordinarily, the design of systems to achieve negative pressure should aim to avoid the chances of failure due to over-complicated control mechanisms. Monitoring devices should be relevant and sensitive to the factors that contribute to safety. Engineers should consider the safety features of the room as a priority when arranging heating and ventilation (such as the dispersal of heat generated by equipment) so that inlet air is uniformly distributed through the room. The operational status of the system and the differential pressure between spaces should be monitored and alarmed to warn designated personnel of improper operation. This should demonstrate that the laboratory does not revert to a positive pressure in any combination of exhaust fan failures.

179 Employers should be able to demonstrate that the laboratory continues to operate to specification. A good way of doing this would be to keep and maintain the documentation provided upon commissioning. Such documentation would usually include details of the number of air changes per hour and the differential pressures between various zones, etc. Additional records of any testing or maintenance of control systems would be very useful in demonstrating that the laboratory is still operating to its original specification.

180 HVAC controls for each zone within the laboratory unit should also be tested at commissioning, including the following tests:

- gasket doors between zones should be opened to check if directional airflow is maintained;
- when doors are opened, the alarms (audible and visual) should be monitored to check that they are working;
- exhaust fans should be engineered to fail individually to determine if the backup exhaust fans function properly;
- the main power supply to the laboratory should be interrupted to check that the emergency generator activates and functions as required;
- if inflatable door gaskets are fitted, the air compressor that supplies the door gaskets should be turned off to check that the gaskets remain inflated.

181 The laboratory should have provision for comfort factors, ie a supply of fresh air, temperature and humidity control.

Information box 3 Laboratory containment and inward airflow

Laboratory containment is usually measured on the basis of the pressure differentials between the laboratory and the external air (either the outside or other parts of the laboratory suite or building). The directional airflow moves from areas of lesser hazard to areas of higher hazard area. As biological material (eg viral cultures and clinical specimens) is always contained during normal operations, the highest hazard areas will be animal and post-mortem rooms. There are no legally specified pressure differentials and guidance values can vary but are approximately -30 Pascals (30 Pa) for each layer of the pressure cascade (ACDP) or (for DEFRA) at not less than -75 Pa total difference between the laboratory and ambient pressure.

Consider the number of rooms within the laboratory unit as this will influence the final required pressure, eg if there are five rooms, each requiring an incremental pressure change, then the final room would have (if increments of 30 Pa were used) a negative pressure of -150 Pa. The important point is that a pressure differential that will create sufficient directional inward airflow should be generated. Using lower differentials does mean that doors are usually easier to open and close. When considering the fact that there may be very high negative pressures involved within the centre of the facility there will be a need to consider the fabric of the building and whether the structure of the facility (eg walls, windows and doors) is able to withstand extreme negative pressures.

Liquid waste inactivation

182 All liquid waste (such as run-off waste from the decontamination shower, autoclaves, laboratory sinks, drains from post-mortem tables etc) must be collected in a separate treatment plant, where it can be inactivated by using a validated method of steam sterilisation or chemical disinfection before release into the environment.

183 The design and construction of waste effluent treatment plants for high containment facilities is a very specialised field. It should only be performed by specialist manufacturers with experience of biological containment. The effluent treatment plant should be constructed in such a way that accidental discharge of the contents is **not** possible. The tanks should be bunded to contain any spills within the plant room. The bund should be sufficient to contain the total contents of the tanks plus an additional 10% of the total volume.

184 The treatment plant should be under negative pressure. Mechanical HEPA-filtered ventilation should be provided and the treatment area should be sealable for fumigation.

185 The system should be completely sealed and leak proof with a minimal number of joints (which should be fully welded and subjected to radiographic tests). All pipe work should be readily accessible for routine inspection – it should not be buried or enclosed (double-wall containment piping may be considered but only with leak-detection systems enclosed within the cavity). Drains should be designed in a way that allows the drainage system to be flooded with potentially corrosive disinfectants while leaving no air spaces in the system. The use of in-series double valves or steam barriers should be considered. Care should be taken with the design of any drains or traps, as infrequently used traps are likely to dry out. All traps and drains should be sealable or deep enough to prevent this.

186 It is good practice for liquid effluent to be gravity fed to a treatment tank. This tank should be of sufficient capacity to prevent accidental overfill. At least two high-

level alarms should be fitted to alert operators to excess filling of the holding tank. Each level alarm should rely on a different method of detection (eg hydrostatic pressure and light beam). The inclusion of an automatic shut-off valve to the laboratory water supply could prevent this from happening and should be considered. Liquid effluent from the holding tank is usually pump-fed into the main treatment tank. More than one holding tank may be necessary to allow work to be carried out continuously while treatment is being carried out.

187 All liquid effluent must be inactivated by a method validated to achieve inactivation of all pathogens deliberately handled in the facility, before discharge into the main sewer. The National Rivers Agency will issue consents for discharge. These consents will usually fix a suitable temperature for discharge of the effluent into the main sewer.

188 All personnel operating effluent treatment plants should receive appropriate training, including implementation of contingency plans should an accidental release occur.

Solid waste inactivation

Autoclaves

189 A double-ended autoclave with interlocking doors (with entry into the laboratory and exit into a clean area) is required. Autoclaves should meet the minimum performance requirement of a type II autoclave in BS EN 12347,[44] with appropriate filtration of exhaust gases and containment of condensate. Autoclaves should be tested on site with full operating loads and appropriate run times.

190 If larger equipment or caging is to be autoclaved, consider providing roll-through autoclaves to minimise the hazards from lifting contaminated equipment into the autoclaves. Such autoclaves could also be used to pass equipment through into the containment laboratory or animal area.

191 The design, manufacture and supply of the autoclave may need to meet one or more Article 95 European Directives (eg Pressure Equipment Directive).[45]

Incineration

192 All general waste from CL4 laboratories should be autoclaved before leaving the laboratory for final disposal by incineration (see paragraph 257).

Disposal of animal carcasses

193 Under COSHH at CL4, there is a requirement for an on-site incinerator for the disposal of animal carcasses infected with high-hazard pathogens. Incinerator plants and their operation are covered by several pieces of legislation made under the Waste Incineration Directive (2000/76/EC).[46] Guidance on this aspect of waste management can be found on the Environment Agency[47] or DEFRA[9] websites. Alternative technologies to incineration, such as heated alkaline hydrolysis, should be discussed with regulators on a case-by-case basis.

Part 4: Principal requirements of Containment Level 4 laboratories

194 There are two main operational systems for CL4 laboratories: work within totally enclosed primary containment systems (Class III microbiological safety cabinets, for example), and the suited laboratory system, where workers wear a protective suit to manipulate organisms within a safety cabinet or in combination with other suitable primary containment.

195 Under COSHH, an employer's primary duty is to prevent exposure to biological agents using measures other than the use of personal protective equipment. Where exposure cannot be prevented, employers must take steps to ensure that exposure is adequately controlled by preparing a risk assessment and using a combination of specified control measures stated in Schedule 3 of COSHH.

196 The principle of COSHH establishes a hierarchy of control measures for restricting exposure:

- prevention of exposure;
- primary containment to restrict exposure;
- design processes and supporting systems of work to minimise the amount of hazardous material present;
- the use of personal protective equipment – but only as a last resort and never as a replacement for other control measures.

197 Schedule 3 of COSHH requires 'infected material, including any animal, is to be handled in a safety cabinet or isolator or other suitable containment'.

198 All work at CL4 should be done under primary containment. However, there may be some projects that contain a number of tasks or component parts for which primary containment may not always be practical or appropriate (eg for large animal work). In such cases, alternative systems to primary containment alone may be considered. For example, a project that may include some work with ferrets; the general nature of these animals makes primary containment impractical. For this type of work, the use of suited systems (in combination with other primary containment measures) would be more suitable.

199 Exposure should be controlled by the best practicable means, but it is accepted that this can be a complex relationship between practicability, animal welfare considerations and the requirement for primary containment. In assessing if the use of protective suits is appropriate, employers should consider:

- their effectiveness in the actual work situation;
- the type and level of exposure to the biological agent;
- the practical difficulties in ensuring their continued correct use;
- the limitations of the suits.

200 The use of alternatives to primary containment should be fully justified in the risk assessment and discussed with regulators before any such work begins.

201 The following sections offer guidance on how to meet the common requirements, with advice on good practice in design principles and operating policies for CL4 laboratories: *Generic issues* (paragraphs 205-265) outlines the basic requirements that would apply to COSHH, GMO(CU) and DEFRA requirements for work with specified animal pathogens under SAPO licences. *Cabinet-line laboratories* (paragraphs 268-289) further outlines the additional control measures that would be applicable to cabinet-line systems and *Suited laboratories* (paragraphs 290-325) deals with additional requirements for using the suited-laboratory system for high-hazard work.

202 Risk assessments for work with GM pathogens may allow for derogations under GMO(CU) not to apply certain control measures specified in Table 2. All requests for derogation must be based on a suitable and sufficient risk assessment and agreed with regulatory authorities. COSHH however, requires that for any work with HG4 pathogens, the ACDP control measures specified in Table 2 must be complied with as a minimum.

203 Where the word 'must' or other imperative wording has been used throughout the rest of this document, this indicates an essential requirement as defined in legislation.

204 Where guidance is given on how to comply with these requirements, this is based on what is considered to be best practice for CL4; however, the guidance is not mandatory and use of the measures suggested should be determined by local risk assessment.

Generic issues

205 This section outlines the basic control requirements for CL4 facilities. Additional, specific control requirements under COSHH will be addressed in the relevant sections below. Many of the measures discussed here will involve general structure and fitting requirements.

Location of the laboratory

206 The CL4 facility will consist of either a separate building or a clearly demarcated and isolated zone within a building. Activities can be separated by locating the laboratory away from main public thoroughfares of the building. The rooms in the unit should be arranged to ensure passage through the changing and decontamination area before entering rooms where work is done with HG4 agents.

General security and access considerations

207 Restriction of access to CL4 facilities is an important safety measure as well as a security issue. Only trained authorised workers should be allowed access to the CL4 facility. The physical security of laboratories, including measures to prevent unauthorised access, should be discussed with NaCTSO officers in order to obtain site-specific information and ensure compliance with ATCSA.

Laboratory structures and fittings

208 Bench surfaces should be constructed of non-porous surfaces. MDF covered with plastic laminate can chip and split and is not recommended for use in these laboratories. Bench tops should have seamless coved splashbacks. If sealing is required, non-shrinking sealant should be used, eg two-part epoxy grout. Benching should also be stable and of a smooth finish.

209 If laboratory sinks are required they may be inset in benches or provided as separate sink units. If required, this should be integral with the bench top without joints or else sealed (as paragraph 208). Polypropylene or epoxy resin bowls and

Information box 4 Permits to work

A planned maintenance programme is essential to ensure the safe operation and longevity of the building and laboratory equipment. In-house engineers or contract staff may perform this maintenance work. An essential component of the programme is a formal permit-to-work procedure. This is an established means of ensuring that a safe system of work is in place to carry out engineering maintenance and other activities related to containment laboratories, eg repair of equipment. It should be recognised that most maintenance staff will not be microbiologists and will therefore be unaware of many biohazards.

Entry to the CL4 laboratory should be restricted to authorised users only. Non-authorised users, such as maintenance technicians, engineers etc, should only be allowed access to the CL4 laboratory during planned 'down time' and through a formal, documented permit-to-work system. There must be a clear record to show that all foreseeable hazards have been considered. A permit to work should only be issued by authorised individuals. The key features of such a procedure are as follows:

- a written permit to work, signed by a designated responsible person, who has carried out a risk assessment of the work area and the work proposed. This constitutes a formal authorisation for the work it describes to be carried out. The work should be completed in the manner described, using the safety precautions detailed, by the recipient or by people under their control;
- people appointed to positions that involve them in permit-to-work systems should have adequate knowledge, experience and training before they are given the authority to issue or receive permits.

On completion of the work, both parties should sign off the permit to work.

drainers are preferable to acid-resisting stainless steel because of their greater resistance to disinfectants. Sinks should drain directly to the effluent waste treatment plant (see paragraphs 182-188).

210 Furniture should be kept to a minimum and under-bench storage should be on castors for ease of cleaning under benches.

211 Floors must be impervious, slip resistant and easy to clean. Any seams present should be appropriately sealed. Flooring should be able to resist the most commonly used disinfectants and be impervious to water to allow proper cleaning and prevent absorption of infectious material onto floor surfaces. For ease of cleaning, floor coverings should be coved to the wall.

212 Floors should be cleaned periodically by wet mopping with a cleaning agent solution. Dry sweeping and dusting should be avoided.

213 CL4 laboratories should not normally have floor drains, so any residual cleaning solution should be removed by wiping over with a disposable dry mop or squeegee mop. For animal facilities that **will** contain floor drains, please refer to current guidance on animal work or seek specialist advice.

214 The interior of safety cabinets should be kept clear of infrequently used equipment and other materials, eg disposables. Work surfaces should be wiped down with an appropriate disinfectant (ie one which has been tested for efficacy under in-use conditions) at regular intervals, eg before restarting work after a break and routinely at the end of each working day. Suitable gloves should always be worn during such decontamination procedures.

215 Laboratory sinks should be cleaned regularly as part of the normal cleaning regime, eg at the end of each working day.

Doors and windows

216 All doors within the suite should be of a solid finish construction, chip resistant and should be of sufficient size to allow passage of equipment likely to be located in the laboratory. The location and type of doors and windows may be influenced by security needs, ie to ensure that the occupants cannot be viewed from outside the building, (eg where animal work is being undertaken). Windows should be sealed and of non-opening design, and designed to avoid crevices or recesses that may be difficult to clean or seal.

217 Consider the type of door required and its location within the laboratory. For example, airlock doors may be either pneumatic sealed doors or hand-wheel operated 'submarine'-style doors. Construction material would primarily be stainless steel, although solid plastic has also been used. Stainless steel doors may be heavy and difficult to operate, if plastic doors withstand the facility's operating and decontamination procedures, they will be a significant engineering improvement. External laboratory doors will need to be fire resistant. Please note that the gasket-sealed doors found in some CL4 facilities have not been fire tested and do not have a fire rating. Where these types of doors are fitted, the laboratory design should ensure that these doors are not external doors. Fire-resistant windows should be sealed in place, double-glazed windows are recommended, which are flush on the inside for ease of cleaning.

218 Entry to the laboratory must be via an air lock system and there should be some means of safeguarding the pressure differential between the laboratory and change area, eg by providing interlocking doors that are alarmed in the event of a pressure drop.

219 There should be a contingency plan in the event of having to leave the laboratory in an emergency. Exits should be arranged so that travel within high-hazard areas is minimised (see Appendix 3 on emergency procedures).

Walls

220 The walls and ceilings should be seamless, free from joints, and not permit leakage of fumigant. Any piped services that enter the room should be sealed around the entry/exit points so that the room can be sealed for fumigation. Sealants should be resistant to disinfectants (eg the fumigant used for disinfection) and should be non-hardening. All sealed joints should be subject to routine monitoring, and also be checked before any planned fumigation in case any small gaps have appeared, eg due to shrinkage or building movement. It is important to recognise that the room, being under negative operating pressure, will need effective seals and gaskets on the positive pressure side of the room as well as in the room itself (where the tendency will be to pull seals away from surfaces).

221 Walls must be smooth and resistant to any pressure effects at normal operating pressure. Walls should be easy to clean and resistant to liquids and disinfectants in common use (including fumigants) in the laboratory. They should be regularly maintained to prevent any loss of integrity through physical knocks, pressure effects etc.

222 Materials that meet these criteria include epoxy or polyester-coated plaster, rubberised paint, or equivalent surfaces. Materials should be resistant to the normally used disinfectants, detergents, acids, alkalis, solvents or other chemical preparations. Junctions of the walls with the ceiling and floor should be coved for easy decontamination.

Means of viewing occupants

223 There must be means of viewing the occupants. This can be achieved by an observation window or closed-circuit television (CCTV). It is recommended that where windows are installed, this should be done so that all occupants can be seen wherever they are working in the room; this may require one or more windows (this will also aid monitoring of gas decontamination procedures from outside the laboratory). Alternatively, strategically placed convex security mirrors may provide a total room view.

224 There should be **NO** lone working within the high-containment area. Local codes of practice should specify any support systems required for workers engaged in high-hazard activities – these should include emergency procedures.

Other services/utilities

225 It is important to ensure that utilities are of sufficient capacity to support the laboratory (consider the need for space to install additional capacity, should the requirements of the laboratory change). Such services should be easy to maintain and, where appropriate, clean. Careful consideration should be given to the design of service/utility provisions to aid maintenance from outside the laboratory where possible.

226 Electrical and other conduit services should be capable of being sealed to prevent escape of fumigant.

227 Standard light fittings and electrical socket outlets are appropriate for use but they should be waterproof/resistant or protected from ingress by liquids and particulates by barriers or covers.

228 Light fittings should be capable of being removed without having to enter the laboratory for cleaning and maintenance.

229 Cylinders used for the local supply of compressed gas should be located outside the laboratory. An alarm may be required to indicate when the cylinder needs to be changed. Controls for all piped services are ideally located in utility cupboards outside the laboratory. This enables maintenance and instrument calibration to be carried out outside the laboratory.

230 Consider the way in which information (experimental data) is recorded and removed from the laboratory. Paper should be avoided for this purpose. Suitable alternatives include computer links, hands-free telephones, e-mail or faxes. If paper is used, arrangements must be made for its decontamination before removal.

Laboratory equipment

231 During the design of high-hazard facilities, careful consideration should be given to the type and amount of laboratory equipment required, to ensure that enough space is provided.

232 As part of any risk assessment, equipment should be considered for its potential to act as a source of contamination for those using or maintaining it. Such equipment should be identified and procedures put in place to decontaminate it regularly, when it leaves the containment facilities or when it is serviced/maintained.

Personal protective equipment and procedures

233 There should be facilities for changing into laboratory wear adjacent to the containment area, this should form part of the entrance lobby area. Storage facilities should be provided for both laboratory clothing and outer clothing removed before entering the laboratory.

234 Suitable protective clothing should be worn in the laboratory. For suited-laboratory systems please refer to paragraphs 290-325 for additional control measures.

235 Procedures specifying how frequently protective clothing should be changed, eg on leaving the laboratory or when obviously contaminated, should be covered in the local code of practice.

236 Disposable protective equipment should be also autoclaved prior to disposal.

Air handling

237 The ventilation system must be dedicated to the laboratory and not integral with the main building exhaust ventilation system. The laboratory should incorporate some means of preventing reverse airflows etc. Air should not be recirculated but vented direct to atmosphere.

238 There must be a continuous inward airflow into the laboratory to maintain a consistent negative pressure at all times, unless the laboratory is down for maintenance etc.

239 Maintenance, examination and test of control measures including local exhaust ventilation (LEV) (including microbiological safety cabinets) must take place at regular intervals. This means that HEPA filters and their fittings and seals must be thoroughly examined and tested at intervals not exceeding 14 months. In practice, it is recommended that testing takes place at six-monthly intervals. Further information on testing HEPA filters can be found in Appendix 2 of *The management, design and operation of microbiological containment laboratories*.[5]

240 Depending on the frequency of use, these tests may be carried out at shorter intervals. A programme of regular validation of the continuing safe operation of control systems (airflows, filters, sensors etc) should be coupled with routine servicing and maintenance of all safety equipment.

HEPA-filtered input and extract air

241 Input and extract air to the laboratory must be HEPA filtered (extract air must pass through two HEPA filters mounted in series before it leaves the laboratory unit).

242 The supply must be filtered through at least one HEPA filter in such a way as to minimise the distance between the filter and the laboratory. Careful consideration should be given to airflow patterns and any potential effects on primary containment equipment. All ductwork must be airtight and leak free.

243 There should be a high-level extract system from the laboratory through two HEPA filters mounted in series and capable of being independently tested. Filters should be mounted in 'safe-change' housings to allow for testing, fumigation and safe changing of **both** filters.

244 The positioning of filters will depend on the laboratory design. For ease of changing, filters should be located outside the laboratory, preferably in the plant room but located as close as possible to the laboratory to minimise the amount of ductwork between the laboratory and the filters. The extract fan should be located at or near the discharge end of the system to maintain the ducting under negative pressure and so ensure minimum leakage (while ensuring that duct length is kept to a minimum). Arrangements will need to be put in place to decontaminate ducting prior to maintenance or repair.

245 Consider the design and installation of equipment with high heat output (eg fridges and incubators). It may be possible for the heat-generating components to be installed outside the primary envelope – this will aid maintenance and thermal regulation of the laboratory.

Disinfection and specified procedures

246 CL4 laboratories must be sealable to permit **disinfection**. In practice, the most likely method of laboratory disinfection will be by gaseous fumigation, traditionally with formaldehyde vapour. The method chosen should be validated to ensure that an appropriate concentration of disinfectant can be achieved. (See Appendix 1 for further information on fumigation.)

247 COSHH requires employers to put in place measures to prevent the spread of any fumigant.[48] In practice, this means that once the laboratory has been filled with the fumigant it must be contained within the laboratory for the required time to allow effective disinfection of the room and should not be allowed to escape until it is extracted safely from the room.

248 The ability to seal the laboratory depends on its physical construction, eg the walls and ceiling. Ceilings should be solid or continuous and coved to the walls. It should be clear where the boundary of the room is, to determine the sealability of the room. The minimum recommendation for the verification of room sealability is the use of a smoke test under normal operating conditions (further guidance on sealability and sealability-testing can be found on HSE's website).[10]

249 Controls for carrying out fumigations would ideally be located outside the laboratory so that re-entry into the room in the event of a spillage would not be required (see paragraph 250). However, remote operation of fumigation is not always possible and there may be an overriding need to re-enter the laboratory (eg to charge the formalin boilers). Any re-entry into the laboratory following a spillage should be appropriately risk assessed and appropriate engineering controls provided as necessary.

250 Automatic fumigators are now available that may offer a number of advantages by allowing a pre-programmed fumigation with formaldehyde and a subsequent neutralisation step using ammonia. This preset operation can give operators plenty of time to vacate the laboratory before any fumigant is released. They also effectively neutralise any formaldehyde for safe re-entry into the laboratory.

251 Fumigation should always be performed following a significant spillage or aerosol release. It will also be required before routine maintenance or at the end of major work programmes as part of decommissioning (to prevent cross-contamination). The fumigation process should be planned and validated (whether it is required in an emergency or as part of scheduled/routine maintenance) and staff should be trained in the correct procedures.

Disinfection procedures

252 Disinfection protocols should be in place for both routine use and for use in spills. As well as documenting how disinfection should be carried out, the protocol should record that the disinfectant has been assessed for its efficacy under in-use conditions. Efficacy may be determined by:

- examining the manufacturer's literature;
- examining relevant peer-reviewed literature; or
- in-house testing. The local protocol should indicate the type of disinfectants, in-use concentrations and contact times that are suitable for the biological agents that may be present in the laboratory.

253 The laboratory should have a clear written procedure, displayed as notices if necessary, for dealing with spillages and other forms of contamination, eg aerosol release. Training on how to deal with spillages should be part of the overall training required for working at CL4. All spillages should be dealt with without delay.

254 A major spillage is very unlikely. However, there should be a local code of practice to deal with any accidents or spillages that result in significant splashing and/or aerosol production.

Waste handling and removal

255 All waste from CL4 laboratories should be autoclaved before it is removed from the laboratory or laboratory suite/unit. Policies and methods for the treatment and disposal of waste should be identified and in place before work begins. As part of the laboratory commissioning, the suitability of waste treatment equipment and methods should be assessed and documented.

256 Steam sterilisation is the preferred treatment method for infectious waste, for both health and safety and quality control reasons. Any method chosen for the removal of infected materials, including all waste for incineration, should be authorised by the laboratory manager and specified in the local code of practice.

Disposal of animal carcasses

257 High-hazard laboratories must have an incinerator on site for disposal of animal carcasses. The incinerator plant must conform to the Waste Incineration (England and Wales) Regulations 2002.[49] These Regulations transpose the requirements of the Waste Incineration Directive (2000/76/EC).[46]

258 Hazardous waste incineration installations are regulated under the Pollution Prevention Control Regime as part A(1) activities under Schedule 1 of the Pollution Prevention and Control (England and Wales) Regulations 2000.[50]

259 There should be documented procedures or protocols incorporating risk assessment of the biological agents likely to be present in the wastes and their concentration, the types and quantities of waste, and the treatment and disposal options. Such procedures should identify each treatment option and operating parameters or conditions known to kill the agents that may be present under the laboratory conditions.

Secure storage of biological agents

260 High-hazard organisms (or any material that contains them) must be located within a locked secure area (eg the laboratory/laboratory suite) to prevent unauthorised access. Premises storing any of the agents or toxins listed on Schedule 5 of ATCSA[29] must register with the Home Office. Appropriate written records of access to the store should be kept.

261 The storage area should be constructed of material that is easy to clean, impervious to water and resistant to acids and alkalis.

262 Fridges and freezers used to store viable agents should be connected to a maintained or back-up power supply. Alternatively, they should have an audible or other alarm to indicate loss of power. There should be contingency plans so that alternative storage arrangements can be used.

263 Access to storage units should be controlled and doors should be locked. One possible mechanism for protecting pathogens stored in a central repository would be to implement a two-person rule for accessing the material (ie one person would have access to the entry door and another person would have access to a key for any additional lock).

264 Management systems that include electronic access systems (iris scanners or other recognition software) are often capable of formally logging access/egress from the storage area. Some systems are also capable of controlling removal/replacement of sample vials from the storage area, to give a much more stringent inventory control. An alternative method could involve the strategic placement of recordable CCTV cameras at the storage station.

Vector control

265 All sites containing a high-hazard facility must have an integrated pest control management system in place to control rodents and insects. This is particularly important when working with diseases that can be spread by insect vectors.

Containment Level 4 laboratories

266 There are two main models used to operate CL4 laboratories:

- primary containment systems, where the handling of biological agents is performed in totally enclosed systems offering a very high degree of personal protection (a Class III cabinet line is a good example); and
- the 'suited' laboratory, where personnel wear a positive-pressure air-fed suit to manipulate organisms either within a safety cabinet or in combination with another primary containment system.

267 In addition to the general controls and procedures mentioned in *Generic issues* (from paragraph 205), additional controls and procedures will be required depending on which laboratory system model is used. To obtain maximum operational flexibility, a combination of suited systems and other means of primary containment may be chosen, subject to a suitable risk assessment of the work programme (see paragraph 195).

Cabinet-line laboratories

General design features

268 The cabinet-line laboratory is usually located in a dedicated room accessed via an airlock of outer and inner change facilities, separated by a personal shower facility. A typical arrangement for cabinet-line facilities is shown in Figure 2. The cabinet-line laboratory must be separated from any other activities in the same building. Access to the laboratory must be restricted to authorised personnel and a key procedure established so that entry is restricted at all times.

269 The cabinet line itself is a highly engineered, custom-made piece of equipment that is essentially several hard-walled Class III cabinets joined together to provide a fully enclosed, leakproof cabinet. Access to the inner chamber is by arm-length protective gloves. Gloves are attached to special ports in the cabinet system by 'O-rings'. The gloves may be the potential weak point in the system because they can become damaged, leak or detach. Daily maintenance checks on the gloves/ports are essential.

270 Modern cabinet lines have evolved into large complex pieces of equipment; however, the basic design remains essentially the same. They have a central spine that runs from the sample entry point (usually a disinfectant-filled dunk tank) at one end, to the sample/waste exit point (usually an autoclave) at the other. Other separate workstations can be added at various points along this spine. For example, an integrated centrifuge unit, microscope unit or refrigerated sample storage unit. Some modern analytical laboratories have included large MRI (magnetic resonance imaging) scanners into the cabinet lines. Cabinet lines should be carefully designed so that individual workstations can be isolated from the main

spine to allow for independent disinfection (fumigation), or to allow removal for maintenance. The cabinet line should be fitted with a visible pressure gauge to show that it is operating at the correct pressure.

271 Whenever possible, samples entering or leaving the cabinet line should do so through a 'dunk tank' containing an effective disinfectant, or through the double-ended autoclave, which is usually integrated into the cabinet line.

272 Movement of samples through cabinet lines can be difficult and time consuming. For smaller cabinet lines, samples can be passed from one unit to another by hand in sealed containers, taking obvious care. For extended cabinet lines this problem has been addressed by the use of a small trolley that can be pulled through the main spine of the cabinet line. This is still a time-consuming operation, but it does help minimise the risk of accidents.

273 Cabinet lines consist of several Class III cabinets joined together and are not covered by BS EN 12469: 2000.[51] However, the cabinet line should still attempt (where possible) to meet the basic performance criteria set out in this standard. For single Class III cabinets, the performance standard is a minimum leak-tightness test equal to (or less than) 10% loss of pressure of 500 Pa in the system after 30 minutes. Extended cabinet lines are unlikely to meet this requirement – a test of 10% loss of 250 Pa pressure after 30 minutes is commonly used.

274 Cabinet lines operate at negative pressure. BS EN 12469 requires a 200 Pa negative pressure differential. A minimum volumetric airflow rate through the inlet filter of 0.05 m^3/s for each cubic metre of cabinet volume (gloves attached, 200 Pa operating pressure) is required by BS EN 12469. This provides a fairly turbulent flow rate through the cabinet-line spine and care must be taken to avoid cross-contamination of the workstations. Such high flow rates are required to maintain an inward airflow velocity of at least 0.7 m/s through a glove port, should a glove become detached during operation.

275 BS EN 12469 specifies that the gloves should conform to the diameter of the glove port and that it should be possible to replace gloves from outside the cabinet during normal operation (cabinet ports usually have space for two O-rings to facilitate a safe change of gloves without having to remove the damaged glove first).

Access

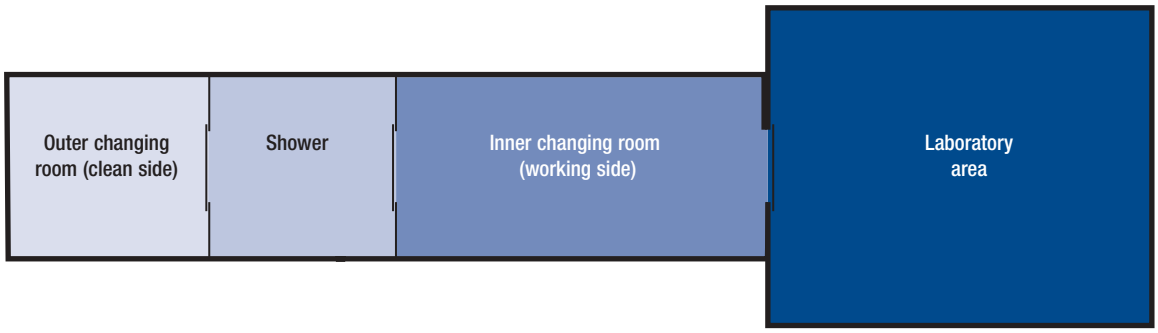
276 Entry into the cabinet-line laboratory must be via an airlock consisting of at least two interlocked doors (with alarmed manual overrides) maintained at a negative pressure relative to the outside. The 'clean' side of the airlock should be separated from the restricted 'working' side by changing and showering facilities. The outer door should be labelled with appropriate biohazard signs and a 'work in progress' sign.

277 Access to the cabinet-line laboratory should be limited by means of secure, locked doors. The laboratory manager, safety officer, or other person responsible for the physical security of the laboratory should control access.

278 A complete change of clothing should be worn in the cabinet-line laboratory. Once work has finished, this clothing should be removed in the 'working' side changing facility and placed into a container for autoclaving. Personnel should then take a shower before changing and leaving the laboratory.

279 During work in the laboratory suite or unit, there should be a second competent person available at all times to assist in case of emergency.

Figure 2: Access sequence to a cabinet-line laboratory



Control of aerosols

280 Manipulations of high-hazard pathogens must be performed within the cabinet line. Air supply to the cabinet line should be HEPA filtered. Safety cabinets must exhaust through a double HEPA filter or equivalent, preferably direct to the outside air or if this is not practicable, via the laboratory air extraction system. If cabinets are exhausted via the laboratory extract, dampers are required to prevent removal of fumigant from cabinets by the extract system. The HEPA filter should ideally be part of the cabinet, but if not they should be located as close to the cabinet exhaust as possible, to avoid inadvertent contamination of the building exhaust system with biological agents.

Movement of materials and equipment

281 An additional fumigation airlock may be required for equipment decontamination before removal from the laboratory, or for bringing in larger items of equipment that cannot pass through the personnel airlock (or autoclave).

282 Large equipment removed or brought into the laboratory should not be passed through the airlock until the laboratory and the equipment has been decontaminated by fumigation or other measures appropriate to the circumstances.

283 All materials should be made safe or safe to handle before removal from the laboratory. A double-ended dunk tank filled with an effective disinfectant (or a safe alternative system) may be required for the removal of items that cannot be autoclaved.

284 The autoclave doors should be automatically controlled so that the exit, or outside door, can only be opened after the autoclave sterilisation cycle has been completed.

Communications

285 There should be a hands-free telephone or other means of outside communication in the laboratory/laboratory suite.

286 An appropriate system of communication must be provided between the laboratory, support facilities, and outside of the containment facility. Within the laboratory, workers can communicate freely with colleagues within the room. However, a telephone call requires the operator to remove their hand from cabinet gloves and sleeves to manually use the telephone. Cordless hands-free telephones should be considered.

Hygiene facilities

287 Facilities should be provided for hand washing (ie separate from other laboratory sinks). A hand-wash basin(s) should be located near to the laboratory exit. Local codes/policies on changing out of protective clothing when leaving the laboratory will determine the exact location and number of basins required. Basins should be of the type that can be operated without using the hands (eg by elbow, foot or knee) or else supplied with automatic controls (eg infrared 'magic eye'). Drainage from such sinks should flow into the effluent waste treatment plant for inactivation by a validated method, before discharge into the main sewer.

Waste removal

288 Biological materials that are to be removed from the laboratory in a viable or intact state should be transferred to a non-breakable, sealed primary container, which is then enclosed in a non-breakable secondary container. The final package should then be removed via the dunk tank, fumigation chamber, or other suitable airlock designed for this purpose.

289 If a dunk tank is used, it should be sealed during fumigation if the disinfectant it contains is likely to react with the fumigant to form toxic compounds.

Figure 3: A cabinet line

Suited laboratories

290 The use of fully encapsulating suits for work with high-hazard pathogens will be new to facilities in the United Kingdom. Suited systems are, of course, used widely in other countries across the world, and indeed, in several countries across Europe. Both cabinet-line and suited systems have their own advantages and disadvantages in convenience, constraint, comfort and efficiency. The primary purpose of a laboratory 'suit' is to protect the operator from exposure to biological agents.

291 For suited-laboratory systems, careful consideration will need to be given to the positioning of equipment within the laboratory, eg convection currents from centrifuges located in close proximity to microbiological safety cabinets may disrupt airflows, leading to loss of containment. Equipment may also be a source of noise, vibration or heat gain, which may interfere with other operations in the laboratory.

292 Whenever a suited laboratory model is used for work with high-hazard pathogens, a full back-up support system, including stand-by generators and

bottled, breathable air, emergency power and a chemical decontamination shower will need to be in place. This is discussed in further detail from paragraph 315 onwards. Suited laboratories must provide appropriate measures to prevent potential positive pressurisation of the laboratory (ie sealed laboratory, airtight doors in chemical shower, etc).

293 The use of suits may require a change in working patterns to accommodate the needs of staff working in such an environment, eg thought should be given to the intake of fluids and appropriate rest breaks during work.

294 In addition to the general requirements of *Generic issues* (paragraphs 205-265) the following measures should also be applied. If suits are to be used in combination with cabinet lines, then the control measures in paragraphs 301-325 must also be applied.

General design considerations
295 The differential airflow should be monitored and alarmed to indicate any malfunction in the system. An appropriate visual pressure device to confirm the operating pressure should be clearly visible at the entry to the clean change room. The air supply and exhaust components should be monitored and a HVAC control system installed to prevent positive pressurisation of the laboratory.

Access
296 The laboratory should provide personal protection and a safe system of work equivalent to that provided by Class III biological safety cabinets. The laboratory must contain airtight access doors.

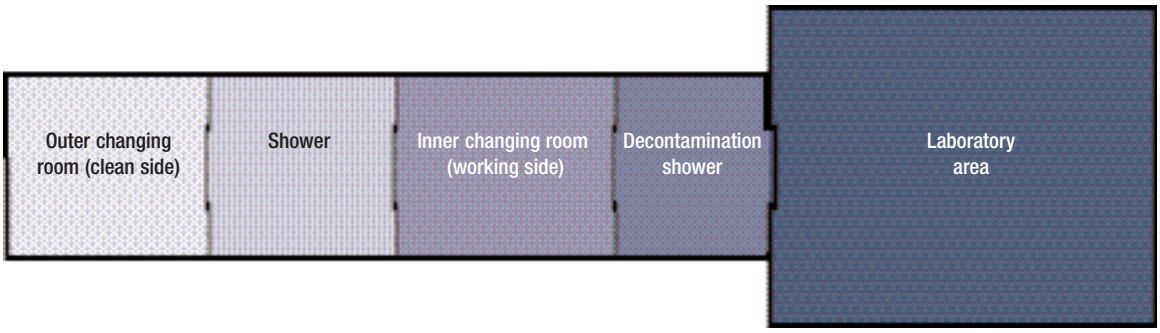
297 Access to a suited laboratory will vary slightly from a cabinet-line system; a 'suit-up' area must be provided as well as change and shower areas (see Figure 4). An air lock should be provided between the suit-up area and the laboratory – this is usually the chemical decontamination shower, which should have interlocked doors between the change area and the laboratory.

298 Access to the laboratory itself should be severely restricted. Consider the choice of access system used; key-codes, for example, may be difficult to operate in suits. Some laboratories have opted for different access control levels for different parts of the secure area, including electronic locks linked to iris-scanners. These scanners can read through the PVC visor and provide a suitable means of secure, hands-free operation. These systems can also be programmed to restrict/record personnel entry into the laboratory area for an additional layer of security.

299 There should be no lone working in a suited laboratory. There should be at least two people working in this type of laboratory at any given time, so that assistance can be given in case of an emergency.

300 Laboratory occupants must be visible at all times, either through the viewing panel or via CCTV within the laboratory.

Figure 4: Typical entry sequence into a CL4 suit laboratory



Suit design

301 There are several manufacturers of suitable suits for work with high-hazard biological agents. These suits will fall within the scope of the Personal Protective Equipment (EC Directive) (Amendment) Regulations 1994,[52] which implement Directive 89/686/EEC.[53] This Directive requires that the manufacture and supply of suits used as PPE must be certified by EC-type examination by an approved inspection body to conform with the provisions of this directive and carry the 'CE' mark.

302 Suits should be one piece, air-tight and constructed out of robust, reasonably impenetrable material with a clear visor for maximum visibility. The visor can be of rigid or flexible PVC and should allow for approximately 270-degree vision. The suits should be closed with a zipper located beneath a sealable PVC flap. It is recommended that suits operate under a positive air pressure of ~180 Pa with respect to the surrounding atmosphere.

303 Some suits are custom-made complete with attached gloves and boots. These suits have to be measured specifically for the user leading to greatly increased costs. In all cases, suits should provide a close, comfortable fit. Consideration should be given to quick-change cuffs at the wrist to allow for safe changes of gloves during operation.

304 Gloves should be visually checked before work begins and checked regularly during work. It is common practice to wear at least two layers of gloves for CL4 work.

305 Suits should be attached to an independent life-support system with a HEPA filter placed in-line between the air supply and the protective suit to prevent contamination during coupling/decoupling from the air supply. The HEPA filter can form part of the attachment valve itself, or be incorporated into the fabric of the suit, depending on the design chosen.

306 Suits should incorporate an audible low-flow alarm to alert the user when the air supply falls to the minimum safe working level.

307 The breathable air supply itself is usually provided via kink-resistant down-drop 'umbilicals' which are strategically located within the laboratory. Movement throughout larger laboratories of this type may require a series of detachments from the air supply. Alternative systems may include bench-level air attachments. The number of connection points should be sufficient to avoid the umbilical air lines being excessively stretched.

308 Air-supply attachments of a standard quick-release type provide a much easier means of movement across large laboratories and are therefore recommended. Attachments of a metal-thread type are available on some suits. For additional security, the connectors may be threaded with Teflon tape to maintain an airtight and waterproof seal. All exhaust air valves should be of an airtight, non-return design.

309 The use of suits for this type of work will be new to the UK. This means that users will have very little practical experience in testing and maintenance. The general recommendation is that suits should be regularly tested and inspected prior to each use until sufficient experience and confidence allows for any relaxation of the procedures outlined below. Adequate space should be provided for testing, drying and robing/disrobing suits. In addition, suits should be:

- visually inspected before each and every use;
- integrity pressure tested before each and every use;
- visually re-checked by a co-worker before entry into the laboratory.

310 The pressure integrity test should ensure that there are no undetected holes, tears or defective seams in the suit. A suitable pressure integrity test is given in BS EN 464: 1994.[54] This involves filling the suit with compressed air (initially to 1750 Pa for at least ten minutes) where it should maintain 1650 Pa for at least a further six minutes. This should be sufficient to detect any defects in suit integrity. Careful attention should be given to refitting any valves that have been removed or obstructed to carry out the integrity test, to ensure that they function satisfactorily after the test. Any suit failing a pressure integrity test should not be used (unless suitably repaired).

311 Even when confidence allows for a relaxation of these recommendations, it is recommended that weekly pressure testing of suits should be performed as a minimum.

312 The exit procedure from a suited laboratory requires the decontamination of the suit in the chemical shower. To minimise the amount of run-off water that has to be treated in the effluent waste tanks, a 'fog' system may be preferred over a 'running water' system. Typically, a mixture of water and an effective disinfectant or biocide is used as a decontamination agent. The nature of the biocide used will be determined by the nature of the organisms handled. This mixture can also be used for general laboratory cleaning and decontamination. Any disinfection protocol should be validated.

313 Suits should be hung up to dry in an area with appropriate drainage to avoid any standing water. This area should be sealable for disinfection.

314 Other disinfectants can be used. Some mixtures will require mixing immediately before use. A regular quality control check on the disinfectant mixture is highly recommended. A surfactant may be added to the disinfectant to aid lather formation – this may also help to detect any leaks in the suit itself but care should be taken to ensure that this does not cause excessive frothing in the waste treatment tanks.

Life-support systems – breathable air supply

315 Positively pressurised suited systems should be ventilated by a robust life-support system. The life-support system should include alarms and emergency back-up breathing tanks.

316 The air supply for the life-support system should be oil-free breathing air provided by dual-system air compressors and holding tanks. One of the supply

compressors will be in service and the second will act as a back-up system. These compressors should be readily accessible for monthly monitoring, maintenance and inspection (consider providing a third compressor to allow for additional redundancy and uninterrupted maintenance).

317 The air being supplied to the user should conform to air purity levels specified in BS 4275: 1974.[55] The air should be free from all perceptible odour and contamination from dust, dirt or other irritating ingredients. Careful consideration should be given to how, and where, these air quality measurements should be taken.

318 The minimum air supply capacity for personal protection should be based on at least 120 litres of air per minute per person. This air should be provided through 'kink'-resistant tubing at a minimum pressure of 34.5 kPa. The air supply should be at ambient temperature and have a relative humidity not exceeding 85%.

319 The breathable air supply should be HEPA filtered at some point between supply and user. It is suggested that a HEPA filter could be fitted at each extreme end of the hose supply.

Back-up emergency supply

320 There should be sufficient redundancy built into any air supply system to provide sufficient back-up air to allow workers enough time to exit the laboratory safely. This will include time shutting down experiments safely and decontaminating before leaving the area. Similarly, sufficient back-up power generation should be available in the event of loss of normal power to allow for appropriate shutdown and exiting procedures.

Emergency air supply

321 Appropriate RPE should be provided on the 'clean' side of the decontamination shower in case support workers are required to enter the laboratory during emergency/rescue operations. For specific advice on appropriate RPE for this purpose please refer to *Respiratory protective equipment at work: A practical guide*.[56]

Communication

322 Air-fed suits can be excessively noisy during use, making direct communication between colleagues very difficult. Noise levels within the suit should be kept to a minimum but experience elsewhere suggests that conversation is often difficult. Communication between users can be made more convenient by the use of radio headsets receiving and transmitting on different frequencies. This can allow for direct communication between users in the laboratory and support workers outside the laboratory. Such systems should be considered.

323 Noise levels within the suits should not exceed 80 dB(A) unless additional control measures are put in place in line with current noise legislation.[57]

324 There should be a hands-free telephone or other means of outside communication in the laboratory/laboratory suite.

325 An appropriate communication system must be provided between the laboratory and the support facilities, and outside of the containment facility.

Figure 5: An example of a positive-pressure air-fed suit

Part 5: Principal requirements for containment of animals infected with high-hazard pathogens

326 Animal welfare is regulated under the Animals (Scientific Procedures) Act 1986[32] and is carefully monitored by Home Office inspectors. The information in this guidance is aimed primarily at human health and safety but it is also intended to take into account the essential need to maintain animal welfare. Further guidance on work with research animals can be found in *Working safely with research animals: Management of infection risks*.[15]

327 This guidance will outline the main requirements of work with animals deliberately infected with high-hazard pathogens in an experimental setting and will be restricted to the use of **small animals** only. There are a limited number of facilities available worldwide capable of working with ACDP HG4 or genetically modified high-hazard pathogens in large animals.

328 For the purposes of this guidance, it is expected that all animal work involving these high-hazard pathogens will be restricted to animal models that can be contained and maintained in an animal isolator.

329 Should the need arise to use large animals for work with high-hazard pathogens, laboratory managers are urged to contact the relevant regulators as soon as possible, before any work begins, to discuss specific regulatory requirements for the programme of work.

330 Any work with animals includes the possibility of worker exposure to respiratory sensitisation through contact with hair and dander and dried excreta (further guidance on animal allergies can be found elsewhere).[58] Care must also be taken against naturally occurring persistent or latent infections, which may pose a hazard to workers. Identification of hazards, including chemical and physical hazards, and identification of the potential routes of exposure, will form part of the overall risk assessment.

331 The type of animals used and the nature of the procedure used will also affect the risk of exposure to infectious hazards: animal husbandry, bleeding procedures and post-mortem examinations all present opportunities for exposure but in different ways and so will require different methods of control. It is very difficult to generalise, so appropriate risk assessments should be made for each type of procedure.

332 Work with animals may also bring additional infection hazards, for example:

- direct physical contact where a sudden movement by the animal (or handler) can lead to scratches, bites or kicks;
- newly acquired animals will be in unfamiliar surroundings and are likely to be agitated and more likely to bite, scratch etc.

333 Animals listed in Schedule 2 of the Animals (Scientific Procedures) Act (ie the common laboratory species) must be obtained from Home Office designated breeding or supply establishments. In general, designated breeders will have

specific screening procedures in place to determine the health status of the animals. The Act, however, does not require that farm animals or poultry are obtained from designated establishments and it is therefore recommended that such animals be obtained from competent animal suppliers who have suitable screening procedures in place.

334 All mammals imported from abroad are subject to control under animal health legislation – Rabies (Importation of Dogs, Cats and Other Mammals) (England) (Amendment) Order 2004.[59]

Definition of terms

335 The following terms are used relating to containment of animals:

- **animal room**: the room in which animals are held;
- **animal unit**: a building or separate area within a building, containing animal rooms and other facilities such as changing rooms, showers, autoclaves, store rooms etc;
- **animal facility**: one or more animal rooms used to house stock, breeding or experimental animals or one which is used for the performance of minor surgical procedures on animals.

Safe working with sharps

336 When carrying out procedures with animals, two of the most common sources of human laboratory-acquired infection are accidental inoculation with a contaminated needle or injury by a sharp instrument contaminated with infectious material. Sudden movement of animals during technical procedures may lead to accidental infection of the operator or assistant. Aerosols generated by the inappropriate use of needle and syringe may also provide a potential source of accidental infection.

337 For all work with high-hazard pathogens, local codes of practice should address the issues of 'sharps' and generation of aerosols. Needles and other sharp instruments should not be unsheathed until immediately before use. On completion of the procedure, the needle or sharp should be discarded into a suitable container at the earliest opportunity. Needles should never be re-sheathed unless there is a safe system of doing so. For work with high-hazard pathogens, the operator is advised to rehearse all procedures before starting work.

Disinfection and disposal procedures

338 There may be specific requirements that need to be taken into account for waste arising from certain activities, including work with agents under DEFRA control, work involving genetically modified organisms and work involving radioactive substances (refer to relevant guidance for further details).[27]

339 Used cages and animal bedding should be placed intact into a double-ended autoclave within the containment area to allow for the safe removal of the bedding for disposal.

340 Following completion of the work programme, ventilated cage racks, flexible-film isolators (FFIs), microbiological safety cabinets and equivalent equipment used to house cages should be suitably decontaminated *in situ* with a gaseous fumigant using recommended procedures.

341 Other specific requirements will include:

- All bench surfaces, walls, floors and ceilings must be impervious to water and resistant to acids, alkalis, solvents and disinfectants. Internal surfaces should be designed and constructed to facilitate decontamination. Internal surfaces of animal rooms should be constructed of smooth, impervious materials with an easily cleanable surface such as epoxy or polyester-coated plaster, or equivalent surfaces which are resistant to the disinfectants normally used. Junctions of the wall with the ceiling and floor should be coved for easy decontamination.
- Where floor drains are installed, the drain traps should be kept filled and sealed until required. The effluent from traps must be rendered non-infective before discharge to a sewage system. The drain traps should be disinfected and cleaned regularly and at the end of each experiment. Drains and other piped services must be proofed against rodents and insects.
- All solid waste must be rendered non-infectious and all viable micro-organisms killed by a validated method before being removed from the containment area. Waste that cannot be autoclaved within the containment area should be removed via a dunk tank containing an effective disinfectant, and subsequently removed in sealed double containers for on-site incineration.
- The animal room must be sealable to permit disinfection. The definition of 'disinfection' may be widely interpreted. In practice, it may be necessary to decontaminate the facility by fumigation following an accidental spillage, for example, or before maintenance work. There must be a specified fumigation/disinfection procedure in place.

Emergency procedures

342 Those working with animals infected with biological agents must have plans in place for dealing with accidents involving biological agents. Such accidents might include fire in the animal facility, intruders or escape of infected animals. It is recommended that such plans be drawn up in consultation with local emergency services. Plans should include arrangements for reporting accidents or incidents under relevant statutory schemes (RIDDOR).

343 There should be suitable communication systems for warning employees who are liable to be affected by an accident. Emergency procedures drawn up under other legislation may be integrated so that arrangements drawn up under COSHH do not duplicate or conflict with other statutory arrangements. Emergency procedures should be practised at regular intervals.

344 As well as procedures for dealing with the scenarios described above, there should also be written procedures for dealing with other incidents that may lead to the exposure of workers:

- **Cuts and scratches**: in the event of being bitten (including scratches and abrasions from cages) the injured person should immediately wash the wound thoroughly with water and, if possible, it should be gently encouraged to bleed. The wound should then be cleaned with soap and water. If water is not available, a suitable antiseptic may be used.
- **Spillages**: procedures for dealing with spillages should be incorporated into written local rules or codes of practice. Consideration should be given to the scale of the spill, the biological agent present and the likelihood of release of infected material to the environment. Spill kits should be available in the animal facility.
- **Recording and reporting**: there should be appropriate procedures in place for recording incidents and if appropriate, for reporting incidents under relevant statutory schemes.

345 Medical facilities should be available for any worker who suffers injury as a result of working with animals.

Protective equipment and procedures

346 The majority of animal work is performed with small animal models (rats, mice, guinea pigs etc) and there is a variety of equipment available that may be used to safely contain small animals inoculated with biological agents. Such equipment includes FFIs, flexible and rigid isolators with half-suits, animal husbandry units, downdraft post-mortem tables, RPE and combinations of these systems. It is essential that these systems be evaluated for operator protection. Risk assessments for this type of work should include a full description of the control measures **and** the procedures used to ensure a high degree of operator protection.

Flexible-film isolators (FFIs)

347 FFIs may be used under negative pressure to contain small animals infected with biological agents. Animal inoculations, collection of blood samples and post-mortem examinations can all take place within FFIs. Sealed carriers that attach to ports on isolators can be used to remove samples, animals and animal wastes from isolators. FFIs are suitable for small animal models such as mice, rats and small numbers of guinea pigs. Training in the use of FFIs is essential, with additional consideration given to operator factors such as fatigue, dexterity and limited mobility.

348 Separate guidance on the use, maintenance and testing of animal isolators will follow as a supplement to this guidance, and will be freely available on HSE's website.

Flexible and rigid isolators with half-suits

349 These can also be used for work with infected animals and may provide more space than FFIs. In addition to some of the factors considered when using FFIs, attention should also be focused on practical aspects and comfort factors, such as entering and exiting the half-suits, variation in body sizes and provision of adequate ventilation for the operator(s). Some practical concerns of the half-suit systems include operator fatigue, poor communication and the need for a 'buddy' system for animal handling.

Figure 6: An example of a half-suit animal isolator

Post-mortem examinations

350 Before a post-mortem examination is performed on an infected animal, a risk assessment must be carried out to determine the appropriate controls required for the procedure.

351 Post-mortem examinations of small animals should normally be carried out in an appropriate animal isolator, away from other animals. For larger animals (eg simians) the use of isolators may not be practical, in which case a combination of downdraft tables and protective suits should be used.

352 Carcasses should be bagged or placed into disposable burn-bins and incinerated. Smaller carcasses may be autoclaved before incineration.

353 Local rules should specify clean-up procedures following post-mortem examinations.

Work with simians

354 More information on working with simians can be found in *Working safely with simians: Management of infection risk*[16] and *Best practice in the accommodation and care of primates used in scientific procedures*.[60]

355 *Herpesvirus simiae* (B virus) is the best-recognised zoonotic hazard of simians and has been responsible for a number of deaths in laboratory and animal workers. Simian viruses also pose a threat to humans through the use of primary monkey tissue cultures in laboratory work and vaccine manufacture (eg SV40 contamination of Polio vaccine). Other viruses of concern are rabies virus, filoviruses (which cause viral haemorrhagic fevers) and retroviruses such as simian immunodeficiency virus (SIV).

356 In general, familiarisation of simians with handlers can reduce stress for both simian and handler and should not be discouraged. However, where there is a known zoonotic risk, simians should be handled as little as possible and preferably kept in pairs for welfare reasons, with the same cage partner throughout. Different consignments and different species should be isolated separately.

357 Staff must always wear protective clothing when in contact with simians and used cages. Local codes of practice should specify the consistent use of protective clothing.

358 Safe working methods (including sedation and adequate restraining methods) should be specified for all procedures. Staff must be trained in their use and be provided with suitable information, instruction and training on the hazards and risks of the work.

Appendix 1: Fumigation

1 Plans for fumigation should be documented in the local code and should include details of the initial validation of the process. Validation can be achieved by using stainless steel coupons with a set amount of *Bacillus subtilis var niger* 'painted on' (the traditional method of using filter paper inoculated with a suspension of the organism may not be suitable if the filter paper absorbs the formaldehyde vapour) and located at various points in the room or cabinet to test penetration of the fumigant. Similarly, a standardised spore suspension can be painted onto small marked areas on surfaces, which are later swabbed to recover any surviving organisms. Contact plates can also be used.

2 Microbiological safety cabinets or cabinet lines should always be fumigated if:

- a large spillage of infectious material occurs within them; and
- before filters are changed or any maintenance work is carried out that involves gaining access to the interior of the cabinet (eg air ducts).

3 The fumigant should be generated and the non-return valves left closed. Passive migration of the fumigant through the filter can occur but the valve could be left open and the fan running for 10-15 seconds to ensure penetration of the filter medium. The valve should then be closed and the fan switched off while the remainder of the fumigant is left to disperse within the cabinet. After at least six hours, or preferably overnight, the fumigant should be exhausted to atmosphere by switching on the fan and allowing air from the room to enter the cabinet. Before venting the formaldehyde in this way, it is essential to ensure that no one is in the vicinity of the exhaust outlet and that the exhaust air cannot enter nearby windows or ventilation air intakes.

Validation of microbiological safety cabinet/cabinet-line fumigation

4 If filters are to be changed after fumigation, the discarded filter unit should be bagged and incinerated.

5 Traditionally, fumigation is performed overnight, but fumigation times may be reduced as long as the process is validated. Fumigant may be extracted from the area by the air-handling system. This method should only be used where there is a total loss ventilation system present so that there is no possibility of formaldehyde vapour contaminating other areas. In all cases, the plant or equipment extracting the air should be operated by an external switch.

Formaldehyde as a fumigant

6 Formaldehyde vapour is the fumigant most commonly used in laboratories. The usual source is formalin, which is readily available as a 40% solution of formaldehyde vapour in water. When heat is applied, the vapour is generated in quantity. Formaldehyde has a workplace exposure limit (WEL) of 2 ppm (parts per

minute) (both eight-hour time-weighted average and short term – currently under review). Formaldehyde vapour is explosive at 7.75% in dry air. Its auto-ignition point is 430°C.

7 The method of generating formaldehyde vapour using a mixture of potassium permanganate, para-formaldehyde and water can lead to potentially explosive mixtures being created. This practice is dangerous and should never be used.

8 A number of factors affect the efficiency of fumigation:

- the ratio of formalin to water used, and thereby the relative humidity created;
- the volume of the space to be fumigated;
- the surface area exposed in that space and the presence of absorbent materials such as cardboard boxes; and
- temperature – formaldehyde fumigation is less effective below 18 °C.

9 Below 9 °C, formaldehyde sublimes and is less easy to vaporise.

10 To have maximum effect, the formaldehyde must be able to:

- penetrate (so pre-cleaning should be carried out if this can be done without compromising safety, eg if fumigation is a planned exercise); and
- dissolve at adequate concentrations in the film of moisture in the immediate vicinity of the organisms to be inactivated. Water vapour generated in the process of dispersing formaldehyde provides the essential optimum level of relative humidity (ie greater than 35% but less than 80%). Too much formaldehyde results in the formation of sticky deposits of para-formaldehyde.

11 There are a number of methods for generating formaldehyde vapour:

- heating a mixture of formalin and water in thermostatically controlled heating unit (such as an electric wok or kettle);
- depolymerisation of para-formaldehyde using commercially available formaldehyde-generating kits; and
- heating formalin in a purpose-made vaporising unit (ie as found in safety cabinets).

Fumigation of rooms

12 Before fumigating with formaldehyde, hydrochloric acid and chlorinated disinfectants should, if possible, be removed from the room. This is to prevent the possibility of forming bis (chloromethyl) ether, which may be carcinogenic.

13 After a validated period of time (preferably overnight), fumigant may be extracted from the area by the air-handling system. This method should only be used where there is a total loss ventilation system present so that there is no possibility of formaldehyde vapour contaminating other areas.

14 After the fumigant has been removed, a thorough check of the level of residual vapour should be carried out before anyone re-enters the laboratory. Staff should not re-enter an area when the fumigant has been generated except in an emergency. Full breathing apparatus (which provides air from an independent source) must be worn and only by those trained in its the use. Respirators are not appropriate for use in the concentrations of formaldehyde vapour achieved when carrying out these procedures.

Alternatives to formaldehyde

15 Further guidance on the use of alternatives to formaldehyde as a fumigant is currently in preparation and will be available from HSE's website (www.hse.gov.uk) in due course.

Appendix 2: Maintenance

1 The Management of Health and Safety at Work Regulations 1999 require an employer to make appropriate arrangements for the effective planning, organisation, control, monitoring and review of preventative and protective measures. The Control of Substances Hazardous to Health Regulations 2002 (as amended) require that where exposure to biological agents cannot be prevented, steps should be taken so that it is adequately controlled.

2 For some control measures, such as local exhaust ventilation (LEV), other regulations may also apply.[61]

3 Maintenance, as far as COSHH regulation 9 is concerned, means any work carried out to sustain the efficiency of control measures, and not just work carried out by maintenance workers. Maintenance, for the purposes of this guidance, will include visual checks on any equipment relevant to the control of exposure, inspection, servicing, observation of systems of work and any remedial action to maintain the effectiveness of control measures. For biological agents it is particularly important to prevent any contaminated equipment spreading infection.

4 Anyone who checks the effectiveness of any element of a control measure should have the competence to do so. Employers must ensure that whoever carries out maintenance is competent to do so in accordance with COSHH regulation 12(4). The frequency of examinations or tests should be linked to the extent of any risk in the event of failure.

Local exhaust ventilation (LEV)

5 People involved in the examination and testing of LEV plants must be competent to perform this task. Further guidance on the selection of a competent person can be found in the United Kingdom Accreditation Service (UKAS) publication *Accreditation for the inspection of local exhaust ventilation (LEV) plant.*[62] Additional guidance can also be found in *Maintenance, examination and testing of local exhaust ventilation*.[63]

6 Regular visual checks are not the same as thorough examination and testing. Visual checks of all LEV, including microbiological safety cabinets and cabinet lines, should be performed once a week. Defined working procedures should also be observed regularly to check that they are still being followed. Standard procedures should be reviewed periodically to ensure that they are still appropriate and to see if they can be improved. Maintenance checks should include the examination and testing of any back-up systems:

- cabinet lines – HEPA filters to be tested and examined every six months in accordance with BS EN 12469: 2000;[51]
- HVAC – HEPA filters to be inspected every six months and tested and examined annually in accordance with BS 1822: 1998.[42]

Personal protective equipment (PPE)

7 An effective PPE maintenance system is essential to make sure the equipment continues to provide the degree of protection for which it was designed. PPE maintenance includes cleaning, disinfection, examination, replacement, repair and testing. The responsibility for carrying out maintenance checks should be laid down, together with details of the procedures to be followed and their frequency. The manufacturer's recommendations should be followed as to the frequency of examination.

8 Employers need to ensure that appropriate storage is provided for PPE in such a way that it can be clearly segregated from contaminated PPE and outdoor clothing.

9 Positive-pressure suits are deemed to be PPE. COSHH requires that the frequency of testing should be determined by the extent of the risk in the event of failure. For positive-pressure suits, the following maintenance tests are recommended:

- visual checks on suit integrity should be done before each use;
- integrity pressure tests before/after every use.

10 In addition, the compressed air systems that provide air to the suits and the back-up air supply to the compressor should not be overlooked and will require specific maintenance under the Pressure Systems and Transportable Gas Containers Regulations 1989.[64] Standards for installation and operation of air compressors are set out in BS 6244: 1982 *Code of Practice for stationary compressors*.[65]

Respiratory protective equipment (RPE)

11 Employers have a duty to specify the type of RPE that should be worn for a specific task. All RPE equipment manufactured after 1 July 1995 must be CE marked to show that it is manufactured to meet the minimum legal requirement. RPE must be checked regularly to ensure that it remains effective. The manufacturer's maintenance recommendations should always be followed. In general, RPE should be examined before each use and should be tested and examined at least every month. Records of examinations should be kept for at least five years. For further detailed information on the selection and maintenance of RPE please see *Respiratory protective equipment at work: A practical guide.*[56]

12 Employers must also provide storage facilities for RPE, including safe storage of any spare parts. Clean equipment should always be kept segregated from RPE awaiting repair, cleaning or maintenance.

Pressure systems

13 In addition to the pressure systems involved in providing compressed air for positive pressure suits, the double-ended autoclave will require periodic testing under the Pressure Systems Safety Regulations 2000.[66] These Regulations stipulate a regular maintenance programme for all pressure systems based on age, operating conditions, maintenance history, risk to health from failure, etc. It is recommended that an autoclave forming part of the control measures for a CL4 laboratory should be maintained, tested and calibrated on an annual basis.

Preventative maintenance

14 A planned preventative maintenance programme should be scheduled regularly. All facilities should ensure that any selected maintenance programme provides a suitable and sufficient level of control at all times and according to appropriate standards and legislation. Control systems should be periodically re-evaluated to ensure that they are operating within their validated parameters.

Building management system (BMS)

15 If the BMS forms part of the CL4 facility safety control system then it should be regularly maintained with pre-planned shutdown periods for specific maintenance of components. Alarm testing should be included in this programme. No changes should be made to the key operating parameters of any BMS without written authorisation.

16 Other equipment, such as the fire, security, electrical, piped gas systems and other alarms, should be tested according to statutory or manufacturer's specifications.

Appendix 3: Emergency procedures

1 The nature of the biological agents handled at CL4 is such that careful consideration should be given to procedures for dealing with emergencies. There are several duties placed on employers for dealing with foreseeable accidents such as fire, flood or public disorder (Management Regulations) that may involve serious and imminent danger. For the purposes of work with high-hazard pathogens, an emergency can be defined as 'any failure to contain the biological agent' and any such incident should invoke specific emergency procedures as required by COSHH and GMO(CU) Regulations.

Table 4: Legislation and key duties

Legislation	Regulation	Key duties
Management of Health and Safety at Work Regulations 1999[12] (Management Regulations)	**Regulation 8:** Procedures for serious and imminent danger and for danger areas	■ Establish appropriate procedures. ■ Nominate competent person(s). ■ Adequate training/information.
Control of Substances Hazardous to Health 2002 (as amended)[4] (COSHH)	**Regulation 7:** Schedule 3 **Regulation 13:** Arrangements for dealing with accidents, incidents and emergencies	■ Prevention or control of exposure. ■ Prepare procedures. ■ Test procedures regularly. ■ Provide information to emergency services.
Genetically Modified Organisms (Contained Use) Regulations 2000[7] (GMO(CU))	**Regulation 20:** Emergency plans **Regulation 21:** Information relating to accidents	■ Plan of measures. ■ Review of plan. ■ Inform emergency services. ■ Plan publicly available. ■ Inform Competent Authority immediately.
DEFRA requirements for work with specified animal pathogens licensed under the Specified Animal Pathogens Order 1998[8] (SAPO)		■ Prepare and test documented procedures. ■ Inform Competent Authority.

2 The response to any emergency should be proportionate to the risk. For work with high-hazard pathogens, a suitable and sufficient emergency plan should include the following to meet the basic requirements of the relevant legislation.

Establish procedures

3 A written emergency plan, based on a risk assessment, must be produced. It should be kept up to date with changes in practices or personnel. Anyone on site who is affected by the plan should be aware of its provisions.

4 The plan will be specific to a given laboratory but should include details covering a full range of risks – from minor injuries through to emergency evacuation in the event of an exposure or other serious medical emergency.

5 It is important that the risk assessment at this stage of planning is undertaken by individuals with full a range of expertise and should include, as a minimum, the senior scientist managing the work, the laboratory manager, the senior engineer responsible for the facility and the biological safety officer/advisor.

6 For 'major' containment failures, it is essential to consult with local emergency services to determine the limits of local response team action and the timing level of external support for the control of a major incident, eg fire.

7 For high-hazard facilities, it is recommended that an incident response team be established to manage any accident involving loss of containment. This team would contain appropriately trained individuals or 'competent persons' who would have defined roles and responsibilities and be able to respond immediately to any accident and mitigate against effects. This team should include technical specialists, mechanical specialists, first-aiders and other nominated individuals with responsibility for evacuation, shutting down plant and to provide first aid/medical help, if needed.

8 Procedures should also be established to warn other workers of any emergency and provide suitable procedures and routes for the safe evacuation of the building if necessary.

9 Once the emergency has been brought under control, due care and consideration should be given to procedures used for clearing up and the safe disposal of any contaminated material.

Safety exercises

10 There should be regular safety drills, covering any aspects of an emergency response including complete evacuation of the building, isolating non-essential equipment, and the steps taken by nominated individuals to help others evacuate the premises and ensure that all areas are clear. Drills can be practiced as a whole or separately.

11 Safety exercises will be particularly important for new ways of working where there will be limited experience in dealing with emergencies. For example, emergency evacuation procedures in a suited-laboratory will require specific procedures and planning. These procedures should be well practiced to ensure that workers are familiar with actions they need to take.

Inform other interested parties

12 A nominated individual should be assigned to co-ordinate any emergency response and to liaise with the emergency services (if required) so that they can be fully informed of the nature of the hazards involved, once on site. The hazards posed by biological agents may affect the strategy used by the Fire Service, for example, or emergency vehicles and other equipment may need special decontamination to avoid transferring biological agents off site. The police may need to be informed of special procedures if the premises are burgled.

13 Other relevant authorities may need to be shown the emergency plan, eg under GMO(CU),[14] the emergency plan should be brought to the attention of the Environment Agency (in England and Wales) and the local water company, for consideration of water pollution. In some cases, the emergency plan must be made publicly available and this should be done in consultation with the local authority who may be able to provide help and assistance with the provision on public information.

14 Any emergency plan should be drawn up in consultation with safety representatives, employees and particularly those people assigned specific roles and responsibilities during an emergency.

Review procedures

15 Emergency procedures should be reviewed regularly to ensure that any personnel changes are reflected in the current plan. Should an incident occur and the plan be put into effect, the effectiveness of the response should be reviewed at an appropriate interval following the accident. Any suggested improvements should be incorporated into a new plan.

Exposure to high-hazard pathogens

16 Careful consideration should be given to the management of cases of potential exposure, as some cases may require hospitalisation for observation and treatment. As part of the emergency response plan, the nearest (or most suitable) local healthcare facility with appropriate isolation facilities should be identified. Clinicians and senior managers of local infectious disease units to which exposed workers may be transferred should be consulted and policies and procedures should be put in place for the safe transfer and care of exposed individuals.

Table 5: Examples of possible exposures

Example	Risk of infection	Response
Small leak in suit, minor spill within a Class III cabinet.	Negligible	Report incident to laboratory manager. No specific action required.
Contact with disinfected cages or instruments. Tear of positive-pressure suit without skin/mucous membrane exposure.	Low	Report incident to laboratory manager. Be cautious of fevers, headaches or malaise occurring within three weeks.
Sharp injury or skin contact with dirty instruments/used cages. Tear of positive-pressure suit with exposure of skin/mucous membranes.	Medium	Report to laboratory manager and relevant statutory authorities. Monitor body temperature twice a day for three weeks. Report any fever, headache, malaise.
Skin/mucous membrane exposure with known contaminated object. Bite from infected animal. Injury and tear to positive-pressure suit with exposure to skin/mucous membranes.	High	Alert emergency team. Monitor body temperature twice a day. If body temperature 'spikes', give medical advice and support and arrange for transfer to local authority healthcare facility for isolation. Notify the relevant authorities.

17 All incidents should be reported to the responsible person in charge of the facility and an assessment should be made and appropriate response given. For example, the detection of a small leak in a positive-pressure suit without injury or exposure to mucous membranes is unlikely to result in exposure. The occupational health providers for the site normally assess issues such as treatment, hospitalisation etc. A system should be in place to provide 24-hour contact in case of emergency.

18 Injuries involving disinfected sharps carry a moderate risk of infection. Workers should be advised to monitor and record body temperature for a three-week period, with increased vigilance for headache, fever and signs of malaise.

19 Accidental needle-stick injuries with contaminated instruments or deep bites from infected animals carry a high risk of infection to workers. Any such incidents should be closely monitored. For all high-risk incidents, appropriate precautions should be taken including monitoring body temperature (twice daily). If body temperature 'spikes', arrangements should be made for medical advice and support and for transfer of the injured worker to a suitable healthcare facility for isolation or strict barrier nursing.

Emergency contact numbers

20 Emergency contact numbers should be readily available for use when needed.

21 During emergencies, employers should make an immediate assessment of the situation and initiate the appropriate response. An emergency response plan should include communication to key facility staff including the senior safety advisor, medical advisor, senior engineering manager and senior facility managers.

22 A list of contacts and arrangements for obtaining further advice and assistance (meteorological information, specialist medical advice, water and agricultural authorities) should be readily available or posted at key information points within the building.

Appendix 4: Non-microbiological hazards

1 In addition to the microbiological hazards that are the subject of this guidance, there are other hazards that need to be assessed when working in a laboratory. The specific controlling legislation is listed in Table 6 together with examples of relevant HSE guidance as sources of further information.

Table 6: Further guidance

Hazard	Legislation	Further guidance
Chemical		
Flammables	Chemicals (Hazard Information and Packaging for Supply) Regulations 2002 (CHIP)[67] Regulatory Reform (Fire Safety) Order 2005[69]	*The safe use and handling of flammable liquids*[68] *The storage of flammable liquids in containers*[70]
Carcinogens	Control of Substances Hazardous to Health Regulations 2002 (as amended) (COSHH)[4]	COSHH Approved Code of Practice Fifth edition)[71]
Toxins	Anti-terrorism, Crime and Security Act 2001[29] – Part 7; Schedule 5	*Security standards for laboratories*[30]
Compressed gases	Chemicals (Hazard Information and Packaging for Supply) Regulations 2002 (CHIP) Regulatory Reform (Fire Safety) Order 2005	*The safe use of gas cylinders*[72]
Radiation		
Radionuclides	Radioactive Substances Act 1993[73]	See Environment Agency website[47]
Equipment that produces radiation	Ionising Radiations Regulations 1999[74]	*Work with ionising radiation. Ionising Radiations Regulations 1999. Approved Code of Practice and guidance*[75]
Physical		
Pressure systems (autoclaves)	Pressure Systems and Transportable Gas Containers Regulations 1989[64] Pressure Equipment Regulations 1999[77]	*Safety at autoclaves*[76]

Continued overleaf

Hazard	Legislation	Further guidance
Physical (continued)		
Lasers	Non-specific – general controls as required under HSW Act[2] and Management Regulations[12]	
UV radiation		
Noise	Control of Noise at Work Regulations 2005[57]	*Controlling noise at work. The Control of Noise at Work Regulations 2005. Guidance on Regulations*[78] *Protect your hearing or lose it!*[79]
Vibration	Control of Vibration at Work Regulations 2005[80]	*Hand-arm vibration. The Control of Vibration at Work Regulations 2005. Guidance on Regulations*[81] *Vibration solutions*[82] *Hand-arm vibration: Advice for employees*[83] *Control the risks from hand-arm vibration: Advice for employers on the Control of Vibration at Work Regulations 2005*[84]
Electricity	Electricity at Work Regulations 1989[85]	*Electricity at work: Safe working practices*[86]
Ergonomics		
General	Non-specific – general controls under HSW Act and Management Regulations	*Understanding ergonomics at work*[87]
Manual handling	Manual Handling Operations Regulations 1992[88]	*Manual handling: Manual Handling Operations Regulations 1992 (as amended). Guidance on Regulations*[89] *Manual handling: Solutions you can handle*[90]
DSE	Health and Safety (Display Screen Equipment) Regulations 1992[91]	*The law on VDUs: An easy guide*[92] *Working with VDUs*[93]

References and further information

References

1 *Categorisation of biological agents* (Fourth edition) HSE Books 1995 ISBN 0 7176 1038 1 (withdrawn)

2 *Health and Safety at Work etc Act 1974 Ch37* The Stationery Office 1974 ISBN 0 10 543774 3

3 'Directive 93/88/EC of 12 October 1993 amending directive 90/679/EC on the protection of workers from risks related to exposure to biological agents at work (seventh individual directive within the meaning of article 16(1) of directive 89/391/EC)' *Official Journal of the European Communities* 1993 (L268) 71-82, now replaced by 'Directive 2000/54/EC on the protection of workers form risks related to exposure to biological agents at work' *Official Journal of the European Communities 2000* **45** (L262) 21-45 ISSN 0378 6978

4 *Control of Substances Hazardous to Health Regulations 2002* (as amended) SI 2002/2677 The Stationery Office 2002 ISBN 0 11 042919 2

5 *The management, design and operation of microbiological containment laboratories* Guidance HSE Books 2001 ISBN 0 7176 2034 4

6 *Biological agents: Managing the risks in laboratories and healthcare premises* HSE 2005 available from: www.hse.gov.uk/biosafety/information.htm

7 *Genetically Modified Organisms (Contained Use) Regulations 2000* (as amended) SI 2000/2831 The Stationery Office 2000 ISBN 0 11 018676 1

8 *Specified Animal Pathogens Order 1998* SI 1998/463 The Stationery Office 1998 ISBN 0 11 065801 9

9 Department for the Environment, Farming and Rural Affairs (DEFRA) website at: www.defra.gov.uk/animalh/diseases

10 The Health and Safety Executive (HSE) website at: www.hse.gov.uk/biosafety/infection.htm

11 *Animal Health Act 1981 Ch22* The Stationery Office 1981 ISBN 0 10 542281 9

12 *Management of Health and Safety at Work Regulations 1999* SI 1999/3242 The Stationery Office 1999 ISBN 0 11 085625 2

13 *Infections in the workplace to new and expectant mothers* Guidance HSE Books 1997 ISBN 0 7176 1360 7

14 *A guide to the Genetically Modified Organisms (Contained Use) Regulations 2000* L29 (Third edition) HSE Books 2000 ISBN 0 7176 1758 0

15 *Working safely with research animals: Management of infection risks* Guidance HSE Books 1997 ISBN 0 7176 1377 1

16 *Working safely with simians: Management of infection risks* MISC134 HSE 1998 (available online at: www.hse.gov.uk/) (Specialist supplement to *Working safely with research animals: Management of infection risks)*[15]

17 *The large-scale contained use of biological agents* Guidance HSE Books 1998 ISBN 0 7176 1544 8

18 *Safe working and the prevention of infection in clinical laboratories and similar facilities* Guidance HSE Books 2003 ISBN 0 7176 2513 3

19 *Safe disposal of clinical waste* Guidance (Second edition) HSE Books 1999 ISBN 0 7176 2492 7, out of print but due to be replaced by NHS guidance

20 *Advisory Committee on Genetic Modification: Compendium of guidance* Report HSE Books 2000 ISBN 0 7176 1763 7, available online at: www.hse.gov.uk/biosafety/gmo/acgm/acgmcomp/index.htm

21 *Biotechnology: Health and safety in education* Guidance HSE Books 1996 ISBN 0 7176 0724 0 (out of print)

22 *Protection against blood-borne infections in the workplace: HIV and hepatitis* The Stationery Office 1995 ISBN 0 11 321953 9

23 *Transmissible spongiform encephalopathy agents: Safe working and the prevention of infection* 2003 available online at: www.advisorybodies.doh.gov.uk

24 *The management and control of viral haemorrhagic fevers* The Stationery Office 1997 ISBN 0 11 321860 5

25 *Code of Practice for the housing and care of animals used in scientific procedures* The Stationery Office 1989 ISBN 0 10 210789 0

26 *Hazardous Waste (England and Wales) Regulations 2005* SI 2005/894 The Stationery Office 2005 ISBN 0 11 072685 5, and the *Hazardous Waste (Wales) Regulations 2005* SI 2005/1806 The Stationery Office 2005 ISBN 0 11 091171 7

27 *Hazardous waste – Interpretation of the definition and classification of hazardous waste* Technical Guidance WM2 Environment Agency 2002 (available from www.environment-agency.gov.uk)

28 British Fire Service. For contacts please log on to: www.fire.org.uk

29 *Anti-terrorism, Crime and Security Act 2001 Ch24* The Stationery Office 2001 ISBN 0 10 542401 3

30 *Security standards for laboratories subject to Part 7 of the Anti-terrorism, Crime and Security Act 2001* Home Office Communications Directorate 2003

31 *Personnel security measures for laboratories* Home Office 2003 (available on request from NaCTSO)

32 *Animals (Scientific Procedures) Act 1986 Ch1* The Stationery Office 1986 ISBN 0 10 987898 1

33 *Guidance on the Operation of the Animals (Scientific Procedures) Act 1986* HC321 The Stationery Office 2000 ISBN 0 10 0556706 X

34 *A guide to the Radiation (Emergency Preparedness and Public Information) Regulations 2001. Guidance on Regulations* L126 HSE Books 2002 ISBN 0 7176 2240 1

35 *Data Protection Act 1998 Ch29* The Stationery Office 1998 ISBN 0 10 542998 8, gives effect to 'European Directive 95/46/EC' *Official Journal of the European Communities* 1995 (L281) 31

36 *A guide to the Reporting of Injuries, Diseases and Dangerous Occurrences Regulations 1995* L73 (Second edition) HSE Books 1999 ISBN 0 7176 2431 5

37 *Construction (Design and Management) Regulations 1994: The role of the designer* Construction Information Sheet CIS41 HSE Books 1995

38 Richmond J Y (editor) *Anthology of Biosafety II – BSL 2 Facility design considerations* American Biological Safety Association 2000 ISBN 1 882 214756 1

39 Richmond J Y (editor) *Anthology of Biosafety V – BSL 4 Laboratories* American Biological Safety Association 2002 ISBN 1 882 14763 4

40 Kletz T (editor) *HAZOP and HAZAN* Taylor and Francis 1992 ISBN 1 56032276 4

41 Rausand M and Hoyland A (editors) *System reliability theory: Models and statistical methods* John Wiley & Sons Inc 2004 ISBN 0 47147 133 X

42 BS EN 1822-1: 1998 *High efficiency air filters (HEPA and ULPA). Classification, performance testing, marking* British Standards Institution ISBN 0 580 29837 X

43 BS EN (IEC) 61508-1: 2002 *Functional safety of electrical/electronic/ programmable electronic safety-related systems. General requirements* British Standards Institution ISBN 0 580 32719 1

44 BS EN 12347: 1998 *Biotechnology. Performance criteria for steam sterilizers and autoclaves* British Standards Institution ISBN 0 580 29944 9

45 'Directive 97/23/EC (PED) 1999: the Pressure Equipment Directive' *Official Journal of the European Communities* 1997 (L181) 1 et seq., corrigendum in *Official Journal of the European Communities* 1997 (L265)

46 'Directive 2000/76/EC of The European Parliament and of The Council of 4 December 2000 on the incineration of waste' *Official Journal of the European Communities* 2000 (L332)

47 Environment Agency website: www.environment-agency.gov.uk/

48 *Fumigation: Health and safety guidance for employers and technicians carrying out fumigation operations* HSG251 HSE Books 2005 ISBN 0 7176 2999 6

49 *Waste Incineration (England and Wales) Regulations 2002* SI 2002/2980 The Stationery Office 2002 ISBN 0 11 044174 5

50 *Pollution Prevention and Control (England and Wales) Regulations 2000* SI 2000/1973 The Stationery Office 2000 ISBN 0 11 099621 6

51 BS EN 12469: 2000 *Biotechnology. Performance criteria for microbiological safety cabinets* British Standards Institution ISBN 0 580 34869 5

52 *Personal Protective Equipment (EC Directive) (Amendment) Regulations 1994* SI 1994/2326 The Stationery Office 1994 ISBN 0 11 045326 3, *Personal Protective Equipment Regulations 2002* SI 2002/1144 The Stationery Office 2002 ISBN 0 11 039830 0 (See also Guidance on the Regulations available on HSE's website: www.hse.gov.uk)

53 'Directive 89/686/EEC of The European Parliament and of the Council of 30 December 1989 on Personal Protective Equipment' *Official Journal of the European Communities* 1989 (L399) 18.

54 BS EN 464: 1994 *Protective clothing. Protection against liquid and gaseous chemicals, including liquid aerosols and solid particles. Test method. Determination of leak-tightness of gas-tight suits (Internal Pressure Test)* British Standards Institution ISBN 0580 22378 7

55 BS 4275: 1974 *Recommendations for the selection, use and maintenance of respiratory protective equipment* British Standards Institution ISBN 0 580 08383 7

56 *Respiratory protective equipment at work: A practical guide* HSG53 (Third edition) HSE Books 2005 ISBN 0 7176 2904 X

57 *Control of Noise at Work Regulations 2005* SI 2005/1643 The Stationery Office 2005 ISBN 0 11 072984 6

58 *Control of laboratory animal allergy* Guidance note EH76 HSE Books 2002

59 *Rabies (Importation of Dogs, Cats and Other Mammals) (England) (Amendment) Order 2004* SI 2004/2364 The Stationery Office 2004 ISBN 0 11 049813 5

60 *Best practice in the accommodation and care of primates used in scientific procedures* Medical Research Council Ethics Guide 2004, available from: www.mrc.ac.uk

61 *An introduction to local exhaust ventilation* HSG37 (Second edition) HSE Books 1993 ISBN 0 7176 1001 2

62 *Accreditation for the inspection of local exhaust ventilation (LEV) plant* RG04 United Kingdom Accreditation Service 2000 (available at: www.ukas.com)

63 *Maintenance, examination and testing of local exhaust ventilation* HSG54 (Second edition) HSE Books 1998 ISBN 0 7176 1485 9

64 *Pressure Systems and Transportable Gas Containers Regulations* 1989 SI 1989/2169 The Stationery Office 1989 ISBN 0 11 098169 3

65 BS 6244: 1982 ISO 5388-1981 *Code of practice for stationary compressors* British Standards Institution ISBN 0 580 12688 9

66 *Pressure Systems Safety Regulations 2000* SI 2000/128 The Stationery Office 2000 ISBN 0 11 085836 0

67 *Chemicals (Hazard Information and Packaging for Supply) Regulations 2002* SI 2002/1689 The Stationery Office 2002 ISBN 0 11 042419 0

68 *Safe use and handling of flammable liquids* HSG140 HSE Books 1996 ISBN 0 7176 0967 7

69 *Regulatory Reform (Fire Safety) Order 2005* SI 2005/1541 The Stationery Office 2005 ISBN 0 11 072945 5

70 *The storage of flammable liquids in containers* HSG51 (Second edition) HSE Books 1998 ISBN 0 7176 1471 9

71 *Control of substances hazardous to health (Fifth edition). The Control of Substances Hazardous to Health Regulations 2002 (as amended). Approved Code of Practice and guidance* L5 (Fifth edition) HSE Books 2005 ISBN 0 7176 2981 3

72 *The safe use of gas cylinders* INDG308(rev1) HSE Books 2002 ISBN 0 7176 2332 7 (out of print)

73 *Radioactive Substances Act 1993 Ch12* The Stationery Office 1993 ISBN 0 10 541293 7 (These Regulations are enforced by The Environment Agency and deal with radioactive wastes)

74 *Ionising Radiations Regulations 1999* (as amended) SI 1999/3232 The Stationery Office 1999 ISBN 0 11 085614 7

75 *Work with ionising radiation. Ionising Radiations Regulations 1999. Approved Code of Practice and guidance* L121 HSE Books 2000 ISBN 0 7176 1746 7

76 *Safety at autoclaves* Guidance Note PM73(rev2) HSE Books 1998 ISBN 07176 1534 0 (out of print)

77 *Pressure Equipment Regulations 1999* SI 1999/2001 The Stationery Office 2001 ISBN 0 11 082790 0

78 *Controlling noise at work. The Control of Noise at Work Regulations 2005. Guidance on Regulations* L108 (Second edition) HSE Books 2005 ISBN 0 7176 6164 4

79 *Protect your hearing or lose it!* Pocket card INDG363(rev1) HSE Books 2005 (single copy free or priced packs of 25 ISBN 0 7176 6166 0)

80 *Control of Vibration at Work Regulations 2005* SI 2005/1093 The Stationery Office 2005 ISBN 0 11 072767 3

81 *Hand-arm vibration. The Control of Vibration at Work Regulations 2005. Guidance on Regulations* L140 HSE Books 2005 ISBN 0 7176 6125 3

82 *Vibration solutions: Practical ways to reduce the risk of hand-arm vibration injury* HSG170 HSE Books 1997 ISBN 0 7176 0954 5

83 *Hand-arm vibration: Advice for employees* Pocket card INDG296(rev1) HSE Books 2005 (single copy free or priced packs of 25 ISBN 0 7176 6118 0)

84 *Control the risks from hand-arm vibration: Advice for employers on the Control of Vibration at Work Regulations 2005* Leaflet INDG175(rev2) HSE Books 2005 (single copy free or priced packs of 10 ISBN 0 7176 6117 2)

85 *Electricity at Work Regulations 1989* SI 1989/635 The Stationery Office 1989 ISBN 0 11 096635 X

86 *Electricity at work: Safe working practices* HSG85 (Second edition) HSE Books 2003 ISBN 0 7176 2164 2

87 *Understanding ergonomics at work: Reduce accidents and ill health and increase productivity by fitting the task to the worker* Leaflet INDG90(rev2) HSE Books 2003 (single copy free or priced packs of 15 ISBN 0 7176 2599 0)

88 *Manual Handling Operations Regulations 1992* SI 1992/2793 The Stationery Office 1992 ISBN 0 11 025920 3

89 *Manual handling. Manual Handling Operations Regulations 1992 (as amended). Guidance on Regulations* L23 (Third edition) HSE Books 2004 ISBN 0 7176 2823 X

90 *Manual handling: Solutions you can handle* HSG115 HSE Books 1994 ISBN 0 7176 0693 7

91 *Health and Safety (Display Screen Equipment) Regulations 1992* SI 1992/2792 The Stationery Office 1992 ISBN 0 11 025919 X

92 *The law on VDUs: An easy guide: Making sure your office complies with the Health and Safety (Display Screen Equipment) Regulations 1992 (as amended in 2002)* HSG90 HSE Books 2003 ISBN 0 7176 2602 4

93 *Working with VDUs* Leaflet INDG36(rev2) HSE Books 2003 (single copy free or priced packs of 10 ISBN 0 7176 2222 3)

While every effort has been made to ensure the accuracy of the references listed in this publication, their future availability cannot be guaranteed.

Useful contacts

National Counter-Terrorism Security Office (NaCTSO)
PO Box 849
London SW1P 1XD
Tel: 020 7931 7142

Office of the Data Protection Commissioner
Wycliffe House
Water Lane
Wilmslow
Cheshire SK9 5AF
Tel: 01625 545745

Further information

HSE produces a wide range of documents. Some are available as printed publications, both priced and free, and others are only accessible via the HSE website, www.hse.gov.uk.

HSE priced and free publications are available by mail order from HSE Books, PO Box 1999, Sudbury, Suffolk CO10 2WA Tel: 01787 881165 Fax: 01787 313995 Website: www.hsebooks.co.uk (HSE priced publications are also available from bookshops and free leaflets can be downloaded from HSE's website: www.hse.gov.uk.)

For information about health and safety ring HSE's Infoline Tel: 0845 345 0055 Fax: 0845 408 9566 Textphone: 0845 408 9577 e-mail: hse.infoline@natbrit.com or write to HSE Information Services, Caerphilly Business Park, Caerphilly CF83 3GG.

British Standards are available from BSI Customer Services, 389 Chiswick High Road, London W4 4AL Tel: 020 8996 9001 Fax: 020 8996 7001 e-mail: cservices@bsi-global.com Website: www.bsi-global.com

The Stationery Office publications are available from The Stationery Office, PO Box 29, Norwich NR3 1GN Tel: 0870 600 5522 Fax: 0870 600 5533 e-mail: customer.services@tso.co.uk Website: www.tso.co.uk (They are also available from bookshops.)

Home Office publications are available from the Home Office Tel: 020 7931 7142

This is guidance prepared, in consultation with HSE, by the Advisory Committee on Dangerous Pathogens (ACDP) which was appointed by the Health and Safety Commission as part of its formal advisory structures. The guidance represents what is considered to be good practice by the members of the Committee. It has been agreed by the Commission. Following this guidance is not compulsory and you are free to take other action. But if you do follow this guidance you will normally be doing enough to comply with the law. Health and safety inspectors seek to secure compliance with the law and may refer to this guidance as illustrating good practice.

This document is available web only at: www.hse.gov.uk/pubns/web09.pdf

Web09 05/06

Published by the Health and Safety Executive