Pathogens and Toxins Guidance

ATCSA 2001 Schedule 5 Order 2007 Notes (SI 2007/929)

Guidance on Notes 1a - d of the Schedule 5 to the Anti-Terrorism, Crime and Security Act 2001 (Modification) Order 2007 (2007/929)

Scope

1. The objective of the Anti-Terrorism, Crime and Security Act (ATCSA) is to build on existing counter-terrorist legislation to ensure that the Government has the necessary powers to counter the threat to the UK. Part 7 of the Act is intended to improve the security of dangerous substances that may be targeted or used by terrorists. This instrument, by providing comprehensive coverage of the substances that could be used in acts of terrorism, is in line with the Act.

2. Since the Act came into force, there has been debate, within government and the UK scientific community, about the substances that are encompassed by the legislation. The original Schedule 5 was a 'classical' list of agents (including pathogens and toxins) from state biological warfare programmes. A cross-government group has reviewed the substances covered by the legislation, and consequently, a new list has been drawn-up. This offers a more comprehensive and meaningful coverage of substances that could be used in acts of terrorism.

3. The list not only covers the wild-type or 'intact' micro-organisms and toxins, but also genetic sequences derived from or coding for such substances. This has led to debate within the scientific community as to the scope of the list and its footnotes. This guidance is intended to provide clarification so that users can ensure that all those substances that might present a security risk in the UK context are identified and kept in a secure manner.

4. The guidance as follows contains several references to *animal pathogens*. From a legislative perspective, it is important to understand that animal pathogens have not simply been added to the original Schedule 5 list of materials. In fact a separate statutory instrument[1] applied the provisions of Part 7 of ATCSA 2001 to a newly created Schedule 5 entitled 'Animal Pathogens'.

5. The legal position is that there are now two separate Schedule 5s to the Act: the modified Schedule 5 entitled 'Pathogens and Toxins' and the new Schedule 5 entitled 'Animal Pathogens'. This new Schedule 5 contains its own 'Notes' section that is very similar to, but not exactly the same as, the 'Notes' that form the basis of this advice. Basically, the Animal Pathogens Notes refer to harm to 'animal health' and not human health.

6. For the sake of simplicity in this guidance, 'animal health' is referenced alongside 'human health' where applicable.

1 Part 7 of the Anti-Terrorism, Crime and Security Act 2001 (Extension to Animal Pathogens) Order 2007 (2007/926)

Guidance

Any reference in this schedule to a micro-organism includes:

(a) intact micro-organisms;

7. This covers viable micro-organisms but excludes non-viable ones and materials such as fixed tissues that may have been treated in such a way as to render viable micro-organisms non-viable.

8. The Act does not apply to micro-organisms or toxins that are packaged or prepared for use as, or are included in, a medicinal product. Regulations made under power of the conferred Act recognise that some of the micro-organisms and toxins are used in clinical, diagnostic and medicinal situations, and consequently exempts them on the basis that they are part of a medicinal product[2]. The exemption will also apply to micro-organisms and toxins that are kept in a form or state that will not allow them to be propagated. Where the micro-organism is intentionally propagated it will be covered by the Act.

9. The only exception to the general exclusion for an organism in its natural state is where it is present as part of a clinical specimen for diagnostic purposes. In that situation, the organism is only exempt where it is disposed of as soon as reasonably practicable after the diagnosis has been made. If continued storage of clinical samples is intended, (for example, for later research or reference purposes), then the micro-organism or toxin will fall within the scope of the Act, and the security provisions will apply. Where doubt exists users should seek advice from Home Office via pathogens@homeoffice.gsi.gov.uk.

(b) micro-organisms which have been genetically modified by any means, but retain the ability to cause serious harm to human health;

10. This covers genetically modified forms of any of the listed micro-organisms if they are still capable of causing serious harm to humans or animals, such that they would require the same level of containment (or higher) as required for the parental organism. The majority of wild-type micro-organisms on the list require containment levels 3 or 4 under the Control of Substances Hazardous to Health (COSHH) regulations, the Specified Animal Pathogens Order (SAPO) 1998 or the Specified Animal Pathogens (Amendment) (England) Order 2006. However, a number that require containment level 2 have been included on the list.

11. It should be noted that this section covers micro-organisms which have been 'genetically modified *by any means'*, which includes techniques such as passage, mutagenesis and protoplast fusion, even though

[2] Paragraph 6 of the Security of Pathogens and Toxins (Exceptions to Dangerous Substances) Regulations 2002 (2002/1281)

these are excluded from the Genetically Modified Organisms (Contained Use) Regulations 2000 (as amended).

12. Established vaccine strains derived from listed micro-organisms, such as the live attenuated Yellow Fever virus vaccine strain 17D, are excluded from the Act, even if they are not incorporated into a medicinal product. This arises because they are incapable of causing serious harm to humans or animals in normal health.

13. A listed micro-organism that has been modified, for example by deletion of genes involved in pathogenicity, will be excluded if it has been demonstrated to be stably attenuated. This would normally require evidence that it does not cause disease in an appropriate animal model. In the case of human pathogens for which there is no suitable animal model, such as some of the listed enteric micro-organisms (e.g. *Salmonella typhi or Shigella flexneri*) data from human volunteer studies will be required. Such evidence is available for a number of well-characterised *S.typhi* strains. Use of published data showing that specific deletions lead to attenuation can be used as supporting evidence, along with molecular data on the particular modified micro-organism.

14. The origin and mechanism of the attenuation should be well understood and will form an important part of the risk assessment. When assessing whether or not a micro-organism is stably attenuated the possibility of reversion or complementation should be considered. The likelihood of reversion will depend on the mechanism of attenuation; deletion mutants are less likely to revert to wild-type than point mutations or conditional lethal mutants. In general, point mutations would not be considered to produce stably attenuated strains, as there is a significant likelihood of reversion to wild-type. However, in some instances, it is recognised that the nature of the attenuation may not be well understood (for example, where it results from passage) but there is a history of safe use. In such instances, the user should seek advice from the Home Office before deciding to work at a lower level of security.

15. The definition of pandemic influenza viruses in an inter-pandemic period poses a particular problem since some subtype A influenza viruses already circulating have the potential to give rise to a pandemic virus. However, certain viruses **can** be identified that pose a particular risk of initiating a future pandemic. These include avian virus subtypes (other than H1 and H3) that have been documented to cause sporadic infections of humans with serious consequences (e.g. H5N1), especially when evidence of limited human to human transmission has prompted WHO to declare pandemic alert phase 3. In addition, two previous pandemic viruses can also be considered to present a future risk; reconstructed 1918 virus (on the basis of its presumed high virulence in humans) and H2N2 virus strains isolated from 1957-1968 (where those under 40 years of age have limited immunity).

(c) any nucleic acid derived from a micro-organism listed in the Schedule (synthetic or naturally derived, contiguous or fragmented, in host chromosomes or in expression vectors) that can encode infectious and/or replication competent forms of any of the listed micro-organisms;

16. This is intended to address situations where a centre is holding the entire genetic sequence of a micro-organism, in a form that can be used to generate an infectious and/or replication competent form of the listed pathogen. For example, this could be as a single cDNA clone, or as a series of plasmids encoding individual genes, such as the pol I/pol II system, with the 8 segments of the H5N1 influenza virus on eight different plasmids. The key point is that the genetic material must be capable of producing the infectious or replicating micro-organism if inserted into permissive cells. A centre holding the 8 plasmids would be covered, but one holding 7 or less would not, as the nucleic acid could not "encode infectious or replication competent forms of the listed micro-organisms". Using currently available technology, this is likely only to apply to listed viruses, as bacterial and eukaryotic genomes are too large and complex to allow regeneration of the parental organism from cloned sequences. Consequently, use of a gene library derived from a listed bacterial or fungal pathogen would not be covered, as it is highly unlikely that the nucleic acid could be used to generate an infectious and/or replication competent agent.

17. Viral replicons would be excluded unless they encode the complete virus sequence. Most viral replicons derived from listed micro-organisms have had their capsid sequences deleted, so that the nucleic acid can replicate and express viral proteins, although these cannot be packaged into viruses. Consequently they would not be covered by the Act unless the missing (capsid) sequences were also being held by the same centre in a form that could be used to reconstitute the wild-type pathogen.

(d) any nucleic acid sequence derived from the micro-organism which when inserted into any other living organism alters or enhances that organism's ability to cause serious harm to human (animal) health.

18. This section considers infectious and/or replication competent micro-organisms which have been modified by the insertion of nucleic acid sequences from any of the listed micro-organisms, such that it alters or enhances its ability to cause serious harm to human or animal health and causing damage, disruption or alarm.

19. A risk assessment for such activities is required under the Genetically Modified Organisms (Contained Use) Regulations 2000 (as amended), and although it is separate legislation from ATCSA, it can be used to inform the decision as to whether or not a genetically modified micro-organism is covered by Schedule 5.

20. For example, if a nucleic acid sequence derived from one of the listed pathogens was inserted into another micro-organism, and there were alterations to tissue tropism, or evasion of host immune system responses, it would be covered if the resulting modified organism was capable of causing serious harm.

21. Such sequences could include the glycoprotein genes (G) from Ebola or Vesicular Stomatitis Virus (VSV), which are commonly used to broaden the host range of other viruses. However, these would only be covered if, when they are inserted into another organism, they produce a micro-organism that is capable of causing serious harm, i.e. requires level 3 or above containment. The key wording is "*which when inserted into another*...". The intention is to cover the final organism, not the sequence. So a replication defective lentiviral vector containing VSV-G would not be covered as it would be unlikely to cause serious human disease, but a replication competent virus whose tropism has been altered through insertion of VSV-G would be covered, if the resulting virus was classified as requiring containment level 3 or above. It is recognised that VSV-G is very widely used to pseudotype a range of viral vectors. The majority of these are stably attenuated, and the pseudotyped vectors can be handled safely at containment level 2 (or lower). Consequently they are not considered to have the ability to cause serious harm to humans or animals, and would not be covered.

22. Annex A provides a consolidated list of the proscribed pathogens and toxins according to the dual Schedule 5 of ATCSA as described in the scope of this document (paragraph 5).

23. Annex B provides a flow diagram to assist users in deciding whether or not their work falls within the scope of the Act.

Annex A

SCHEDULE 5

PATHOGENS AND TOXINS

VIRUSES (AFFECTING HUMANS)

Chikungunya virus
Congo-Crimean haemorrhagic fever virus
Dengue fever virus
Dobrava/Belgrade virus
Eastern equine encephalitis virus
Ebola virus
Everglades virus
Getah virus
Guanarito virus
Hantaan virus
Hendra virus (Equine morbillivirus)
Herpes simiae (B virus)
Influenza viruses (pandemic strains)
Japanese encephalitis virus
Junin virus
Kyasanur Forest virus
Lassa fever virus
Louping ill virus
Lymphocytic choriomeningitis virus
Machupo virus
Marburg virus
Mayaro virus
Middleburg virus
Mobala virus
Monkey pox virus
Mucambo virus
Murray Valley encephalitis virus
Ndumu virus
Nipah virus
Omsk haemorrhagic fever virus
Polio virus
Powassan virus
Rabies virus
Rift Valley fever virus
Rocio virus
Sabia virus
Sagiyama virus
Sin Nombre virus
St Louis encephalitis virus
Tick-borne encephalitis virus (Russian Spring-Summer encephalitis virus)
Variola virus
Venezuelan equine encephalitis virus

Western equine encephalitis virus
West Nile fever virus
Yellow fever virus

VIRUSES (AFFECTING ANIMALS OTHER THAN MAN)

African horse sickness virus
African swine fever virus
Bluetongue virus
Classical swine fever virus
Contagious bovine pleuropneumonia
Foot and mouth disease virus
Goat pox virus
Hendra virus (Equine morbillivirus)
Highly pathogenic avian influenza (HPAI) as defined in Annex I(2) of Council Directive 2005/94/EC
Lumpy skin disease virus
Newcastle disease virus
Peste des petits ruminants virus
Rift Valley fever virus
Rabies and rabies-related Lyssaviruses
Rinderpest virus
Sheep pox virus
Swine vesicular disease virus
Vesicular stomatitis virus

RICKETTSIAE

Coxiella burnetii
Rickettsia prowazeki
Rickettsia rickettsii
Rickettsia typhi (mooseri)

BACTERIA

Bacillus anthracis
Brucella abortus
Brucella canis
Brucella melitensis
Brucella suis
Burkholderia mallei (Pseudomonas mallei)
Burkholderia pseudomallei (Pseudomonas pseudomallei)
Chlamydophila psittaci
Clostridium botulinum
Clostridium perfringens
Enterohaemorrhagic Escherichia coli, serotype 0157 and verotoxin producing strains
Francisella tularensis
Multiple-drug resistant Salmonella paratyphi
Mycobacterium tuberculosis
Salmonella paratyphi A, B, C

Salmonella typhi
Shigella boydii
Shigella dysenteriae
Shigella flexneri
Vibrio cholerae
Yersinia pestis

FUNGI

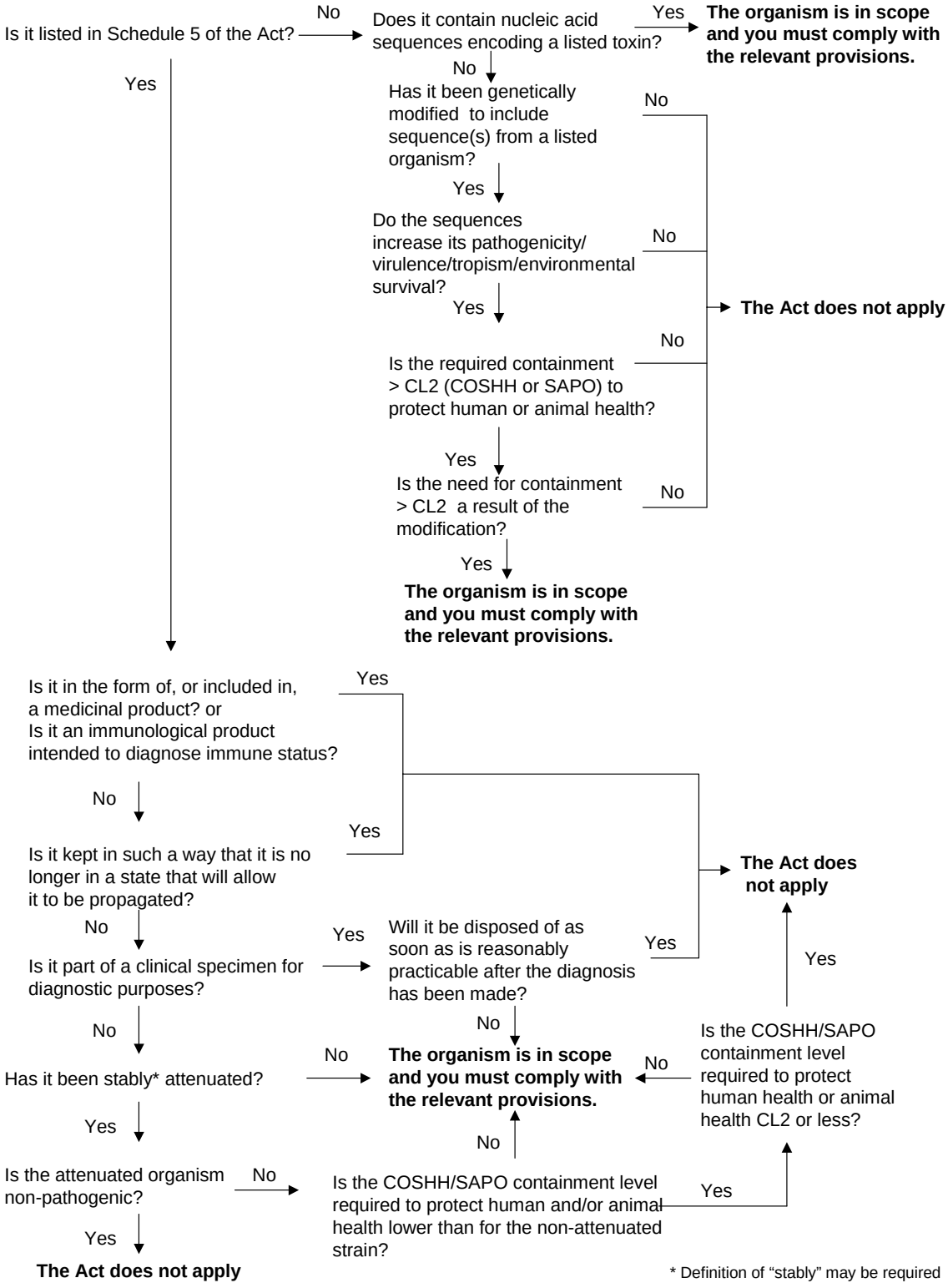
Cladophialophora bantiana
Cryptococcus neoformans

TOXINS

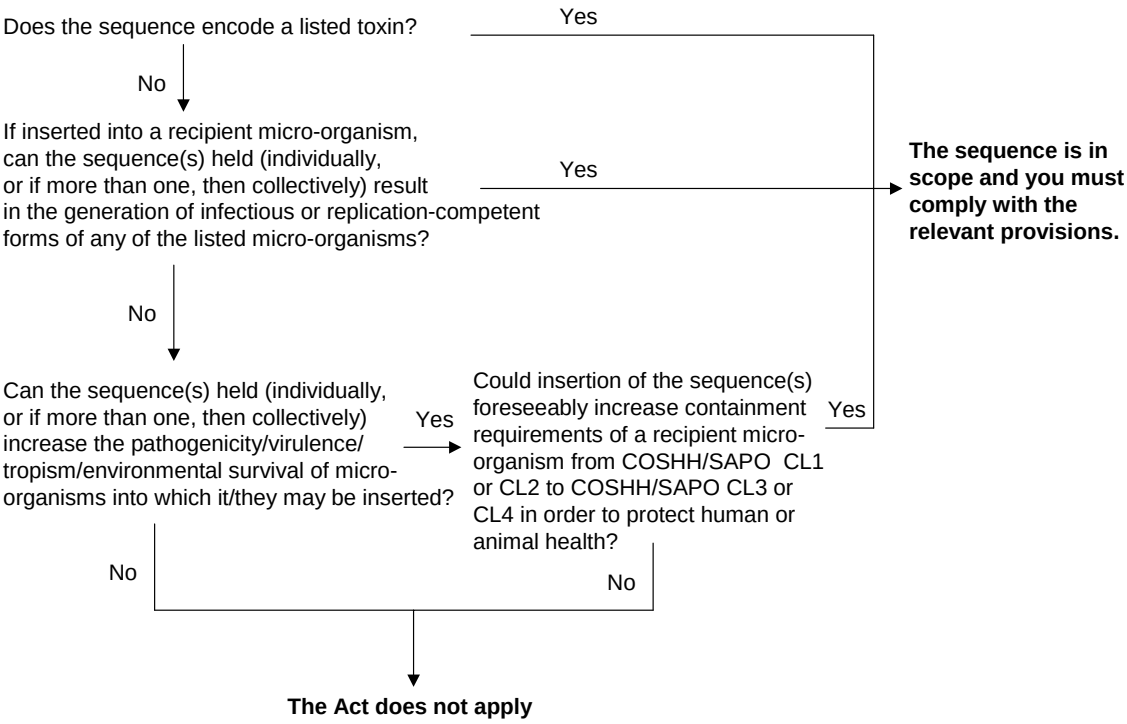
Abrin
Botulinum toxins
Clostridium perfringens epsilon toxin
Clostridium perfringens enterotoxin
Conotoxin
Modeccin toxin
Ricin
Saxitoxin
Shiga and shiga–like toxins
Staphylococcal enterotoxins
Tetrodotoxin
Viscum Album Lectin 1 (Viscumin)
Volkensin toxin

Annex B

Micro-organisms



Nucleic Acid Sequences



Toxins