Appendix D

Agriculture Pathogen Biosafety

The contents of this Appendix were provided by USDA. All questions regarding its contents should be forwarded to the USDA.

Contents

I. INTRODUCTION

Risk assessment and management guidelines for agriculture differ from human public health standards. Risk management for agriculture research is based on the potential economic impact of animal and plant morbidity, and mortality, and the trade implications of disease. Agricultural guidelines take this difference into account. Worker protection is important but great emphasis is placed on reducing the risk of agent escape into the environment. This Appendix describes the facility parameters and work practices of what has come to be known as BSL-3-Ag. BSL-3-Ag is unique to agriculture because of the necessity to protect the environment from an economic, high risk pathogen in a situation where studies are conducted employing large agricultural animals or other similar situations in which the ***facility barriers now serve as primary containment***. Also described are some of the enhancements beyond BSL-3 that may be required by USDA/APHIS when working in the laboratory or vivarium with veterinary agents of concern. This Appendix provides guidance and is not regulatory nor is it meant to describe policy. Conditions for approval to work with specific agricultural agents are provided at the time USDA/APHIS permits a location to work with an agent.

II. BSL-3-AG FOR WORK WITH LOOSE-HOUSED ANIMALS

In agriculture, special biocontainment features are required for certain types of research involving high consequence livestock pathogens in animal species or other research where the room provides the primary containment. To support such research, USDA has developed a special facility designed, constructed and operated at a unique animal containment level called BSL-3-Ag. Using the containment features of the standard ABSL-3 facility as a starting point, BSL-3-Ag facilities are specifically designed to protect the environment by including almost all of the features ordinarily used for BSL-4 facilities as enhancements. All BSL-3-Ag containment spaces must be designed, constructed and certified as primary containment barriers.

The BSL-3-Ag facility can be a separate building, but more often it is an isolated zone within a facility operating at a lower biosafety level, usually at BSL-3. This isolated zone has strictly controlled access with special physical security measures and functions on the "box within a box" principle. All BSL-3-Ag facilities that cannot readily house animals in primary containment devices require the features for an ABSL-3 facility with the following enhancements typical of BSL-4 facilities:

1. Personnel change and shower rooms that provide for the separation of laboratory clothing from animal facility clothing and that control access to the containment spaces. The facility is arranged so that personnel ingress and egress are only through a series of rooms consisting of: a ventilated vestibule with compressible gaskets on the two doors, a "clean" change room outside containment, a shower room at the non-containment/containment boundary, and a "dirty" change room within containment. Complete animal facility clothing (including undergarments, pants and shirts or jump suits, and shoes and gloves) is typically provided in the "dirty" change room, and put on by personnel before entering the research areas. In some facilities, complete animal facility clothing and personal protective equipment are provided in the "clean" change room, where they can be stored and stowed for use without entry into containment. When leaving a BSL-3-Ag animal space that acts as the primary barrier and that contains large volumes of aerosols containing highly infectious agents (an animal room, necropsy room, carcass disposal area, contaminated corridor, etc.), personnel usually would be required to remove "dirty" lab clothing, take a shower, and put on "clean" lab clothing immediately after leaving this high risk animal space and before going to any other part of the BSL-Ag facility. When leaving the facility, these personnel would take another shower at the access control shower and put on their street clothing. Soiled clothing worn in a BSL-3-Ag space is autoclaved before being laundered. Personnel moving from one space within containment to another will follow the practices and procedures described in the biosafety manual specifically developed for the particular facility and adopted by the laboratory director.

2. Access doors are self closing and lockable. Emergency exit doors are provided, but are locked on the outside against unauthorized use. The architect or engineer shall consider the practicality of providing vestibules at emergency exits.

3. Supplies, materials and equipment enter the BSL-3-Ag space only through an airlock, fumigation chamber, an interlocked and double-door autoclave or shower.

4. Double-door autoclaves engineered with bioseals are provided to decontaminate laboratory waste passing out of the containment area. The double doors of the autoclaves must be interlocked so that the outer door can

be opened only after the completion of the sterilizing cycle, and to prevent the simultaneous opening of both doors. All double door autoclaves are situated through an exterior wall of the containment area, with the autoclave unit forming an airtight seal with the barrier wall and the bulk of the autoclave situated outside the containment space so that autoclave maintenance can be performed conveniently. A gas sterilizer, a pass-through liquid dunk tank, or a cold gas decontamination chamber must be provided for the safe removal of materials and equipment that are steam or heat sensitive. Disposable materials must be decontaminated through autoclaving or other validated decontamination method followed by incineration.

5. Dedicated, single pass, directional, and pressure gradient ventilation systems must be used. All BSL-3-Ag facilities have independent air supply and exhaust systems that are operated to provide directional airflow and a negative air pressure within the containment space. The directional airflow within the containment spaces moves from areas of least hazard potential toward areas of greatest hazard potential. A visible means of displaying pressure differentials is provided. The pressure differential display/gauge can be seen inside and outside of the containment space, and an alarm sounds when the preset pressure differential is not maintained. The air supply and exhaust systems must be interlocked to prevent reversal of the directional airflow and positive pressurization of containment spaces in the event of an exhaust system failure.

6. Supply and exhaust air to, and from the containment space, is HEPA filtered. Exhaust air is discharged in such a manner that it cannot be drawn into outside air intake systems. The HEPA filters are outside of containment but are located as near as possible to the containment space to minimize the length of potentially contaminated air ducts. The HEPA filter housings are fabricated to permit scan testing of the filters in place after installation, and to permit filter decontamination before removal. Backup HEPA filter units are strongly recommended to allow filter changes without disrupting research. The most severe requirements for these modern, high level biocontainment facilities include HEPA filters arranged both in series and in parallel on the exhaust side, and parallel HEPA filters on the supply side of the HVAC systems serving “high risk” areas where large amounts of aerosols containing BSL-3-Ag agents could be expected (e.g., animal rooms, contaminated corridors, necropsy areas, carcass disposal facilities, etc.). For these high-risk areas, redundant supply and exhaust fans are recommended. The supply and exhaust air systems should be equipped with pre-filters (80-90% efficient) to prolong the life of the HEPA filters. Air handling systems must provide 100% outside conditioned air to the containment spaces.

7. Liquid effluents from BSL-3-Ag areas must be collected and decontaminated in a central liquid waste sterilization system before disposal into the sanitary sewers. Typically, a heat decontamination system is utilized in these facilities and equipment must be provided to process, heat and hold the contaminated

liquid effluents to temperatures, pressures and times sufficient to inactivate all biohazardous materials that reasonably can be expected to be studied at the facility in the future. The system may need to operate at a wide range of temperatures and holding times to process effluents economically and efficiently. Double containment piping systems with leak alarms and annular space decontaminating capability should be considered for these wastes. Effluents from laboratory sinks, cabinets, floors and autoclave chambers are sterilized by heat treatment. Under certain conditions, liquid wastes from shower rooms and toilets may be decontaminated by chemical treatment systems. Facilities must be constructed with appropriate basements or piping tunnels to allow for inspection of plumbing systems.

8. Each BSL-3-Ag containment space shall have its interior surfaces (walls, floors, and ceilings) and penetrations sealed to create a functional area capable of being certified as airtight. It is recommended that a pressure decay test be used (new construction only). Information on how to conduct a pressure decay test may be found within Appendix 9B of the ARS Facilities Design Manual (Policy and Procedure 242.1M-ARS; http://www.afm.ars.usda.gov/). This requirement includes all interior surfaces of all animal BSL-3-Ag spaces, not just the surfaces making up the external containment boundary. All walls are constructed slab to slab, and all penetrations, of whatever type, are sealed airtight to prevent escape of contained agents and to allow gaseous fumigation for biological decontamination. This requirement prevents cross contamination between individual BSL-3-Ag spaces and allows gaseous fumigation in one space without affecting other spaces. Exterior windows and vision panels, if required, are breakage-resistant and sealed. Greenhouses constructed to meet the BSL-3-Ag containment level will undergo the following tests, or the latest subsequent standards: (a) an air infiltration test conducted according to ASTM E 283-91; (b) a static pressure water resistance test conducted according to ASTM E 331-93; and (c) a dynamic pressure water resistance test conducted according to AAMA 501.1-94.

9. All ductwork serving BSL-3-Ag spaces shall be airtight (pressure tested-consult your facility engineer for testing and certification details).

10. The hinges and latch/knob areas of all passage doors shall be sealed to airtight requirements (pressure decay testing).

11. All airlock doors shall have air inflated or compressible gaskets. The compressed air lines to the air inflated gaskets shall be provided with HEPA filters and check valves.

12. Restraining devices shall be provided in large animal rooms.

13. Necropsy rooms shall be sized and equipped to accommodate large farm animals.

14. Pathological incinerators, or other approved means, must be provided for the safe disposal of the large carcasses of infected animals. Redundancy and the use of multiple technologies need to be considered and evaluated.

15. HEPA filters must be installed on all atmospheric vents serving plumbing traps, as near as possible to the point of use, or to the service cock, of central or local vacuum systems, and on the return lines of compressed air systems. All HEPA filters are installed to allow in-place decontamination and replacement. All traps are filled with liquid disinfectant.

16. If BSCs are installed they should be located such that their operation is not adversely affected by air circulation and foot traffic. Class II BSCs use HEPA filters to treat their supply and exhaust air. Selection of the appropriate type of Class II BSCs will be dependent upon the proposed procedures and type of reagents utilized. BSC selection should be made with input from a knowledgeable safety professional well versed on the operational limitations of class II biohazard cabinetry. Supply air to a Class III cabinet is HEPA filtered, and the exhaust air must be double filtered (through a cabinet HEPA and then through a HEPA in a dedicated building exhaust system) before being discharged to the atmosphere.

III. BSL-3 AND ABSL-3 PLUS POTENTIAL FACILITY ENHANCEMENTS FOR AGRICULTURE AGENT PERMITTING

The descriptions and requirements listed above for BSL-3-Ag studies are based on the use of high-risk organisms in animal systems or other types of agriculture research where the facility barriers, usually considered secondary barriers, now act as primary barriers. Certain agents that typically require a BSL-3-Ag facility for research that utilizes large agricultural animals may be studied in small animals in an enhanced BSL-3 laboratory or enhanced ABSL-3 when the research is done within primary containment devices. In these situations the facility no longer serves as the primary barrier as with the large animal rooms. Therefore, when manipulating high consequence livestock pathogens in the laboratory or small animal facility, facility design and work procedures must meet the requirements of BSL-3 or ABSL-3 with additional enhancements unique to agriculture. Agriculture enhancements are agent, site and protocol dependent. The facility may have personnel enter and exit through a clothing change and shower room, have a double-door autoclave and/or fumigation chamber, HEPA filter supply and exhaust air, and a validated or approved system in place to decontaminate research materials and waste. Surfaces must be smooth to support wipe-down decontamination and penetrations should be sealed and the room capable of sealing in case gaseous decontamination is required. Because all work with infectious material is conducted within primary containment, there is no requirement for pressure decay testing the room itself.

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The need for any potential agriculture enhancements is dependant upon a risk assessment. Therefore, after an assessment and in consultation with USDA/APHIS, the required agriculture enhancement(s) may include:

1. Personnel change and shower rooms that provide for the separation of street clothing from laboratory clothing and that control access to the containment spaces. The facility is arranged so that personnel ingress and egress are only through a series of rooms (usually one series for men and one for women) consisting of: a ventilated vestibule with a “clean” change room outside containment, a shower room at the non-containment/containment boundary, and a “dirty” change room within containment. Complete laboratory clothing (including undergarments, pants and shirts or jump suits, and shoes and gloves) is provided in the “dirty” change room, and put on by personnel before entering the research areas. In some facilities, complete laboratory clothing and personal protective equipment are provided in the “clean” change room, where they can be stored and stowed for use without entry into containment. When leaving a BSL-3 enhanced space, personnel usually would be required to remove their “dirty” laboratory clothing, take a shower, and put on “clean” laboratory clothing immediately after leaving the BSL-3 enhanced space and before going to any other part of the facility. Soiled clothing worn in a BSL-3 enhanced space should be autoclaved before being laundered outside of the containment space. Personnel moving from one space within containment to another will follow the practices and procedures described in the biosafety manual specifically developed for the particular facility and adopted by the laboratory director.

2. Access doors to these facilities are self closing and lockable. Emergency exit doors are provided but are locked on the outside against unauthorized use. The architect or engineer shall consider the practicality of providing vestibules at emergency exits.

3. Supplies, materials and equipment enter the BSL-3 enhanced space only through the double-door ventilated vestibule, fumigation chamber or an interlocked and double-door autoclave.

4. Double-door autoclaves engineered with bioseals are provided to decontaminate laboratory waste passing out of the containment area. The double doors of the autoclaves must be interlocked so that the outer door can be opened only after the completion of the sterilizing cycle, and to prevent the simultaneous opening of both doors. All double door autoclaves are situated through an exterior wall of the containment area, with the autoclave unit forming an airtight seal with the barrier wall and the bulk of the autoclave situated outside the containment space so that autoclave maintenance can be performed conveniently. A gas sterilizer, a pass-through liquid dunk tank, or a cold gas decontamination chamber must be provided for the safe removal of materials and equipment that are steam or heat sensitive. All other materials

must be autoclaved or otherwise decontaminated by a method validated to inactivate the agent before being removed from the BSL-3 enhanced space. Wastes and other materials being removed from the BSL-3 enhanced space must be disposed of through incineration or other approved process.

5. Dedicated, single pass, directional, and pressure gradient ventilation systems must be used. All BSL-3 enhanced facilities have independent air supply and exhaust systems operated to provide directional airflow and a negative air pressure within the containment space. The directional airflow within the containment spaces moves from areas of least hazard potential toward areas of greatest hazard potential. A visible means of displaying pressure differentials is provided. The pressure differential display/gauge can be seen inside and outside of the containment space, and an alarm sounds when the preset pressure differential is not maintained. Supply and exhaust air to and from the containment space is HEPA filtered, with special electrical interlocks to prevent positive pressurization during electrical or mechanical breakdowns.

6. The exhaust air is discharged in such a manner that it cannot be drawn into outside air intake systems. HEPA filters located outside of the containment barrier are located as near as possible to the containment space to minimize the length of potentially contaminated air ducts. The HEPA filter housings are fabricated to permit scan testing of the filters in place after installation, and to permit filter decontamination before removal. Backup parallel HEPA filter units are strongly recommended to allow filter changes without disrupting research. Air handling systems must provide 100% outside conditioned air to the containment spaces.

7. Contaminated liquid wastes from BSL-3 enhanced areas must be collected and decontaminated by a method validated to inactivate the agent being used before disposal into the sanitary sewers. Treatment requirement will be determined by a site-specific, agent-specific risk assessment. Floor drains are discouraged in ABSL-3 and BSL-3 agriculture enhanced laboratories lacking a liquid waste central sterilization system. If floor drains are present they should be capped and sealed. Facilities should be constructed with appropriate basements or piping tunnels to allow for inspection of plumbing systems, if a central liquid waste sterilization system is used.

8. Each BSL-3 enhanced containment space shall have its interior surfaces (walls, floors, and ceilings) and penetrations sealed to create a functional area capable of being decontaminated using a gaseous or vapor phase method. All walls are contiguous with the floor and ceiling, and all penetrations, of whatever type, are sealed. Construction materials should be appropriate for the intended end use. Exterior windows and vision panels, if required, are breakage-resistant and sealed.

9. All exhaust ductwork prior to the HEPA exhaust filter serving BSL-3 enhanced spaces shall be subjected to pressure decay testing before acceptance of the facility for use. Consult your facility engineer for testing and commissioning details.

IV. PATHOGENS OF VETERINARY SIGNIFICANCE

Some pathogens of livestock, poultry and fish may require special laboratory design, operation, and containment features. This may be BSL-3, BSL-3 plus enhancements or BSL-4 and for animals ABSL-2, ABSL-3 or BSL-3-Ag. The importation, possession, or use of the following agents is prohibited or restricted by law or by USDA regulations or administrative policies.

This Appendix does not cover manipulation of diagnostic samples; however, if a foreign animal disease agent is suspected, samples should be immediately forwarded to a USDA diagnostic laboratory (The National Veterinary Services Laboratories, Ames, IA or the Foreign Animal Disease Diagnostic Laboratory, Plum Island, NY). A list of agents and their requirements follows.

African horse sickness virus[a,b]	Louping ill virus [a]
African swine fever virus [a, b, c]	Lumpy skin disease virus [a, b, c]
Akabane virus [b]	Malignant catarrhal fever virus (exotic strains or alcelaphine herpesvirus type 1) [b]
Avian influenza virus (highly pathogenic) [a, b, c]	Menangle virus [b]
Bacillus anthracis [a, b]	*Mycobacterium bovis*
Besnoitia besnoiti	*Mycoplasma agalactiae*
Bluetongue virus (exotic) [a, b]	*Mycoplasma mycoides* subsp. *mycoides*, (small colony type) [a, b, c]
Borna disease virus	*Mycoplasma capricolum* [a, b, c]
Bovine infectious petechial fever agent	Nairobi sheep disease virus (Ganjam virus)
Bovine spongiform encephalopathy prion [b]	Newcastle disease virus (velogenic strains) [a, b, c]
Brucella abortus [a, b]	Nipah virus [a, b, d]
Brucella melitensis [a, b]	Peste des petits ruminants virus (plague of small ruminants) [a, b, c]
Brucella suis [a, b]	Rift Valley fever virus [a, b, c]
Burkholderia mallei/Pseudomonas mallei	Rinderpest virus [a, b, c]

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(Glanders) [a, b]	
Burkholderia pseudomallei [a, b]	Sheep pox virus [a, b]
Camelpox virus [b]	Spring Viremia of Carp virus
Classical swine fever virus[a, b, c]	Swine vesicular disease virus [b]
Coccidioides immitis [b]	Teschen disease virus [a]
Cochliomyia hominivorax (Screwworm)	*Theileria annulata*
Coxiella burnetti (Q fever) [b]	*Theileria lawrencei*
Ephemeral fever virus	*Theileria bovis*
Ehrlichia (Cowdria) ruminantium (heartwater) [b]	*Theileria hirci*
Eastern equine encephalitis virus [a, b]	*Trypanosoma brucei*
Foot and mouth disease virus [a, b, c,]	*Trypanosoma congolense*
Francisella tularensis [b]	*Trypanosoma equiperdum (dourine)*
Goat pox [a, b]	*Trypanosoma evansi*
Hemorrhagic disease of rabbits virus	*Trypanosoma vivax*
Hendra virus [a, b, d]	Venezuelan equine encephalomyelitis virus [a, b]
Histoplasma (Zymonema) farciminosum	Vesicular exanthema virus
Infectious salmon anemia virus	Vesicular stomatitis virus (exotic) [a, b]
Japanese encephalitis virus [a, b]	Wesselsbron disease virus

Notes:
[a] Export license required by Department of Commerce (See http://www.bis.doc.gov/index.htm).
[b] Agents regulated as Select Agents under the Bioterrorism Act of 2002. Possession of these agents requires registration with either the CDC or APHIS and a permit issued for interstate movement or importation by APHIS-VS. Most require BSL-3/ABSL-3 or higher containment (enhancements as described in this Appendix or on a case-by-case basis as determined by APHIS-VS).
[c] Requires BSL-3-Ag containment for all work with the agent in loose-housed animals.
[d] Requires BSL-4 containment for all work with the agent.

A USDA/APHIS import or interstate movement permit is required to obtain any infectious agent of animals or plants that is regulated by USDA/APHIS. An import permit is also required to import any livestock or poultry product such as blood, serum, or other tissues.

V. SUMMARIES OF SELECTED AGRICULTURE AGENTS

African Swine Fever Virus (ASFV)

ASF is a tick-borne and contagious, febrile, systemic viral disease of swine.[1,2,3] The ASF virus (ASFV) is a large (about 200 nm) lipoprotein-enveloped, icosahedral, double-stranded DNA virus in the family *Asfarviridae*, genus *Asfivirus*. This virus is quite stable and will survive over a wide range of pH. The virus will survive for 15 weeks in putrefied blood, three hours at 50^{o}C, 70 days in blood on wooden boards, 11 days in feces held at room temperature, 18 months in pig blood held at 4^{o}C, 150 days in boned meat held at 39^{o}F, and 140 days in salted dried hams. Initially, domestic and wild pigs (Africa: warthog, bush pig, and giant forest hog; Europe: feral pig) were thought to be the only hosts of ASFV. Subsequently, researchers showed that ASFV replicates in *Ornithodoros* ticks and that there is transstadial, transovarial, and sexual transmission. ASF in wild pigs in Africa is now believed to cycle between soft ticks living in warthog burrows and newborn warthogs. *Ornithodoros* ticks collected from Haiti, the Dominican Republic, and southern California have been shown to be capable vectors of ASFV, but in contrast to the African ticks, many of the ticks from California died after being infected with ASFV. Because ASFV-infected ticks can infect pigs, ASFV is the only DNA virus that can qualify as an arbovirus.

Even though the soft tick has been shown to be a vector (and in Africa probably the reservoir of ASFV), the primary method of spread from country to country has been through the feeding of uncooked garbage containing ASFV-infected pork scraps to pigs.

Aerosol transmission is not important in the spread of ASF. Because ASFV does not replicate in epithelial cells, the amount of virus shed by an ASF-infected pig is much less than the amount of virus shed by a hog-cholera-infected pig. The blood of a recently infected pig contains a very high ASFV titer.

LABORATORY SAFETY

Humans are not susceptible to ASFV infection. The greatest risk of working with the virus is the escape of the organism into a susceptible pig population, which would necessitate USDA emergency procedures to contain and eradicate the disease.

CONTAINMENT RECOMMENDATIONS

ASF is considered a foreign animal disease in the United States. Due to the highly contagious nature of the agent and the severe economic consequences of disease in the United States, this organism should only be handled *in vitro* in a BSL-3 laboratory with enhancements as required by the USDA and *in vivo* in a USDA-approved BSL-3-Ag facility for loosely housed animals. Special consideration should be given to infected vector control.

SPECIAL ISSUES

The importation, possession, or use of this agent is prohibited or restricted by law or by USDA regulations or administrative policies. A USDA/APHIS import or interstate movement permit is required to obtain this agent or any livestock or poultry product, such as blood, serum, or other tissues containing the agent.

African Horse Sickness Virus (AHSV)

AHSV is a member of genus *Orbivirus* in the family *Reoviridae*. Nine serotypes, numbers 1-9, are recognized. AHSV grows readily in embryonated chicken eggs, suckling mice, and a variety of standard cell cultures. AHSV infects and causes viremia in equids. Most horses die from the disease, about half of donkeys and most mules survive, but zebras show no disease. Viremias may last up to one month despite the rapid development of neutralizing antibodies. AHSV may cause disease in dogs, but these are not thought to be important in the natural history of the disease.[4,5]

AHSV has been recognized in central Africa and periodically spreads to naive populations in South and North Africa, the Iberian Peninsula, the Middle East, Pakistan, Afghanistan, and India. AHSV is vectored by *Culicoides* species and perhaps by mosquitoes, biting flies, and ticks limiting viral spread to climates and seasons favorable to the vectors. At least one North American *Culicoides* species transmits AHSV. AHSV may infect carnivores that consume infected animals but these are not thought to be relevant to natural transmission to equids.

OCCUPATIONAL INFECTIONS

Encephalitis and uveochorioretinitis were observed in four laboratory workers accidentally exposed to freeze-dried modified live vaccine preparations. Although AHSV could not be conclusively linked to disease, all four had neutralizing antibodies. Encephalitis was documented in experimentally infected monkeys.

LABORATORY SAFETY

Virus may be present in virtually any sample taken from an infected animal, but the highest concentrations are found in spleen, lung, and lymph nodes. The only documented risk to laboratory workers involves aerosol exposure to large amounts of vaccine virus. AHSV is unusually stable in blood or serum stored at 4°C.

Containment Recommendations

AHS is considered a foreign animal disease in the United States. Due to the severe economic consequences of disease presence in the United States, this organism should only be handled *in vitro* in a BSL-3 laboratory with enhancements as required by the USDA and *in vivo* in a USDA-approved ABSL-3 animal facility with enhancements. Blood, serum, or tissues taken from equids in areas where AHSV exists are potential

means of transmitting the agent long distances. Special consideration should be given to infected vector containment.

SPECIAL ISSUES

The importation, possession, or use of this agent is prohibited or restricted by law or by USDA regulations or administrative policies. A USDA/APHIS import or interstate movement permit is required to obtain this agent or any livestock or poultry product, such as blood, serum, or other tissues containing the agent.

Akabane Virus (AKAV)

AKAV is a member of the genus *Orthobunyavirus* in the Simbu serogroup of the family *Bunyaviridae*. The Simbu serogroup also includes *Aino, Peaton,* and *Tinaroo* viruses that can cause similar disease. Experimental infection of pregnant hamsters leads to death of the fetus. This virus grows and causes disease in chick embryos. Isolated in suckling mice and hamster lung cell cultures, AKAV is an important cause of disease in ruminants. The virus does not cause overt disease in adults but infects the placenta and fetal tissues in cattle, sheep, and goats to cause abortions, stillbirths, and congenital malformations. The broad range of clinical signs in the fetus is related primarily to central nervous system damage that occurs during the first trimester of pregnancy.[6,7]

AKAV is not known to infect or cause disease in humans; concern focuses only on effects to agriculture and wildlife. Common names of disease include congenital arthrogryposis-hydranencephaly syndrome, Akabane disease, acorn calves, silly calves, curly lamb disease, curly calf disease, and dummy calf disease. The host range of naturally occurring Akabane disease appears limited to cattle, sheep, swine, and goats but other animals including swine and numerous wildlife species become infected. AKAV is an Old World virus, being found in Africa, Asia, and Australia. Disease is unusual in areas where the virus is common because animals generally become immune before pregnancy. AKAV spreads naturally only in gnat and mosquito insect vectors that become infected after feeding on viremic animals.

LABORATORY SAFETY

AKAV may be present in blood, sera, and tissues from infected animals, as well as vectors from endemic regions. Parenteral injection of these materials into naive animals and vector-borne spread to other animals represents a significant risk to agricultural interests.

Containment Recommendations

Akabane disease is considered a foreign animal disease in the United States. Due to the severe economic consequences of disease presence in the United States, this organism should only be handled *in vitro* in a BSL-3 laboratory with enhancements as required by

the USDA and *in vivo* in a USDA-approved ABSL-3 animal facility with enhancements. Special consideration should be given to infected vector containment.

SPECIAL ISSUES

Although it is virtually certain AKAV will grow and cause disease in New World livestock, it is not known if it will cause viremias in New World wildlife high enough to infect vectors, if it can be vectored by New World insects, or if it will cause disease in New World wildlife. Because fetal disease may not become evident until months after virus transmission, an introduction into a new ecosystem may not be recognized before the virus has become firmly entrenched.

The importation, possession, or use of this agent is prohibited or restricted by law or by USDA regulations or administrative policies. A USDA/APHIS import or interstate movement permit is required to obtain this agent or any livestock or poultry product, such as blood, serum, or other tissues containing the agent.

Bluetongue Virus (BTV)

BTV is a member of the family *Reoviridae*, genus *Orbivirus*. There are 24 recognized serotypes numbered 1-24. BTV is notable for causing disease in sheep and cattle and is very similar to other orbiviruses that cause disease in deer (epizootic hemorrhagic disease of deer virus) and horses (AHSV), and a few that cause disease in man (Colorado tick fever virus and others). These viruses have dsRNA genomes distributed amongst 10 segments, enabling efficient reassortment. Growth on a wide variety of cultured cells is usually cytocidal. Growth in animals results in viremia within three to four days that endures as long as 50 days despite the presence of high levels of neutralizing antibodies.[8,9]

BTV infects all ruminants, but bluetongue disease is unusual except in sheep and is unpredictable even in sheep. Disease is evidenced by fever, hyperemia, swelling, and rarely erosions and ulceration of the buccal and nasal mucosa. Hyperemia of the coronary bands of the hooves may cause lameness. In the worst cases, the disease progresses through weakness, depression, rapid weight loss, prostration, and death. Maternal transmission to the fetus may cause abortion or fetal abnormalities in the first trimester. Bluetongue disease also occurs in cattle but is rarely diagnosed. BTV may infect fetal calves and result in abortion or fetal brain damage. The full host range of BTV is still unknown but includes wild ruminants, neonatal mice, dogs, and chicken embryos.

BTV infection occurs in tropical, subtropical, and temperate climates where the *Culicoides* vectors exist. Global warming may be expanding the geographic range of *Culicoides*, and therefore BTV, into higher latitudes. Most countries have a unique assortment of the 24 serotypes. For example, BTV serotypes 2, 10, 11, 13, and 17 are currently active in the United States, but serotypes 1, 3, 4, 6, 8, 12, and 17 were present in the Caribbean basin when last surveyed. Concern over the spread of individual serotypes by trade in animals and animal products has engendered costly worldwide trade barriers.

The primary natural mode of transmission is by *Culicoides* midges. Only a few of more than 1,000 species of *Culicoides* transmit BTV. A strong correlation between the vector species and the associated BTV suggests these viruses may have adapted to their local vector. Thus, BTV does not exist in areas such as the Northeast United States where the local *Culicoides* fails to transmit BTV. Virus is present in semen at peak of viremia, but this is not considered a major route of transmission. Because of the prolonged viremia, iatrogenic transmission is possible. Only modified-live (attenuated) virus vaccines are available and a vaccine for only one serotype is currently available in the United States.

LABORATORY SAFETY

BTV is not known to cause disease in humans under any conditions. BTV commonly enters the laboratory in blood samples. The virus is stable at -70°C and in blood or washed blood cells held at 4°C. Sera prepared from viremic animals may represent some risk if introduced parenterally into naive animals. Blood, sera, and bovine semen can carry BTV across disease control boundaries.

Containment Recommendations

The most significant threat from BTV occurs when virus is inoculated parenterally into naive animals. If appropriate *Culicoides* are present, virus can be transmitted to other hosts. Therefore, BTV-infected animals must be controlled for the two-month period of viremia and protected against *Culicoides* by physical means and/or performing experiments at least two months before local *Culicoides* emerge. Thus, BTV exotic to the United States should only be handled *in vitro* in a BSL-3 laboratory with enhancements as required by the USDA and *in vivo* in a USDA-approved ABSL-3 with enhancements. Special consideration should be given to infected vector containment. Special containment is only needed when working with serotypes of BTV that are exotic to the country or locality. BTV on laboratory surfaces is susceptible to 95% ethanol and 0.5% sodium hypochlorite solution.

SPECIAL ISSUES

The importation, possession, or use of this agent is prohibited or restricted by law or by USDA regulations or administrative policies. A USDA/APHIS import or interstate movement permit is required to obtain this agent or any livestock or poultry product, such as blood, serum, or other tissues containing the agent.

Classical Swine Fever Virus (Hog Cholera)

Classical swine fever is a highly contagious viral disease of swine that occurs worldwide in an acute, a subacute, a chronic, or a persistent form.[10-12] In the acute form, the disease is characterized by high fever, severe depression, multiple superficial and internal hemorrhages, and high morbidity and mortality. In the chronic form, the signs of depression, anorexia, and fever are less severe than in the acute form, and recovery is

occasionally seen in mature animals. Transplacental infection with viral strains of low virulence often results in persistently infected piglets, which constitute a major cause of virus dissemination to noninfected farms. Although minor antigenic variants of classical swine fever virus (CSFV) have been reported, there is only one serotype. Hog cholera virus is a lipid-enveloped pathogen belonging to the family *Flaviviridae*, genus *Pestivirus*. The organism has a close antigenic relationship with the bovine viral diarrhea virus (BVDV) and the border disease virus (BDV). In a protein-rich environment, hog cholera virus is very stable and can survive for months in refrigerated meat and for years in frozen meat. The virus is sensitive to drying (desiccation) and is rapidly inactivated by a pH of less than 3 and greater than 11.

The pig is the only natural reservoir of CSFV. Blood, tissues, secretions and excretions from an infected animal contain virus. Transmission occurs mostly by the oral route, though infection can occur through the conjunctiva, mucous membrane, skin abrasion, insemination, and percutaneous blood transfer (e.g., common needle, contaminated instruments). Airborne transmission is not thought to be important in the epizootiology of classical swine fever. Introduction of infected pigs is the principal source of infection in classical swine fever-free herds. Farming activities such as auction sales, livestock shows, visits by feed dealers, and rendering trucks also are potential sources of contagion. Feeding of raw or insufficiently cooked garbage is a potent source of hog cholera virus. During the warm season, insect vectors common to the farm environment may spread hog cholera virus mechanically. There is no evidence, however, that hog cholera virus replicates in invertebrate vectors.

LABORATORY SAFETY

Humans being are not susceptible to infection by CSFV. The greatest risk of working with these viruses is the escape of the organism into susceptible domestic or feral pig populations, which would necessitate USDA emergency procedures to contain and eradicate the diseases.

Containment Recommendations

The virus is considered cause of a foreign animal disease in the United States. Due to the highly contagious nature of the agent and the severe economic consequences of disease presence in the United States, this organism should only be handled *in vitro* in a BSL-3 laboratory with enhancements as required by the USDA and *in vivo* in a USDA-approved BSL-3-Ag facility for loosely housed animals. Laboratory workers should have no contact with susceptible hosts for five days after working with the agent.

SPECIAL ISSUES

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Contagious Bovine Pleuropneumonia Agent (CBPP)

CBPP is a highly infectious acute, subacute, or chronic disease, primarily of cattle, affecting the lungs and occasionally the joints, caused by *Mycoplasma mycoides mycoides*.[13-15] Contagious bovine pleuropneumonia is caused by *M. mycoides mycoides* small-colony type (SC type). *M. mycoides mycoides* large-colony type is pathogenic for sheep and goats but not for cattle. *M. mycoides mycoides* (SC type) survives well only *in vivo* and is quickly inactivated when exposed to normal external environmental conditions. The pathogen does not survive in meat or meat products and does not survive outside the animal in nature for more than a few days. Many of the routinely used disinfectants will effectively inactivate the organism.

CBPP is predominantly a disease of the genus *Bos*; both bovine and zebu cattle are naturally infected. There are many reported breed differences with respect to susceptibility. In general, European breeds tend to be more susceptible than indigenous African breeds. In zoos the infection has been recorded in bison and yak. Although it has been reported that the domestic buffalo (*Bubalus bubalis*) is susceptible, the disease is difficult to produce experimentally in this species.

CBPP is endemic in most of Africa. It is a problem in parts of Asia, especially India and China. Periodically, CBPP occurs in Europe, and outbreaks within the last decade have occurred in Spain, Portugal, and Italy. The disease was eradicated from the United States in the nineteenth century, and it is not present currently in the Western hemisphere.

CBPP is spread by inhalation of droplets from an infected, coughing animal. Consequently, relatively close contact is required for transmission to occur. Outbreaks usually begin as the result of movement of an infected animal into a naive herd. There are limited anecdotal reports of fomite transmission, but fomites are not generally thought to be a problem.

LABORATORY SAFETY

Humans are not susceptible to infection by CBPP. The greatest risk of working with these mycoplasma is the escape of the organism into susceptible domestic bovine populations, which would necessitate USDA emergency procedures to contain and eradicate the diseases.

Containment Recommendations

CBPP is considered a foreign animal disease in the United States. Due to the highly contagious nature of the agent and the severe economic consequences of disease presence in the United States, this organism should only be handled *in vitro* in a BSL-3 laboratory with enhancements as required by the USDA and *in vivo* in a USDA-approved BSL-3-Ag facility for loosely housed animals.

Appendix D

SPECIAL ISSUES

The importation, possession, or use of this agent is prohibited or restricted by law or by USDA regulations or administrative policies. A USDA/APHIS import or interstate movement permit is required to obtain this agent or any livestock or poultry product, such as blood, serum, or other tissues containing the agent.

Contagious Caprine Pleuropneumonia Agent (CCPP)

CCPP is an acute highly contagious disease of goats caused by a mycoplasma and characterized by fever, coughing, severe respiratory distress, and high mortality.[16-18] The principal lesion at necropsy is fibrinous pleuropneumonia. The causative agent of CCPP is considered to be *M. mycoides capri* (type strain PG-3) or a new mycoplasma *M. capricolum subsp. capripneumoniae* (designated F-38).[19-21] Neither of these agents occurs in North America.

M. mycoides mycoides has also been isolated from goats with pneumonia. This agent (the so-called large colony or LC variant of *M. mycoides mycoides*) usually produces septicemia, polyarthritis, mastitis, encephalitis, conjunctivitis, hepatitis, or pneumonia in goats. Some strains of this agent (LC variant) will cause pneumonia closely resembling CCPP, but the agent is not highly contagious and is not considered to cause CCPP. It does occur in North America. *M. capricolum capricolum*, a goat pathogen commonly associated with mastitis and polyarthritis in goats, can also produce pneumonia resembling CCPP, but it usually causes severe septicemia and polyarthritis. This agent (which does occur in the United States) is closely related to mycoplasma F-38 but can be differentiated from it using monoclonal antibodies.

CCPP is a disease of goats, and where the classical disease has been described, only goats were involved in spite of the presence of sheep and cattle. Mycoplasma F-38, the probable cause of the classic disease, does not cause disease in sheep or cattle. *M. mycoides capri*, the other agent considered a cause of CCPP, will result in a fatal disease in experimentally inoculated sheep and can spread from goats to sheep. It is however, not recognized as a cause of natural disease in sheep.

CCPP has been described in many countries of Africa, the Middle East, Eastern Europe, the former Soviet Union, and the Far East. It is a major scourge in many of the most important goat-producing countries in the world and is considered by many to be the world's most devastating goat disease.

CCPP is transmitted by direct contact through inhalation of infective aerosols. Of the two known causative agents, F-38 is far more contagious. Outbreaks of the disease often occur after heavy rains (e.g., after the monsoons in India) and after cold spells. This is probably because recovered carrier animals start shedding the mycoplasmas after the stress of sudden climatic change. It is believed that a long-term carrier state may exist.

LABORATORY SAFETY

Humans are not susceptible to infection by the agent that causes CCPP. The greatest risk of working with this mycoplasma is the escape of the organism into susceptible domestic caprine populations, which would necessitate USDA emergency procedures to contain and eradicate the diseases.

Containment Recommendations

CCPP is considered a foreign animal disease in the United States. Due to the highly contagious nature of the agent and the severe economic consequences of disease in the United States, this organism should only be handled *in vitro* in a BSL-3 laboratory with enhancements as required by the USDA and *in vivo* in a USDA-approved BSL-3-Ag facility for loosely housed animals.

SPECIAL ISSUES

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Foot and Mouth Disease Virus (FMD)

FMD is a severe, highly communicable viral disease of cloven-hoofed animals (cattle, swine, sheep, and goats), causing fever, malaise, vesicular lesions in affected livestock and in some cases death in young animals due to myocardial lesions.[22] It can also affect a variety of wild ruminants (e.g., deer, bison). FMD is one of the most devastating diseases of livestock, causing large economic losses when introduced to FMD-free countries. The etiologic agent, FMD virus (FMDV), is a member of the *aphtovirus* genus, family *picornaviridae* with seven serotypes (A, O, C, Asia1, SAT1, SAT2 and SAT3).[23] Humans are considered accidental hosts for FMDV and rarely become infected or develop clinical disease. Historically, humans have been exposed to large quantities of FMDV both during natural outbreaks among large herds of animals and in laboratory settings. Despite this, there has been an extremely low incidence of human infections reported and many have been anecdotal. Reports of fever, headaches and vesicles in the skin (especially at an accidental inoculation site) and oral mucosa have been associated with documented FMDV infections. The symptoms can be easily mistaken with those of Hand, Foot and Mouth Disease caused by coxsackie A viruses. On the other hand, humans have been shown to carry virus in their throats for up to three days after exposure to aerosols from infected animals, potentially making them carriers of FMDV. Humans and their clothing and footwear have been implicated as fomites for transmission of FMDV during outbreaks. Therefore, most FMDV laboratories impose a five day period of contact avoidance with susceptible species for personnel working with the viruses.

LABORATORY SAFETY

Laboratory practices for FMDV are principally designed to prevent transmission to susceptible livestock, but also to protect workers. The greatest risk of working with FMD is the escape of the organism into susceptible animal populations, which would necessitate USDA emergency procedures to contain and eradicate the disease.

Containment Recommendations

The virus is considered a cause of a foreign animal disease in the United States. Due to the highly contagious nature and the severe economic consequences of disease presence in the United States, this virus should only be handled *in vitro* in a BSL-3 laboratory with enhancements as required by the USDA (See Section IV of this appendix) and *in vivo* in USDA-approved BSL-3-Ag animal facilities. Infected animals are handled with standard protection (gloves, protective clothing). Change of clothing, personal showers and clearing of the throat and nose are required upon exiting contaminated areas in order to minimize virus transmission to susceptible species. Laboratory workers should have no contact with susceptible hosts for five days after working with the agent. In the United States, the Plum Island Animal Disease Center in New York is the only laboratory authorized to possess and work with this agent.

SPECIAL ISSUES

FMDV is a Select Agent. Possession, transfer and use of this agent requires application of procedures as detailed in the Agricultural Bioterrorism Protection Act of 2002 and codified in 9CFR Part 121. All rules concerning the possession, storage, use, and transfer of select agents apply. Please review Appendix F of this document for further instructions regarding Select Agents. Law prohibits research with FMD on the United States mainland.

Heartwater Disease Agent (HD)

HD is a non-contagious disease of domestic and wild ruminants caused by *Ehrlichia ruminantium*.[24] *E. ruminantium* (formerly *Cowdria ruminantium*) is a member of the family *Rickettsiaceae* characterized by organisms that are obligate intracellular parasites. These organisms often persist in the face of an immune response due to their protected intracellular status. Rickettsias in natural conditions are found in mammals and blood-sucking arthropods. Ticks of the genus *Amblyomma* transmit *E. ruminantium*. HD occurs primarily in Africa, but has been recognized in the West Indies since the 1980's. The pathogen is transmitted by ticks of the genus *Amblyomma*, most importantly *A. variegatum* (tropical bont tick). This tick has wide distribution in Africa and is present on several Caribbean islands. Three North American tick species, *A. maculatum* (Gulf Coast tick), *A. cajennese*, and *A. dissimile*, can transmit the organism, causing concern that competent vectors could transmit *E. ruminantium* in the United States.

Severe HD comprises fever, depression, rapid breathing, and convulsions in cattle, sheep, goats and water buffalo. Whitetail deer also are susceptible to *E. ruminantium* infection

and develop severe clinical disease. HD has not been diagnosed in the United States but occurs in numerous Caribbean islands, as well as in most countries of Africa, south of the Sahara Desert.

LABORATORY SAFETY

E. ruminantium can be found in whole blood, brain and experimentally in liver and kidney. It is not a human pathogen. Humans are not susceptible to infection with the agent that causes HD. The greatest risk of working with this agent is the escape of this organism (or infected ticks) into a susceptible domestic bovine population which would necessitate USDA emergency procedures to contain and eradicate the disease.

Containment Recommendations

HD is considered a foreign animal disease in the United States. *E. ruminantium* should be handled *in vitro* in BSL-3 laboratory facilities. Animal work should be conducted in ABSL-3 animal facilities or in ABSL-2 animal facilities with special modifications such as tick dams (where applicable).

SPECIAL ISSUES

The importation, possession, or use of this agent is prohibited or restricted by law or by USDA regulations or administrative policies. A USDA/APHIS import or interstate movement permit is required to obtain this agent or any livestock or poultry product, such as blood, serum, or other tissues containing the agent.

Infectious Salmon Anemia (ISA) Virus

ISA is a disease of Atlantic salmon (*Salmo salar*) caused by an orthomyxovirus in the family *Orthomyxoviridae*, genus *Isavirus*. Both wild and cultured Atlantic salmon are susceptible to infection, as are brown trout (*Salmo trutta*), rainbow trout (*Oncorhynchus mykiss*) and herring. The first clinical cases of ISA in Atlantic salmon were reported from Norway in 1984. Since then, ISA has been observed in Canada (1996), Scotland (1998), Chile (1999), Faroe Islands (2000) and the U.S. (2001).[25,26] There is significant molecular difference between virus isolates (i.e., “Norwegian”, “Scottish” and “North American”).[27] Clinical signs of ISA include severe anemia, swelling and hemorrhaging in the kidney and other organs, pale gills, protruding eyes, darkening of the posterior gut, fluid in the body cavity and lethargy. The infection is systemic and most noted in blood and mucus, muscle, internal organs and feces. The principal target organ for ISA virus (ISAV) is the liver. Signs usually appear two to four weeks after the initial infection.

Reservoirs of ISAV infection are unknown, but the spread of infection may occur due to the purchase of subclinically infected smolts, from farm to farm, and from fish slaughterhouses or industries where organic material (especially blood and processing water) from ISAV-infected fish is discharged without necessary treatment.[28]

LABORATORY SAFETY

Humans are not susceptible to ISAV infection. The greatest risk of working with this virus is the escape of the organism into a susceptible fish population, which would necessitate USDA emergency procedures to contain and eradicate the disease.

Containment Recommendations

ISA is considered a reportable disease in the United States. ISAV should be handled *in vitro* in BSL-2 laboratory facilities with enhancements as required by USDA. Animal inoculations should be handled in ABSL-3 animal facilities with special modifications as required. Recommended precautions include incineration of fish, tissues, blood and materials (gloves, laboratory coats, etc.) used in the collection and processing of fish samples. All surfaces exposed to potentially infected fish should be disinfected with 0.04 to 0.13% acetic acid, chlorine dioxide at 100 parts/million for five minutes or sodium hypochlorite 30 mg. available chlorine/liter for two days or neutralized with sodium thiosulfate after three hours. General principles of laboratory safety should be practiced in handling and processing fish samples for diagnostic or investigative studies. Laboratory managers should evaluate the need to work with ISAV and the containment capability of the facility before undertaking work with the virus or suspected ISAV-infected fish.

SPECIAL ISSUES

The importation, possession, or use of this agent is prohibited or restricted by law or by USDA regulations or administrative policies. A USDA/APHIS import or interstate movement permit is required to obtain this agent or any livestock or poultry product, such as blood, serum, or other tissues containing the agent.

Lumpy Skin Disease (LSD)Virus

LSD is an acute to chronic viral disease of cattle characterized by skin nodules that may have inverted conical necrosis (sit fast) with lymphadenitis accompanied by a persistent fever.[29-31] The causative agent of LSD is a capripoxvirus in the family *Poxviridae*, genus *Capripoxvirus*. The prototype strain of LSD virus (LSDV) is the Neethling virus. LSDV is one of the largest viruses (170-260 nm by 300-450 nm) and there is only one serotype. The LSDV is very closely related serologically to the virus of sheep and goat pox (SGP) from which it cannot be distinguished by routine virus neutralization or other serological tests. The virus is very resistant to physical and chemical agents, persists in necrotic skin for at least 33 days and remains viable in lesions in air-dried hides for at least 18 days at ambient temperature.

LSD is a disorder of cattle. Other wild ungulates have not been infected during epizootics in Africa. Lumpy skin disease was first described in Northern Rhodesia in 1929. Since then, the disease has spread over most of Africa in a series of epizootics and most

recently into the Middle East. Biting insects play the major (mechanical) role in the transmission of LSDV. Direct contact seems to play a minor role in the spread of LSD.

LABORATORY SAFETY

Human beings are not susceptible to infection by LSDV. The greatest risk of working with this virus is the escape of the organism into susceptible domestic animal populations, which would necessitate USDA emergency procedures to contain and eradicate the diseases.

Containment Recommendations

Lumpy skin disease is considered a foreign animal disease in the United States. Due to the highly contagious nature of the agent and the severe economic consequences of disease in the United States, this organism should only be handled *in vitro* in a BSL-3 laboratory with enhancements as required by the USDA and *in vivo* in a USDA-approved BSL-3-Ag facility for loosely housed animals.

SPECIAL ISSUES

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Malignant Catarrhal Fever Virus (MCFV) (Exotic Strains)

Alcelaphine herpesvirus 1 (AlHV-1*)* is a herpesvirus of the *Rhadinovirus* genus in the *Gammaherpesvirinae* subfamily.[32] Common names for AlHV-1 include wildebeest-associated malignant catarrhal fever virus (MCFV), African form MCFV, and exotic MCFV. It also was previously called bovine herpesvirus 3. As a typical herpesvirus, AlHV-1 is a linear double-stranded DNA, enveloped virus. The virus can be propagated in certain primary or secondary cell cultures such as bovine thyroid and testis cells. The isolation of AlHV-1 requires the use of viable lymphoid cells from the diseased animal or cell-free virus in ocular/nasal secretions from wildebeest calves during a viral shedding period. Like other herpesviruses, AlHV-1 is fragile and quickly inactivated in harsh environments (for example, desiccation, high temperatures, and UV/sunlight), and by common disinfectants.

Wildebeest-associated MCF caused by AlHV-1 is also known as the African form of MCF, malignant catarrh, or snotsiekte (snotting sickness). The disease primarily affects many poorly adapted species of *Artiodactyla* that suffer very high case mortality (>95%) but low case morbidity (<7%). Wildebeest are the reservoir for AlHV-1 and the virus does not cause any significant disease in its natural host. Wildebeest-associated MCF primarily occurs in domestic cattle in Africa and in a variety of clinically susceptible ruminant species in zoological collections where wildebeest are present. Virtually all

free-living wildebeest are infected with the virus and calves less than four months of age serve as the source of virus for transmission. The disease can be experimentally transmitted between cattle only by injection with infected viable cells from lymphoid tissues of affected animals. The disease cannot be transmitted by natural means from one clinically susceptible host to another, because there is essentially no cell-free virus in tissues or secretions of diseased animals. MCF is not a contagious disease.

LABORATORY SAFETY

There is no evidence that AlHV-1 can infect humans. Virus can be grown in several bovine cell lines at relatively low titers (ranging from 10^3 to 10^5 $TCID_{50}$). Infectivity in blood and tissues of affected animals is generally associated with viable lymphoid cells. The virus can be easily inactivated by wiping down surfaces with common disinfectants (such as bleach and sodium hypochlorite) and by autoclaving virus-contaminated materials.

Containment Recommendations

This organism should only be handled *in vitro* in a BSL-3 laboratory with enhancements as required by the USDA and *in vivo* in a USDA-approved ABSL-3 animal facility with enhancements.

SPECIAL ISSUES

The importation, possession, or use of this agent is prohibited or restricted by law or by USDA regulations or administrative policies. A USDA/APHIS import or interstate movement permit is required to obtain this agent or any livestock or poultry product, such as blood, serum, or other tissues containing the agent.

Menangle Virus (MenV)

MenV caused a single outbreak of reproductive disease in an Australian swine operation. Clinical signs included stillborn, deformed, mummified piglets and a drop in the farrowing rate. Transmission between pigs has been postulated to be of a fecal-oral nature. A serological survey of fruit bats living near the swine operation revealed the presence of antibodies to MenV. Fruit bats are considered to be the natural host of the virus and their proximity to the affected premises led to an incidental infection in the pig population.[33,34]

MenV is a member of the family *Paramyxoviridae*, subfamily *Paramyxovirinae*. Other members of this family include *Hendra virus*, *Nipah virus* and *Tioman virus* of which Hendra and Nipah have been found to be fruit bat-associated. This virus was isolated from stillborn piglets from a single outbreak of reproductive disease in a commercial swine operation in New South Wales, Australia in 1997.

Occupational Infections

There was serological evidence of MenV infection in two people that had close contact with infected pigs on the affected premises. They demonstrated clinical signs similar to those seen with influenza such as chills, fever, drenching sweats, headache and rash. Both workers recovered fully from their illness.

LABORATORY SAFETY

Laboratory practices for MenV are principally designed to prevent transmission to susceptible livestock, but also to protect workers. The greatest risk of working with MenV is the escape of the organism into susceptible animal populations, which would necessitate USDA emergency procedures to contain and eradicate the disease.

Containment Recommendations

MenV is considered cause of a foreign animal disease in the United States and is a human pathogen. Due to the severe economic consequences of disease presence in the United States, this organism should only be handled *in vitro* in a BSL-3 laboratory with enhancements as required by the USDA and *in vivo* in a USDA-approved ABSL-3 animal facility with enhancements.

SPECIAL ISSUES

The importation, possession, or use of this agent is prohibited or restricted by law or by USDA regulations or administrative policies. A USDA/APHIS import or interstate movement permit is required to obtain this agent or any livestock or poultry product, such as blood, serum, or other tissues containing the agent.

Newcastle Disease (ND) Virus

ND is one of the most serious infectious diseases of poultry worldwide. It is primarily a respiratory disease, but nervous and enteric forms occur. All bird species are probably susceptible to infection with ND virus (NDV). The severity of the disease caused by any given NDV strain can vary from an unapparent infection to 100% mortality. The chicken is the most susceptible species. The bio-containment requirements for working with a particular strain are based on the virulence of the virus as determined by chicken inoculation and more recently by determination of amino acid sequence of the fusion protein cleavage site (as defined by the World Organization for Animal Health).[35] The virus is shed in respiratory secretions and in feces. Natural transmission among birds occurs by aerosol inhalation or by consumption of contaminated feed or water.[36,37]

NDV is classified in the *Avulavirus* genus within the family *Paramyxoviridae,* subfamily *Paramyxovirinae,* in the order *Mononegavirales*. All NDV isolates are of a single serotype avian paramyxovirus type 1 (APMV-1) that includes the antigenic variants isolated from pigeons called pigeon paramyxovirus 1. All strains are readily propagated

in embryonated chicken eggs and a variety of avian and mammalian cell cultures although special additives may be required to propagate the low virulence (lentogenic) viruses in some cell types.[35-37]

Occupational Infections

The most common infection is a self-limiting conjunctivitis with tearing and pain that develops within 24 hours of an eye exposure by aerosol, splash of infective fluids, or eye contact with contaminated hands. The occurrence of upper respiratory or generalized symptoms is rare.[38]

LABORATORY SAFETY

NDV isolates may be recovered from any infected bird, but on occasion may be recovered from humans infected by contact with infected poultry. Humans treated with live NDV in experimental cancer therapies, or those who are exposed by laboratory contamination also are sources of the virus.[38] The greatest risk is for susceptible birds that may be exposed to NDV. If isolates of moderate to high virulence for chickens are used for human cancer therapies, those isolates are probably of greater risk for inadvertent exposure of birds and poultry than they are to the humans handling or being treated with those viruses.

Containment Recommendations

ND (produced by moderate or highly virulent forms of the virus) is considered a foreign animal disease in the United States. Due to the highly contagious nature of the agent and the severe economic consequences of disease presence in the United States, this organism should only be handled *in vitro* in a BSL-3 laboratory with enhancements as required by the USDA and *in vivo* in a USDA-approved BSL-3-Ag facility for loosely housed animals. Laboratory workers should have no contact with susceptible hosts for five days after working with the agent. Laboratory and animal studies with low virulence viruses or diagnostic accessions should be handled at BSL-2.

SPECIAL ISSUES

Velogenic strains of NDV are USDA Select Agents. Possession, transfer and use of this agent requires application of procedures as detailed in 9CFR Part 121, Agricultural Bioterrorism Protection Act of 2002; Possession, Use and Transfer of Biological Agents and Toxins. All rules concerning the possession, storage, use, and transfer of select agents apply. Please review Appendix F of this document for further instructions regarding Select Agents. An importation or interstate movement permit for NDV must be obtained from USDA/APHIS/VS.

Peste Des Petits Ruminants Virus (PPRV)

PPRV causes disease variously termed stomatitis pneumoenteritis complex, kata, goat plague and pseudorinderpest. The virus affects sheep and especially goats, and is regarded as the most important disease of goats and possibly sheep in West Africa where they are a major source of animal protein. The disease is reported from sub-Saharan Africa north of the equator, the Arabian Peninsula, the Middle East, and the Indian Subcontinent. The virus has particular affinity for lymphoid tissues and epithelial tissue of the gastrointestinal and respiratory tracts, causing high fever, diphtheritic oral plaques, proliferative lip lesions, diarrhea, dehydration, pneumonia and death. In susceptible populations morbidity is commonly 90% and mortality 50-80%, but can reach 100%.[39]

PPRV is a member of the family *Paramyxoviridae*, subfamily *Paramyxovirinae*, genus *Morbillivirus*, and species *peste-des-petits-ruminants virus*. Other important morbilliviruses include measles virus, rinderpest virus and canine distemper virus. As in all morbilliviruses, it is pleomorphic, enveloped, about 150 nm in diameter and contains a single molecule of linear, non-infectious, negative sense ssRNA.[40]

The virus is environmentally fragile and requires close direct contact for transmission. Outbreaks typically occur after animal movement and commingling during seasonal migrations or religious festivals. Sources of virus include tears, nasal discharge, coughed secretions, and all secretions and excretions of incubating and sick animals. There is no carrier state, and animals recovering from natural infection have lifetime immunity.

LABORATORY SAFETY

PPRV is not known to infect humans in either laboratory or field settings. The greatest risk of working with PPRV is the escape of the organism into a susceptible sheep or goat population, which would necessitate USDA emergency procedures to contain and eradicate the disease.

Containment Recommendations

The virus is considered cause of a foreign animal disease in the United States. Due to the highly contagious nature of the agent and the severe economic consequences of disease presence in the United States, this organism should only be handled *in vitro* in a BSL-3 laboratory with enhancements as required by the USDA and *in vivo* in a USDA-approved BSL-3-Ag facility for loosely housed animals. Laboratory workers should have no contact with susceptible hosts for five days after working with the agent.

SPECIAL ISSUES

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Rinderpest Virus (RPV)

Rinderpest (RP) is a highly contagious viral disease of domestic cattle, buffaloes, sheep, goats and some breeds of pigs and a large variety of wildlife species.[41] It is characterized by fever, oral erosions, diarrhea, lymphoid necrosis and high mortality. The disease is present in the Indian subcontinent, Near East and sub-Saharan Africa including Kenya and Somalia.

RPV is a single stranded RNA virus in the family *Paramyxoviridae*, genus *Morbillivirus*. It is immunologically related to canine distemper virus, human measles virus, peste des petits ruminants virus, and marine mammal morbilliviruses. There is only one serotype of RPV including several strains with a wide range of virulence.[42]

RPV is a relatively fragile virus. The virus is sensitive to sunlight, heat, and most disinfectants. It rapidly inactivates at pH 2 and 12. Optimal pH for survival is 6.5-7.0. Glycerol and lipid solvents inactivate this virus.

Spread of RPV is by direct and indirect contact with infected animals. Aerosol transmission is not a significant means of transmission. Incubation period varies with strain of virus, dosage, and route of exposure. Following natural exposure, the incubation period ranges from 3 to 15 days but is usually 4 to 5 days.

LABORATORY SAFETY

There are no reports of RPV being a health hazard to humans. The greatest risk of working with RPV is the escape of the organism into susceptible animal populations, which would necessitate USDA emergency procedures to contain and eradicate the disease.

Containment Recommendations

The virus is considered cause of a foreign animal disease in the United States. Due to the highly contagious nature of the agent and the severe economic consequences of disease presence in the United States, this organism should only be handled *in vitro* in a BSL-3 laboratory with enhancements as required by the USDA and *in vivo* in a USDA-approved BSL-3-Ag facility for loosely housed animals. Laboratory workers should have no contact with susceptible hosts for five days after working with the agent.

SPECIAL ISSUES

The importation, possession, or use of this agent is prohibited or restricted by law or by USDA regulations or administrative policies. A USDA/APHIS import or interstate movement permit is required to obtain this agent or any livestock or poultry product, such as blood, serum, or other tissues containing the agent.

Appendix D

Sheep and Goat Pox Virus (SGPV)

Sheep and goat pox (SGP) is an acute to chronic disease of sheep and goats characterized by generalized pox lesions throughout the skin and mucous membranes, a persistent fever, lymphadenitis, and often a focal viral pneumonia with lesions distributed uniformly throughout the lungs. Subclinical cases may occur. The virus that causes SGP is a capripoxvirus (SGPV), one of the largest viruses (170-260 nm by 300-450 nm) in the *Poxviridae* family, genus *Capripoxvirus*. It is closely related to the virus that causes lumpy skin disease. The SGPV is very resistant to physical and chemical agents.[43-45]

SGPV causes clinical disease in sheep and goats. The virus replicates in cattle but does not cause clinical disease. The disease has not been detected in wild ungulate populations. It is endemic in Africa, the Middle East, the Indian subcontinent, and much of Asia.

Contact is the main means of transmission of SGPV. Inhalation of aerosols from acutely affected animals, aerosols generated from dust contaminated from pox scabs in barns and night holding areas, and contact through skin abrasions either by fomites or by direct contact are the natural means of transmitting SGPV. Insect transmission (mechanical) is possible. The virus can cause infection experimentally by intravenous, intradermal, intranasal, or subcutaneous inoculation.

LABORATORY SAFETY

Humans are not susceptible to infection by these poxviruses. The greatest risk of working with these agents is the escape of the organism into susceptible domestic animal populations, which would necessitate USDA emergency procedures to contain and eradicate the diseases.[46]

Containment Recommendations

These viruses are considered cause of a foreign animal disease in the United States. Due to the highly contagious nature of the agent and the severe economic consequences of disease presence in the United States, this organism should only be handled *in vitro* in a BSL-3 laboratory with enhancements as required by the USDA and *in vivo* in a USDA-approved ABSL-3 animal facility with enhancements.

SPECIAL ISSUES

The importation, possession, or use of this agent is prohibited or restricted by law or by USDA regulations or administrative policies. A USDA/APHIS import or interstate movement permit is required to obtain this agent or any livestock or poultry product, such as blood, serum, or other tissues containing the agent.

Spring Viremia of Carp Virus (SVCV)

Spring Viremia of Carp virus (SVCV) is a rhabdovirus in the family *Rhabdoviridae*, genus *Vesiculovirus* that infects a broad range of fish species and causes high mortality in susceptible hosts in cold water. It is a World Organization for Animal Health Office International des Épizooties (OIE) reportable disease. Infections have occurred in common and koi carp (*Cyprinus carpio*), grass carp (*Crenopharyngodon idellus*), silver carp (*Hypophthalmichthys molitix*), bighead (*Aristichthys nobilis*), cruian carp (*Carassius carassius*), goldfish (*C. auratus*), roach (*Rutilus rutilus*), ide (*Leuciscus idus*), tench (*Tinca tinca*) and sheatfish (*Silurus glanis*). Long indigenous to Europe, the Middle East and Asia, the disease was reported recently in South and North America. In the spring of 2002, SVCV was isolated from koi carp farmed in North Carolina. That year the virus was detected in fish in several lakes and rivers in Wisconsin, including the Mississippi River. SVCV causes impairment in salt-water balance in fish resulting in edema and hemorrhages.

Reservoirs of SVCV are infected fish and carriers from either cultured, feral or wild fish populations.[47] Virulent virus is shed via feces, urine, and gill, skin and mucus exudates. Liver, kidney, spleen, gill and brain are the primary organs containing the virus during infection.[48] It is surmised that horizontal transmission occurs when waterborne virus enters through the gills. Vertical transmission may be possible, especially via ovarian fluids. This virus may remain infective for long periods of time in water or mud. Once the virus is established in a pond or farm it may be difficult to eradicate without destruction of all fish at the farm.[25,28,49]

LABORATORY SAFETY

Human beings are not susceptible to SVCV infection. The greatest risk of working with SVCV is the escape of the organism into a susceptible fish population, which would necessitate USDA emergency procedures to contain and eradicate the disease.

Containment Recommendations

SVC is considered a reportable disease in the United States. SVCV should be handled *in vitro* in BSL-2 laboratory facilities with enhancements as required by USDA. Animal inoculations should be handled in ABSL-3 animal facilities with special modifications as required. The OIE Diagnostic Manual for Aquatic Animal Disease has specifications for surveillance programs to achieve and maintain health status of aquaculture facilities.[48] Recommendations for preventing the disease and spread of disease include the use of a water source free of virus, disinfection of eggs and equipment, and proper disposal of dead fish.

SPECIAL ISSUES

The importation, possession, or use of this agent is prohibited or restricted by law or by USDA regulations or administrative policies. A USDA/APHIS import or interstate

movement permit is required to obtain this agent or any livestock or poultry product, such as blood, serum, or other tissues containing the agent.

Swine Vesicular Disease Virus (SVDV)

Swine vesicular disease virus (SVDV) is classified in the genus *Enterovirus*, the family *Picornaviridae*, and is closely related to the human enterovirus *coxsackievirus B5*.[50] The virus is the causative agent of SVD, a contagious disease of pigs characterized by fever and vesicles with subsequent erosion in the mouth and on the snout, feet, and teats. [51,52] The major importance of SVD is that it clinically resembles FMD, and any outbreaks of vesicular disease in pigs must be assumed to be FMD until proven otherwise by laboratory tests.

OCCUPATIONAL INFECTIONS

SVDV can cause an "influenza-like" illness in man[1] and human infection has been reported in laboratory personnel working with the virus.[53,54] The virus may be present in blood, vesicular fluid, and tissues of infected pigs. Direct and indirect contacts of infected materials, contaminated laboratory surfaces, and accidental autoinoculation, are the primary hazards to laboratory personnel.

LABORATORY SAFETY

Laboratory practices for SVDV are principally designed to prevent transmission to susceptible livestock, but also to protect workers. Gloves are recommended for the necropsy and handling of infected animals and cell cultures. The greatest risk of working with SVD is the escape of the organism into susceptible animal populations, which would necessitate USDA emergency procedures to contain and eradicate the disease.[55]

Containment Recommendations

SVD is considered a foreign animal disease in the United States. Due to the severe economic consequences of disease presence in the United States, SVDV should only be handled *in vitro* in a BSL-3 laboratory with enhancements as required by the USDA and *in vivo* in a USDA-approved ABSL-3 animal facility with enhancements.

SPECIAL ISSUES

The importation, possession, or use of this agent is prohibited or restricted by law or by USDA regulations or administrative policies. A USDA/APHIS import or interstate movement permit is required to obtain this agent or any livestock or poultry product, such as blood, serum, or other tissues containing the agent.

Appendix D

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