

SELECT AGENTS

(For assistance, please contact EHS at (402) 472-4925, or visit our web site at <http://www.ehs.unl.edu>)

Some biological agents are capable of causing substantial harm to human, animal, or plant health and are high-risk agents for illegitimate use. Hence, the United States Department of Health and Human Services (HHS) and the United States Department of Agriculture (USDA) have established regulatory requirements for the possession, receipt, or transfer of such agents. USDA regulations are administered by the Animal and Plant Health Inspection Service (APHIS). HHS regulations are administered by the Centers for Disease Control (CDC). These regulations can be found at 42 CFR 73 (human/overlap select agents and toxins), 9 CFR 121 (animal/overlap select agents and toxins), and 7 CFR 331 (plant select agents). The term “overlap select agents and toxins” refers to those regulated select agents that are pathogenic to both humans and animals. Biological agents subject to these regulations are listed at the end of this document, along with key definitions from the regulations.

In accordance with regulatory requirements, all facilities that possess, receive, or transfer regulated agents must be registered, except diagnostic laboratories. However, certain conditions must be met to take advantage of the diagnostic laboratory exclusion (see EHS SOP, **Select Agents – Diagnostic Activities**). Registration is specific to location and type of work. **Hence, Principal Investigators (PIs) who wish to possess, receive, or transfer select agents must gain approval from their department head/chair and notify EHS at least twelve weeks prior to such action to allow adequate time to complete the registration process.**

Projects involving the use of regulated select agents are subject to prior IBC review and approval, regardless of whether such projects involve recombinant DNA. Major provisions of the regulations for such projects are described below. Consult the actual regulations or contact EHS for a full description of regulatory requirements.

- The United States Departments of Health and Human Services or Agriculture must approve personnel who work with and/or have access to regulated select agents. No person should possess or have access to select agents without first having obtained approval. This process is referred to as Security Risk Assessments. Approvals are valid for a maximum of five years.
- The registration process with CDC/APHIS must be completed prior to possessing or commencing work with select agents. Registration is valid for a maximum of three years.
- Entities (i.e., UNL) that possess, receive, or transfer regulated agents must designate a Responsible Official (RO). At UNL, the Director of EHS serves in this capacity. The EHS Biosafety Officer serves as the Alternate Responsible

Official. The RO is responsible for all official correspondence with federal agencies, including coordination of the registration and security risk assessment processes, oversight and inspection of laboratories, reporting and recordkeeping, and training. PIs also have similar responsibilities with respect to their individual laboratories.

- Work with select agents is subject to the following requirements:
 - Development and implementation of a written safety plan that is consistent with BMBL, NIH Guidelines for Recombinant DNA, 29 CFR 1910.1450 (OSHA's Lab Standard), 29 CFR 1910.1200 (OSHA's Hazard Communication Standard).
 - Development and implementation of a security plan. Some elements of the plan will be covered by institutional procedures and policies. Work/project specific elements will include: IT (information technology) security, barriers (i.e., locks, video surveillance, maintenance and custodial activities, passwords, etc.), etc.
 - Separation of agent use and storage locations from public areas of the building.
 - Establishment of an emergency response plan.
 - Initial and annual refresher training for all workers.
 - Maintenance of an accurate inventory.
- All transfers (off-site and intra-facility) must be managed through EHS with appropriate documentation/records.
- In some cases, destructions must be managed through EHS with appropriate documentation/records.
- Immediate notification of theft, loss, or release.

Regulated Agents

Agent	Type
Viruses	
African horse sickness virus	Animal
African swine fever virus	Animal
Akabane virus	Animal
Avian influenza virus (highly pathogenic)	Animal
Bluetongue virus (exotic)	Animal
Bovine spongiform encephalopathy agent	Animal
Camel pox virus	Animal
Cercopithecine herpesvirus 1 (Herpes B virus)	Human
Classical swine fever virus	Animal
Crimean-Congo haemorrhagic fever virus	Human
Eastern Equine Encephalitis virus	Human
Ebola virus	Human
Foot and Mouth disease virus	Animal
Goat pox virus	Animal
Hendra virus	Overlap
Japanese encephalitis virus	Animal
Lassa fever virus	Human
Lumpy skin disease virus	Animal
Malignant catarrhal fever virus (Alcelaphine herpesvirus type 1)	Animal
Marburg virus	Human

Menangle virus	Animal
Monkeypox virus	Human
Newcastle disease virus (virulent)* (see footnote)	Animal
Nipah virus	Overlap
Peste des petits ruminants virus	Animal
Reconstructed 1918 influenza virus (Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight genes segments)	Human
Rift Valley fever virus	Overlap
Rinderpest virus	Animal
Sheep pox virus	Animal
South American haemorrhagic fever viruses (Junin, Machupo, Sabia, Flexal, Guanarito)	Human
Swine vesicular disease virus	Animal
Tick-borne encephalitis complex (flavi) viruses (Central European tick-borne encephalitis, Far Eastern tick-borne encephalitis, Russian spring and summer encephalitis, Kyasanur forest disease, Omsk hemorrhagic fever)	Human
Variola major virus (Smallpox virus)	Human
Variola minor virus (Alastrim)	Human
Venezuelan equine encephalitis virus	Overlap
Vesicular stomatitis virus (exotic): Indiana subtypes VSV-IN2, VSV-IN3	Animal
Bacteria	
Bacillus anthracis	Overlap
Brucella abortus	Overlap
Brucella melitensis	Overlap
Brucella suis	Overlap
Burkholderia mallei (formerly Pseudomonas mallei)	Overlap
Burkholderia pseudomallei (formerly Pseudomonas pseudomallei)	Overlap
Botulinum neurotoxin producing species of Clostridium	Human
<i>Ehrlichia ruminantium</i> (Heartwater)	Animal
Francisella tularensis	Human
<i>Mycoplasma capricolum</i> subspecies <i>capripneumoniae</i> (contagious caprine pleuropneumonia)	Animal
<i>Mycoplasma mycoides</i> subspecies <i>mycoides</i> small colony (MmmSC)(contagious bovine pleuropneumonia)	Animal
Ralstonia solanacearum, race 3, biovar 2	Plant
Rathayibacter toxicus	Plant
Xanthomonas oryzae	Plant
Xylella fastidiosa (citrus variegated chlorosis strain)	Plant
Yersinia pestis	Human
Rickettsial	
Coxiella burnetii	Human
Rickettsia prowazekii	Human
Rickettsia riskettsii	Human
Fungi	
Coccidioides immitis	Human
Coccidioides posadasii	Human
Peronosclerospora philippinensis (Peronosclerospora sacchari)	Plant
Phoma glycinicola (formerly Pyrenochaeta glycinis)	Plant
Sclerophthora rayssiae, var. zeae	Plant
Synchytrium endobioticum	Plant
Toxins	
Abrin	Human
Botulinum neurotoxins	Human

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Clostridium perfringens epsilon toxin	Human
Conotoxins	Human
Diacetoxyscirpenol	Human
Ricin	Human
Saxitoxin	Human
Shigatoxin	Human
Shiga-like ribosome inactivating proteins	Human
Staphylococcal enterotoxins	Human
T-2 toxin	Human
Tetrodotoxin	Human

- A virulent Newcastle disease virus (avian paramyxovirus serotype 1) has an intracerebral pathogenicity index in day-old chicks (*Gallus gallus*) of 0.7 or greater or has an amino acid sequence at the fusion (F) protein cleavage site that is consistent with virulent strains of Newcastle disease virus. A failure to detect a cleavage site that is consistent with virulent strains does not confirm the absence of a virulent virus.

Key Definitions

Biological Agent: Any microorganism (including, but not limited to, bacteria, viruses, fungi, rickettsiae, or protozoa), or infectious substance, or any naturally occurring, bioengineered, or synthesized component of any such microorganism or infectious substance, capable of causing:

- (1) Death, disease, or other biological malfunction in a human, an animal, a plant, or another living organism;
- (2) Deterioration of food, water, equipment, supplies, or material of any kind; or
- (3) Deleterious alteration of the environment

Toxin: The toxic material or product of plants, animals, microorganisms (including, but not limited to, bacteria, viruses, fungi, rickettsiae, or protozoa), or infectious substances, or a recombinant or synthesized molecule, whatever their origin and method of production, and includes:

- (1) Any poisonous substance or biological product that may be engineered as a result of biotechnology produced by a living organism; or
- (2) Any poisonous isomer or biological product, homolog, or derivative of such a substance.

Clarifications

Genetic Elements

The following genetic elements, recombinant nucleic acids, and recombinant organisms are also subject to these regulations:

- a. Nucleic acids that can produce infectious forms of any of the select agent viruses listed above. Recombinant nucleic acids that encode for the functional form(s) of any of the toxins listed above if the nucleic acids: Can be expressed *in vivo* or *in vitro*, or
 - b. Are in a vector or recombinant host genome and can be expressed *in vivo* or *in vitro*.
- (2) Genetically modified viruses, bacteria, fungi, and toxins

Exclusions

The following select agents and toxins are excluded from the regulations if they meet any of the following criteria:

- (1) Any select agent or toxin that is in its naturally occurring environment provided the select agent or toxin has not been intentionally introduced, cultivated, collected, or otherwise extracted from its natural source.
- (2) Select agents that are non-viable or nonfunctional toxins.
- (3) Toxins under the control of a principle investigator, treating physician or veterinarian, or commercial manufacturer or distributor, if the aggregate amount does not, at any time, exceed the following amounts:

Abrin- 100 mg
Botulinum toxin- 0.5 mg
Clostridium perfringens epsilon toxin- 100 mg
Conotoxins- 100 mg
Diacetoxyscirpenol- 1,000 mg
Ricin- 100 mg
Saxitoxin- 100 mg
Shigatoxin- 100 mg
Shiga-like ribosome inactivating proteins- 100 mg
Staphylococcal enterotoxins- 5 mg
T-2 toxin- 1,000 mg
Tetrodotoxin- 100 mg check

Prohibitions

The following experiments require express prior approval from the Secretary of HHS/USDA:

- Experiments utilizing recombinant DNA that involve the deliberate transfer of a drug resistance trait to select agents that are not known to acquire the trait naturally, if such acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture.
- Experiments involving the deliberate formation of recombinant DNA containing genes for the biosynthesis of select agent toxins lethal for vertebrates at an LD₅₀ of less than 100 ng/kg body weight.

Generally, HHS and USDA require Agency review and approval of any protocol or project involving the transfer of an antibiotic resistance trait to a listed agent, regardless of whether the antibiotic is used to treat infections in humans or animals.

Exclusions/Attenuated Strains

HHS and/or USDA have excluded some attenuated strains of listed agents. These exclusions are published on the CDC and APHIS web sites and are limited to stated purpose/activities.

Genetic modifications to excluded attenuated strains may require submission, review, and approval of a separate exclusion request. Consult with EHS to determine applicability of any published exclusion to an attenuated, and/or genetically modified strain. In general, the following types of activities require registration or application for specific exclusion:

- Genetic manipulations of excluded, attenuated strains that enhance or restore virulence are subject to registration. Generally, genetic manipulations that delete or inactivate genes of excluded, attenuated strains would not reasonably be expected to increase virulence and are therefore not subject to registration. However, registration must be sought if the PI later determines that the modification has enhanced virulence.
- Introduction of antibiotic resistance markers **may** require registration or application for a specific exclusion. However, introduction of sequences encoding reporter genes (e.g., GFP or beta-galactosidase) are not subject to registration or separate exclusion. A determination is generally based on whether the antibiotic resistance could compromise the use of the drug to control disease agents used in humans, veterinary medicine, or agriculture.

All provisions of the regulations remain in full-force until such time as the Agency provides positive, written consideration of an exemption request.