Enhanced Select Agents and Toxins Overview

26 October 2023

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

USDA


Select Agents & Toxins
That Have Been Modified
or Enhanced

Work with Modified Select Agents and Toxins that Have the Potential to Pose an Enhanced Risk

- Due to advancements in science and technology, modifying pathogens in ways that have the potential to pose an enhanced risk has become more feasible.
- Entities should consider whether their work with modified select agents and toxins has the potential to pose an enhanced risk.

https://www.thermofisher.com/blog/life-in-the-lab/the-many-unsung-breakthroughs-of-crispr/

Objectives

- Provide an overview of work with modified select agents and toxins that have the potential to pose an enhanced risk
- Discuss the reasoning for enhanced oversight
- Provide an overview of updates to guidance documents
- Outline what entities should do if they are working with modified select agents and toxins that may enhance risk

Examples of Experiments that May Increase Risk (1/2)

Experiments that deliberately or passively alter a select agent or toxin to modify its genotype or phenotype may have the potential to enhance the risk characteristics of the select agent or toxin, including but not limited to:

- Disruption of host immunity or the effectiveness of an immunization against the agent or toxin.
- The ability for the agent or toxin to evade detection methodologies.
- Resistance of the agent or toxin to investigative drugs or therapies.

Examples of Experiments that May Increase Risk (2/2)

Experiments that deliberately or passively alter a select agent or toxin to modify its genotype or phenotype may have the potential to enhance the risk characteristics of the select agent or toxin, including but not limited to:

- Increased stability, transmissibility, or pathogenicity of a select agent or toxin, or an increased ability to disseminate the agent or toxin.
- Alteration of the host range or tropism of the agent or toxin.
- An increase in susceptibility of a host population to an agent or toxin due to modifications made to the agent or toxin.
- Increase in the resistance to select agent inactivation methods.

Regulations Relating to Enhanced Risk: 3(c) and 4(c)

7 C.F.R. 331.3(c), 9 C.F.R. 121.3(c) and 121.4(c), and 42 C.F.R. 73.3(c) and 73.4(c):

(c) Genetic Elements, Recombinant and/or Synthetic Nucleic Acids, and Recombinant and/or Synthetic Organisms:

(3) Select agents and toxins listed in paragraph (b) of this section that have been genetically modified.

https://www.bio-rad.com/en-us/category/pglo-bacterial-transformation-gfp-kits?ID=f75948d2-dc20-4a32-b4e5-b7e0fe4c21ed

Regulations Relating to Enhanced Risk: 12(a)(2)

7 C.F.R. 331.12(a)(2), 9 C.F.R. 121.12(a)(2), and 42. C.F.R. 73.12(a)(2):

An individual or entity required to register under this part must develop and implement a written biosafety plan that is commensurate with the risk of the select agent or toxin, given its intended use. The biosafety plan must contain sufficient information and documentation to describe the biosafety and containment procedures for the select agent or toxin, including any animals (including arthropods) or plants intentionally or accidentally exposed to or infected with a select agent. The current biosafety plan must be submitted for initial registration, renewal of registration, or when requested. The biosafety plan must include the following provisions:

(2) Safeguards in place with associated work practices to protect entity personnel, the public, and the environment from exposure to the select agent or toxin including, but not limited to: Personal protective equipment and other safety equipment; containment equipment including, but not limited to, biological safety cabinets, animal caging systems, and centrifuge safety containers; and engineering controls and other facility safeguards;

Regulations Relating to Enhanced Risk: 12(a)(1)

7 C.F.R. 331.12(a)(1), 9 C.F.R. 121.12(a)(1), and 42. C.F.R. 73.12(a)(1):

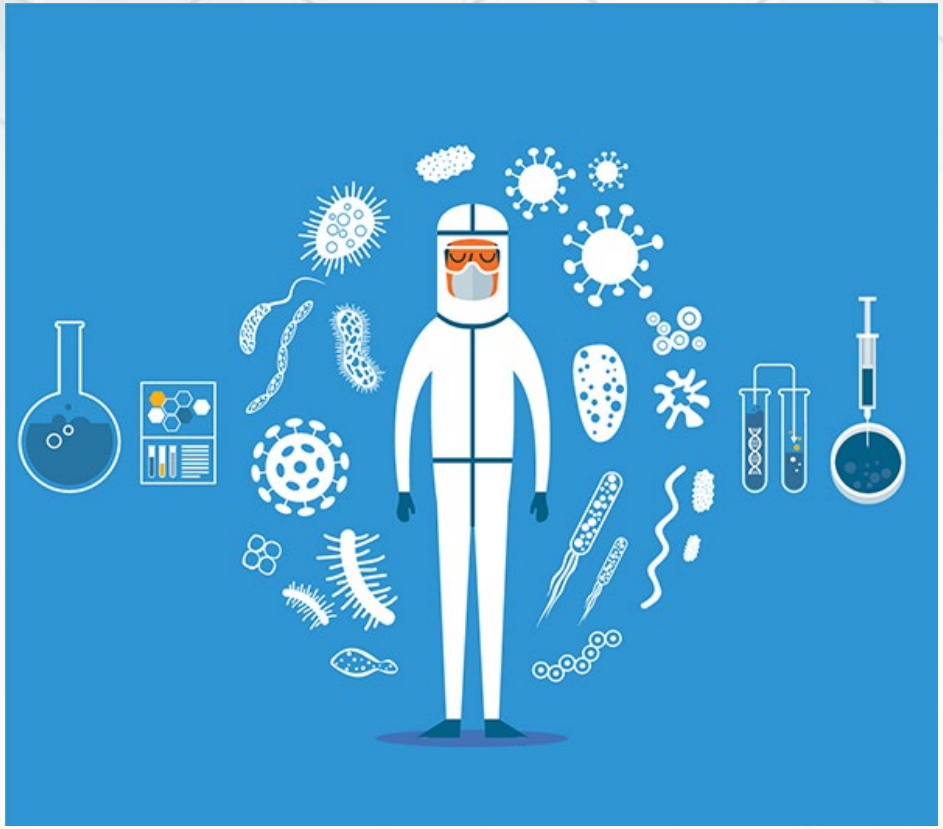
An individual or entity required to register under this part must develop and implement a written biosafety plan that is commensurate with the risk of the select agent or toxin, given its intended use. The biosafety plan must contain sufficient information and documentation to describe the biosafety and containment procedures for the select agent or toxin, including any animals (including arthropods) or plants intentionally or accidentally exposed to or infected with a select agent. The current biosafety plan must be submitted for initial registration, renewal of registration, or when requested. The biosafety plan must include the following provisions:

(1) The hazardous characteristics of each agent or toxin listed on the entity's registration and the biosafety risk associated with laboratory procedures related to the select agent or toxin.

Regulations Relating to Enhanced Risk: 12(b)

7 C.F.R. 331.12(b), 9 C.F.R. 121.12(b), and 42. C.F.R. 73.12(b):

The biosafety and containment procedures must be sufficient to contain the select agent or toxin (e.g., physical structure and features of the entity, and operational and procedural safeguards).



https://health.usf.edu/publichealth/ghidr/bsl3

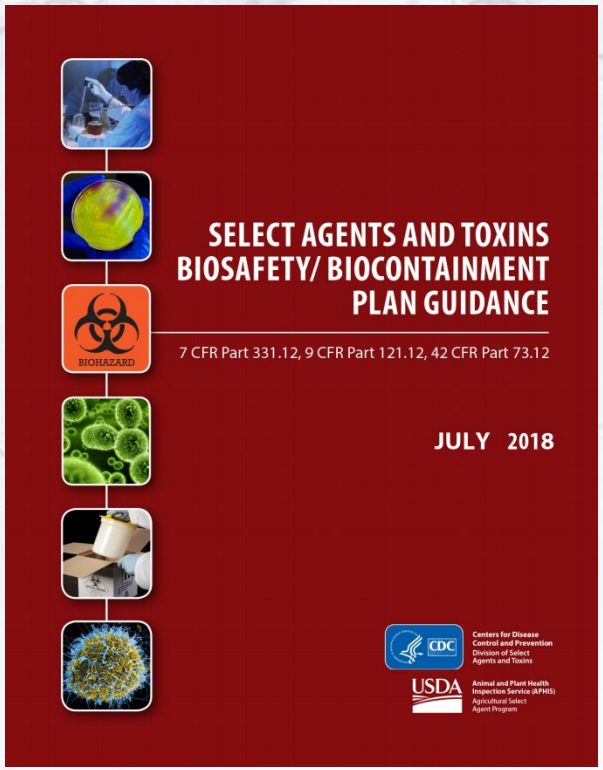
Enhanced Risk Research vs Restricted Experiments

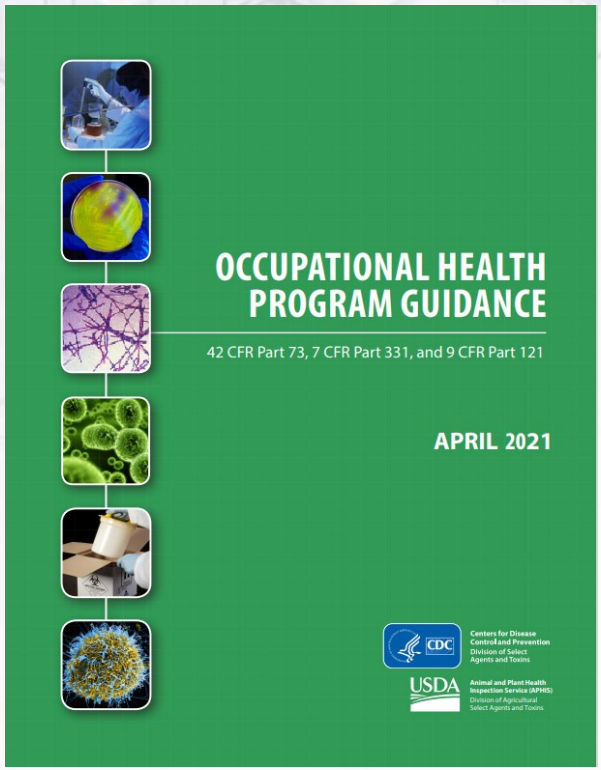
- Please note that work with modified select agents and toxins that may pose an enhanced risk is different than restricted experiments, which are outlined in 42 CFR 73.13 (HHS), 7 CFR 331.13 (APHIS-Plant Protection and Quarantine) and 9 CFR 121.13 (APHIS-Veterinary Services).
- Work with modified select agents and toxins that may pose an enhanced risk does not require prior approval from FSAP, if the experiments do not meet the definition of a restricted experiment.

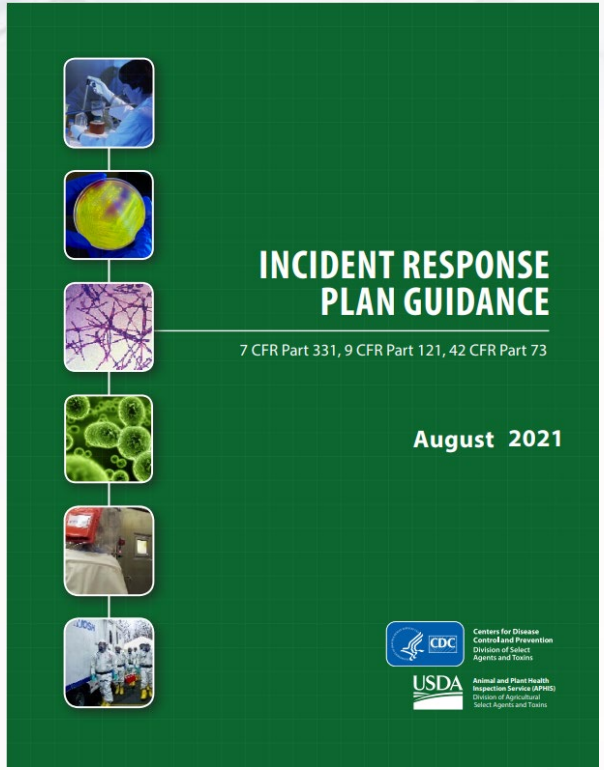
https://www.gavi.org/vaccineswork/bacteria-shuffle-their-genetics-around-develop-antibiotic-resistance-demand

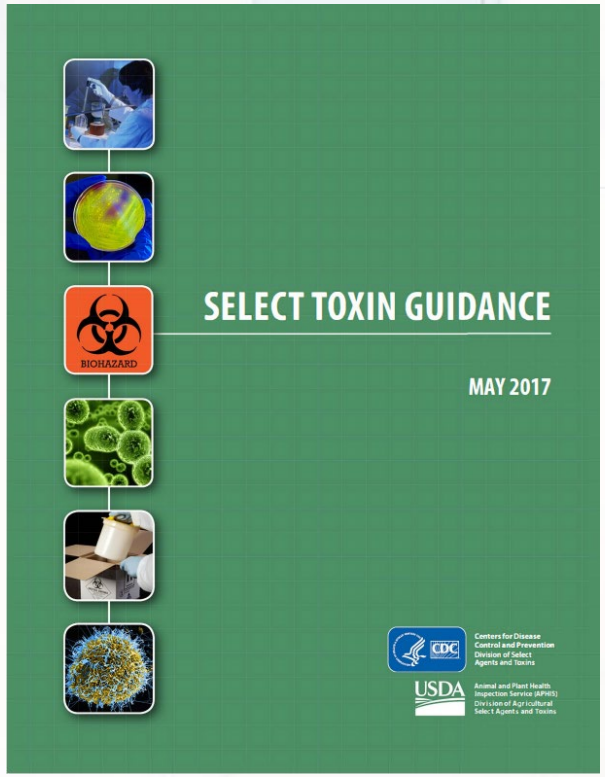
Guidance Document Changes

Proposed Updates to Guidance Documents





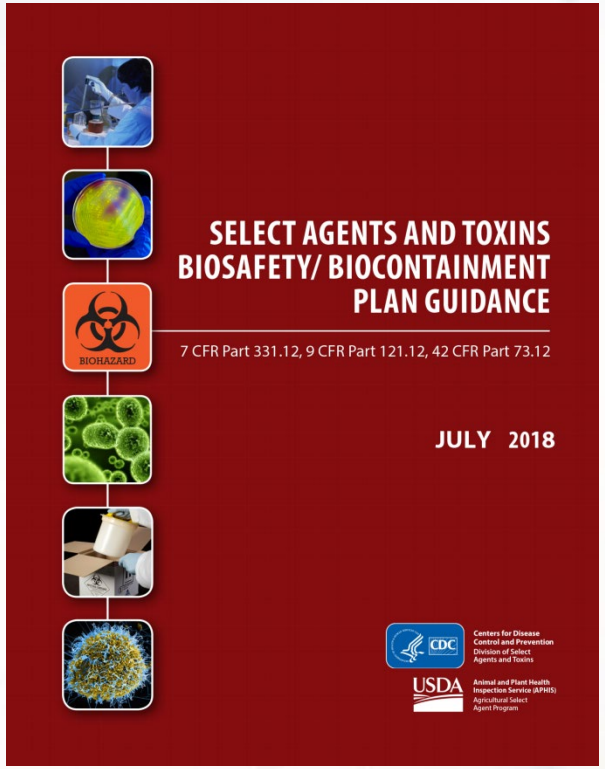




Biosafety/Biocontainment Plan Guidance (1/3)

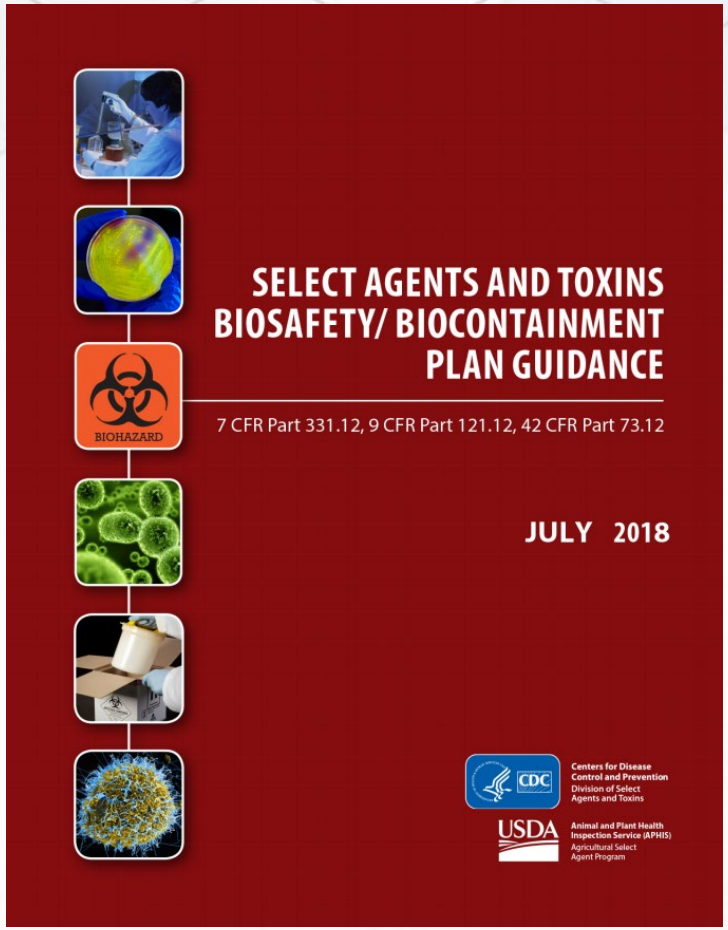
New section created, titled “Work with Modified Select Agents and Toxins that Have the Potential to Pose an Enhanced Risk”

- Examples of modifications that may result in the creation of a select agent or toxin that poses an enhanced risk.
- Examples of biosafety measures that may be considered if an entity’s work is considered to be enhanced risk.
- Explanation of the difference between enhanced risk work and restricted experiments.



Biosafety/Biocontainment Plan Guidance (2/3)

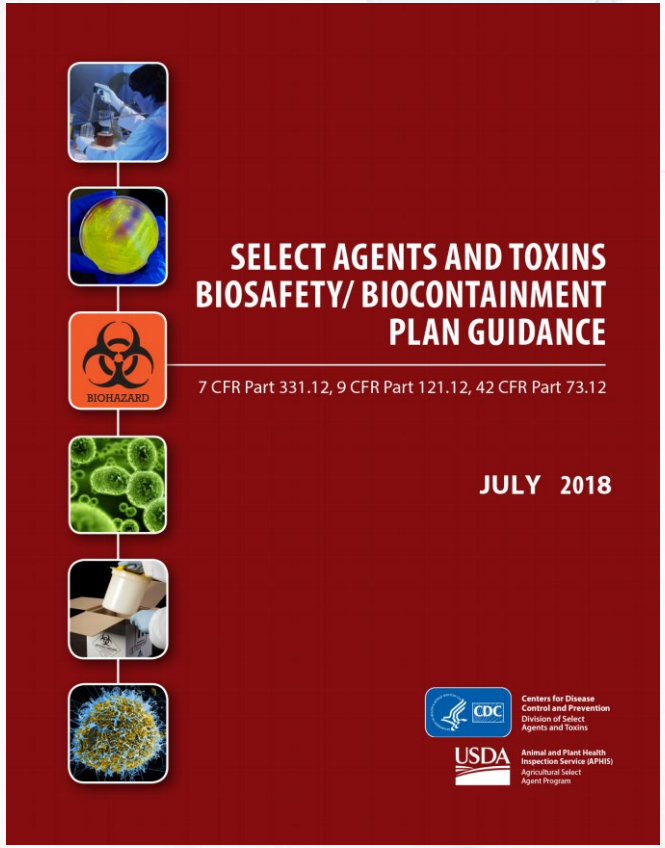
- Biosafety plans must meet the requirements as outlined in 7 C.F.R. 331.12, 9 C.F.R. 121.12, and 42 C.F.R. 73.12.
- If work with a select agent or toxin is considered an enhanced risk, additional measures should be considered to account for the enhanced risk.
- Determining whether additional biosafety measures are necessary should be supported by a biological risk assessment.



Biosafety/Biocontainment Plan Guidance (3/3)

Examples of biosafety measures or enhancements for enhanced risk work:

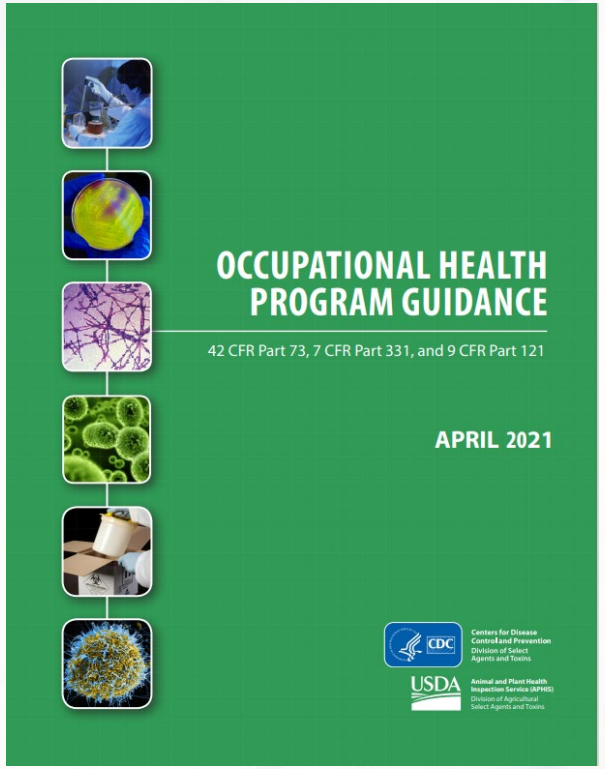
- Increased Personal Protective Equipment (PPE).
- Additional vaccination recommendations or requirements.
- Implementation of additional personnel health measures such as treatment strategies or coordination with health practitioners to mitigate the risk associated with an exposure or release.
- Modifications to the treatment of exposures to an enhanced risk select agent or toxin.
- Enhanced work practices and/or procedures to address the increased risk associated with an enhanced select agent or toxin.
- Institutional oversight.



Occupational Health Program Guidance (1/3)

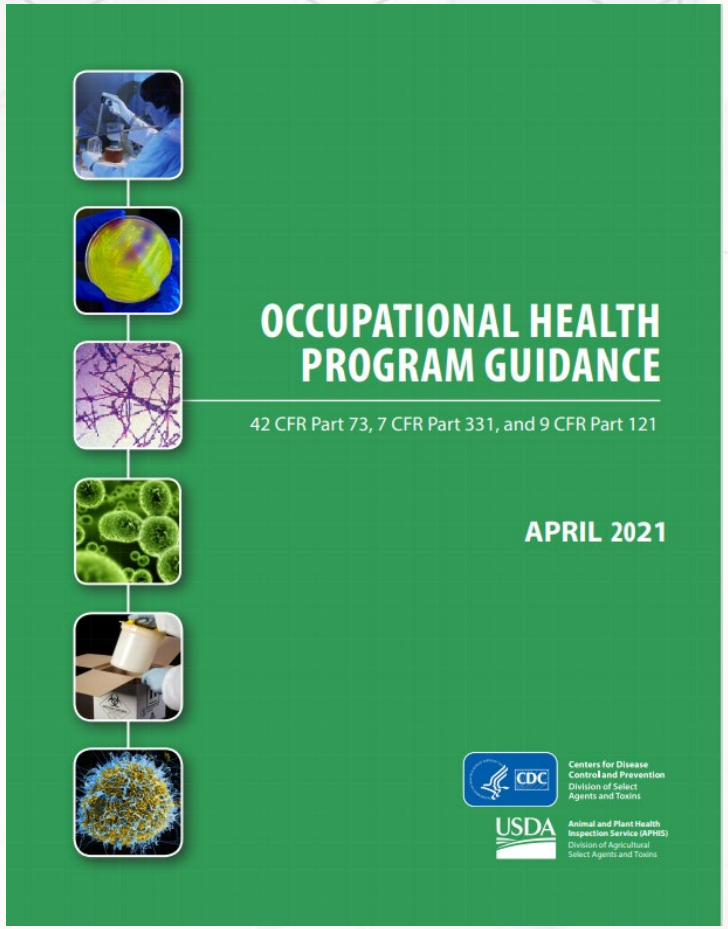
New section created, titled “Modified Select Agents and Toxins that Have the Potential to Pose an Enhanced Risk”

- Discusses considerations for an occupational health plan informed by a biological risk assessment for those working with enhanced select agents and toxins that require an occupational health plan.



Occupational Health Program Guidance (2/3)

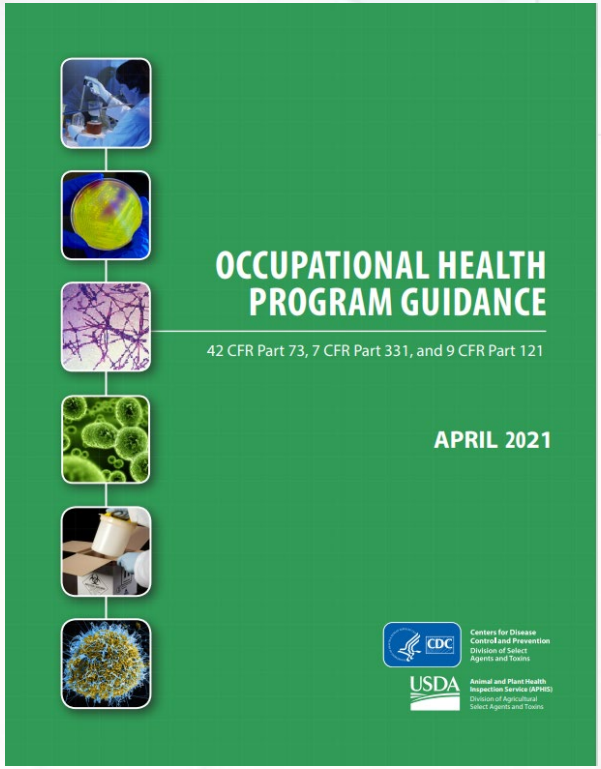
- An Occupational Health Program (OHP) should be developed and implemented for all employees with access to enhanced risk select agents or toxins **requiring an OHP.**
- Development of an OHP should be informed by a biological risk assessment that considers how the known or potentially generated enhancements may impact all segments of an effective OHP.



Occupational Health Program Guidance (3/3)

Additional considerations may be needed regarding, but not limited to:

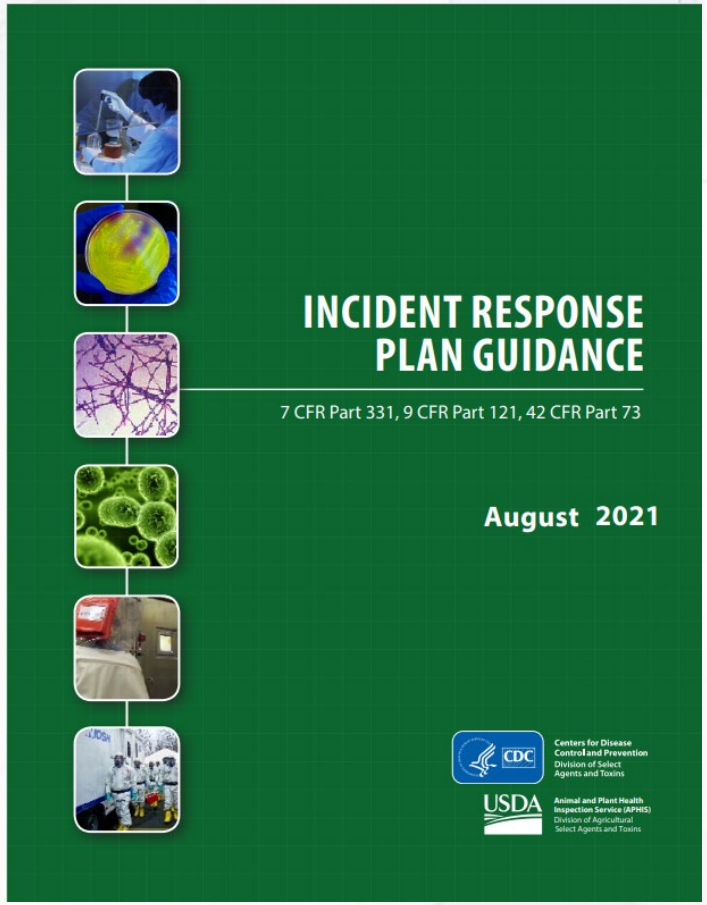
- Considerations for medical surveillance and the ability to discern positivity for modified select agents or toxins that may pose an enhanced risk.
- Isolation of staff potentially exposed to a modified select agent or toxin that may pose an enhanced risk.
- Diminished efficacy of investigational drugs that may be clinically relevant at a later date.
- Diminished efficacy of currently implemented vaccination programs.
- Differences in treatments or medical countermeasures if exposed to enhanced risk select agents or toxins.
- Enhanced respiratory protection program.



Incident Response Plan Guidance

Questions and concepts to consider when working with modified select agents and toxins with potentially enhanced risk:

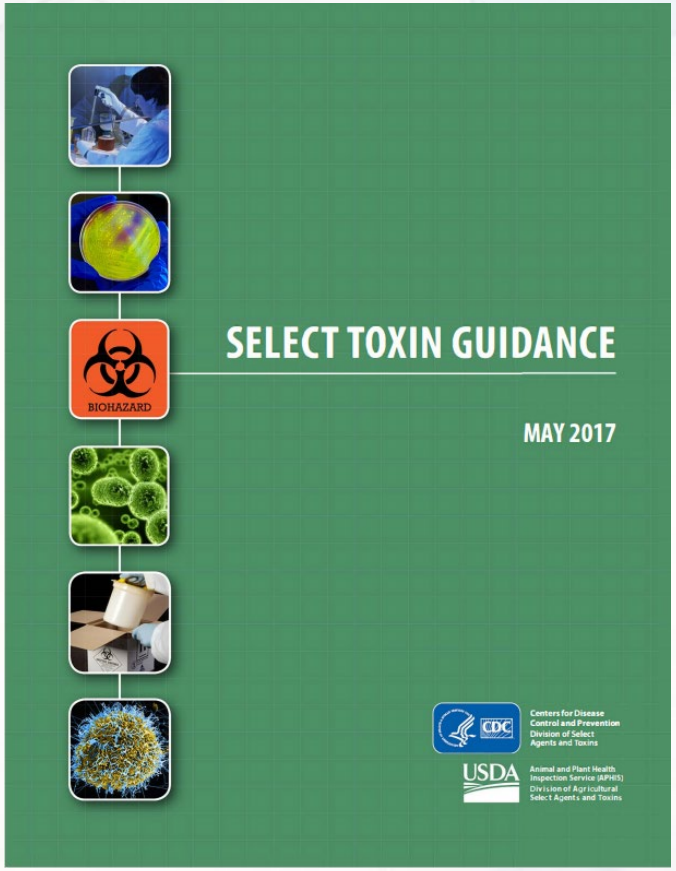
- Does the plan identify the risks posed to individuals, agriculture, and/or the environment by any enhanced select agent or toxin?
- How do the procedures implemented mitigate the biosafety risks posed by enhanced select agents or toxins?
- Does the plan address the availability of countermeasures such as vaccines and medications to employees?
- What changes in medical surveillance or treatment will need to be implemented by an Occupational Health group, that are not required for exposure to a non-modified agent?



Select Toxins Guidance (1/2)

New section added, titled “Work with Modified Select Toxins that Have the Potential to Pose an Enhanced Risk”

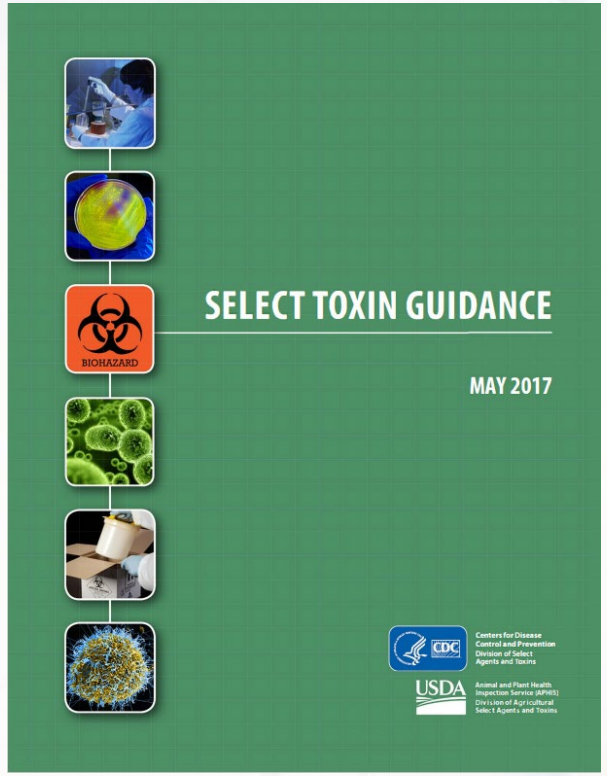
- Examples of modifications that may result in the creation of an enhanced select toxin.
- Refers to the biosafety/biocontainment plan guidance for additional information.



Select Toxins Guidance (2/2)

A select toxin may be considered enhanced or modified to be more potent or toxic if the modifications made to the toxin may result in any of the following:

- Disruption of host immunity against the toxin.
- The ability for the toxin to evade detection methodologies.
- Resistance of the toxin to investigative drugs or therapies.
- Increased stability or potency of a toxin, or an increased ability to disseminate the toxin.
- Alteration of the host range of the toxin.
- An increase in susceptibility of a host population to a toxin due to modifications made to the toxin.



What Should Entities Do?

Considering Select Agent and Toxin Enhanced Work

- Does this apply to all entities? Yes, but…
  - Many entities do not perform this type of work.
  - This only applies to entities that perform work that may modifications that enhance the select agent or toxin in ways that lead to enhanced risk characteristics of the select agent or toxin.

Review Risk Assessments

- Review risk assessments related to enhanced work.
- Make determinations based on risk assessments.
- Assess whether biosafety and biocontainment measures are in place commensurate with the enhanced work being done.
  - Biosafety/biocontainment level, engineering controls, occupational health considerations (if required), Standard Operating Procedures (SOPs), PPE, etc.

Updates to APHIS/CDC Form 1

- Review your Form 1, Section 7A/C (and attachments) to ensure that the work objectives listed for each Principal Investigator (PI) accurately describe any projects or experiments that could potentially enhance the risk characteristics of a select agent or toxin.
- Work with your Point of Contact (POC)/File Manager to submit any amendments to your registration that are needed.

Inventory

- Review your inventory that includes non-wild type select agents or toxins.
- Identify modified or enhanced organisms that could potentially pose an increased biosafety risk.
- Consider a method to easily identify these enhanced risk select agents and prevent them from mixing with wild type select agents and toxins.
- Update your Form 1, Section 7B strain table to indicate any select agents or toxins that have been modified and could be potentially pose an enhanced risk.

Summary

- Assess whether you plan to or are working with select agents and toxins that have been modified.
- Review your risk assessments.
- Ensure that your biosafety (including occupational health program, if required) and incident response plans consider the risks of working with select agents or toxins that may pose an enhanced risk.

www.selectagents.gov

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Animal and Plant Health Inspection Service.