Yale *Environmental Health & Safety*

Yale EHS Biosafety Guidance for Research Involving Prion-like Proteins

Background

Prion-like proteins, also referred to as proteopathic seeds or prionoids, are misfolded protein aggregates capable of inducing abnormal folding of their native protein counterparts through a self-propagating "seeding" mechanism. These aggregates are associated with several neurodegenerative diseases, such as tau (tauopathies), α-synuclein (Parkinson's disease), amyloid-β (Alzheimer's disease), TAR DNA-binding protein 43 (ALS, Alzheimer's disease), and polyglutamine-containing proteins (Huntington's disease).

Unlike classical prions, prion-like proteins are not currently considered naturally transmissible infectious agents. However, a growing body of experimental evidence demonstrates that prion-like protein aggregates can seed protein misfolding in cultured cells and animal models following direct inoculation or other experimental exposures, supporting a precautionary approach when handling prion-like proteins.

BSL-2 Work Practices

Laboratories working with prion-like proteins should incorporate the following enhanced practices:

- Perform manipulations over disposable absorbent material to contain spills and facilitate decontamination
- Whenever practical, use disposable plastic laboratory ware instead of reusable glassware to minimize surface contamination
- Use screw-cap tubes with O-ring seals. Avoid snap-cap tubes, particularly for samples that will be vortexed, sonicated, or centrifuged
- Open tubes inside a certified biological safety cabinet (BSC) after procedures that may generate aerosols (e.g., vortexing, centrifugation)
- Transport samples in sealed, gasketed secondary containers to prevent leakage during movement between laboratories
- Minimize aerosol generation whenever possible

Equipment

- During centrifugation, use sealed safety cups or safety buckets
- For sonication or tissue homogenization, use closed or sealed systems whenever feasible to reduce aerosol generation

Personal Hygiene

- Keep your hands away from your face
- Do not eat, drink, or smoke in the lab
- Do not mouth pipette
- Always wash hands after removing protective clothing and before leaving lab

Decontamination

Although prion-like proteins are generally more susceptible to inactivation than classical prions, routine laboratory disinfectants have not been extensively validated for all aggregate types. As a precaution:

- Decontaminate work surfaces using either 1% sodium dodecyl sulfate (SDS), or 2% Hellmanex
    - Maintain a minimum contact time of 1 hour before wiping or rinsing surfaces
- Collect liquid waste and treat to a final concentration of 1% SDS prior to disposal

Dispose of disposable materials that contact prion-like proteins as biohazardous laboratory waste, overpacked in secondary containment and discarded via incineration only

References:

1. University of Michigan Environment, Health & Safety. (2023, October). *Prion and prion-like protein guidance*. https://ehs.umich.edu/wp-content/uploads/2023/10/Prion-and-Prion-Like-Protein-Guidance.pdf
2. Fielding L, Menard MA, Roth J, Iuliano M, Dehay B, Aguilar-Calvo P, Volpicelli-Daley LA. Current safety recommendations for handling mouse and human αsynuclein pre-formed fibrils. Neurobiol Dis. 2025 Mar;206:106820. doi: 10.1016/j.nbd.2025.106820. Epub 2025 Jan 30. PMID: 39889858.

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