Prions, the infectious agents of fatal and transmissible neurodegenerative disorders of humans and animals, are comprised of assemblies of misfolded forms of prion protein (PrP). The recent death of a 33-year old prion-disease researcher from variant Creutzfeldt-Jakob disease (vCJD, the strain of disease derived from bovine spongiform encephalopathy) nine years after a percutaneous exposure to prion-contaminated material, and two other possible occupational cases in Europe, emphasises the importance of statutory guidance for laboratory safety when working with dangerous pathogens[1]. We have also received numerous contacts from laboratories handling diagnostic blood, CSF and other low-risk biofluid samples from patients with or suspected to have CJD that have led us to conclude that the existing guidance was not sufficiently clear or proportionate.

Over recent years, evidence has accrued of the potential for proteins other than PrP to adopt abnormal conformations, self-propagate and cause transmissible pathologies and diseases in humans and laboratory animals[2,3]. Such proteins share a range of pathological properties with PrP but are also distinct from PrP prions in several important ways, including that there are no known animal or human epidemics or established occupational risks. Experiments that involve inoculating, concentrating or synthesising these so-called "proteopathic seeds" have become routine in the last decade, but no statutory guidance about safety is available. Human-human transmission of amyloid beta proteopathic seeds has been observed in some specific circumstances that historically transmitted prion infection (e.g. use of cadaver-derived human pituitary hormones or dura mater in neurosurgery), and can cause iatrogenic cerebral amyloid angiopathy and fatal brain haemorrhage after long latencies[4]. The relatively recent popularity of this field of research, and the long latencies that are to be expected for disease, means that occupational exposures may not yet have resulted in any clinical consequences. It is prudent therefore to consider potential risks from laboratory work involving these agents.

The UK's Advisory Committee for Dangerous Pathogens convened a Subgroup to revise guidance for safe working with prions and to consider if any measures were needed for proteopathic seeds, involving experts from prion and other neurodegenerative disease research laboratories, infectious disease specialists, pathologists, veterinarians, and Health and Safety experts. In the new Guidance we emphasise a distinction between (1) high-risk central nervous system (CNS) tissues and research samples that contain high concentrations of PrP prions which need to be managed in specialised laboratories with strict policies; and (2) low-risk biofluids, such as blood and cerebrospinal fluid, from patients suspected to have CJD with no or very low concentrations of PrP prions, managed in a high-throughput diagnostic laboratory setting through adherence to appropriate general laboratory practices.

We concluded that the uncertain human pathogenicity of proteopathic seeds when prepared in concentrated forms for biochemical, structural or transmission studies means that they should now be considered as Hazard Group 2 Pathogens, necessitating work in a Containment Level 2 facility. The range of safety measures recommended includes special attention to risk assessment and staff training; recording of accidental exposures; particular caution with the use of any sharp tools to avoid percutaneous injury; work inside a microbiological safety cabinet, the use of spill trays, absorbent material, and defined procedures to decontaminate equipment and spills to avoid contamination of the laboratory environment.

Importantly, we do not recommend any changes to existing procedures for the routine handling of tissues and biofluids from patients with non-prion neurodegenerative conditions for diagnostic or research purposes. We hope that this new guidance will be seen as proportionate and precautionary and help organisations have more confidence about the safety of their employees [*ref published version*].

ACDP Prion Diseases Subgroup

Members:

1. Brandel JP, Vlaicu MB, Culeux A, et al. Variant Creutzfeldt-Jakob Disease Diagnosed 7.5 Years after Occupational Exposure. *N Engl J Med.* 2020;383(1):83-85.
2. Lauwers E, Lalli G, Brandner S, et al. Potential human transmission of amyloid beta pathology: surveillance and risks. *Lancet Neurol.* 2020;19(10):872-878.
3. Jaunmuktane Z, Brandner S. Invited Review: The role of prion-like mechanisms in neurodegenerative diseases. *Neuropathol Appl Neurobiol.* 2020;46(6):522-545.
4. Jaunmuktane Z, Mead S, Ellis M, et al. Evidence for human transmission of amyloid-beta pathology and cerebral amyloid angiopathy. *Nature.* 2015;525(7568):247-250.