ANNEX A1

Distribution of TSE infectivity in human tissues and body fluids

A1.1 There is evidence that the distribution of the disease-specific partially protease-resistant form of prion protein (PrP^{TSE}) in tissues is more widespread in the body in variant CJD (vCJD) patients than in patients affected by sporadic CJD (1, 2, 3). In sporadic CJD, the presence of abnormal prion protein in patients with clinical disease appears to be restricted to the central nervous system (CNS). However, abnormal prion protein has been detected in various lymphoid tissues, including tonsils, spleen, gastrointestinal lymphoid tissue (appendix and rectum), lymph nodes, thymus and adrenal gland of patients with clinical vCJD. Abnormal prion protein has also been detected in lymphoid tissues within the appendix removed from 2 patients some 8 and 24 months before they developed vCJD (4, 5) suggesting that abnormal prion protein could be present in the lymphoid tissue of people incubating vCJD for some time before the onset of clinical disease. In similar tests, abnormal prion protein has not been detected in these tissues from sporadic CJD patients. Infectivity has been demonstrated in tonsil and spleen in vCJD by experimental transmission (6).

A1.2 PrP^{TSE} has been identified in posterior spinal nerve roots in only an occasional case of sporadic CJD and GSS (7), but not in peripheral nerve in vCJD (3, 8). Transmission studies on peripheral nerve samples from cases of sporadic CJD by intracerebral inoculation into primates have shown no evidence of infectivity (9). PrP^{TSE} has been detected in spinal dorsal root ganglia and trigeminal ganglia in vCJD (8), and in trigeminal ganglia in sporadic CJD (10). PrP^{TSE} has also been detected in olfactory epithelium in sporadic CJD patients at post mortem (11), and in the olfactory tract in vCJD (12). Infectivity and PrP^{TSE} have not been detected in dental pulp in a series of sporadic CJD cases (13), and PrP^{TSE} was not detected in the alveolar nerve, dental pulp, gingiva, salivary gland, tongue in a small series of vCJD cases (14).

A1.3 Table A1 presents current information on the distribution of infectivity in tissues and body fluids in CJD other than vCJD, and in vCJD, based on data from experimental studies, where available, and on information from other

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studies of natural TSE disease in humans and animals. It also shows where PrP^{TSE} has been detected in tissues.

A1.4 The precise relationship between the presence of PrP^{TSE} and infectivity is not certain – for example, the absence of detectable PrP^{TSE} does not necessarily mean absence of infectivity. Conversely, detection of small amounts of PrP^{TSE} in a tissue does not necessarily mean that it will transmit disease in all circumstances. This guidance has been formulated on the basis of likelihood of the presence of infectivity using the identification of PrP^{TSE} as a specific marker. In general terms, there is thought to be a broad correlation between PrP^{TSE} load in a given tissue and the likelihood that the given tissue might present a risk of infection. The relative levels of PrP^{TSE} in different tissues provide useful information for the assessment of relative risks of different procedures.

A1.5 In Table A1, tissue infectivity is classified as high, medium or low, on the basis of infectivity assays in experimental animals. Although such studies are limited in CJD and vCJD tissues, the preliminary data that are available support the findings in tissues from other natural and experimental TSE models. Therefore the relative levels of PrP^{TSE} in different tissues provide useful information for the assessment of relative risks of different surgical and endoscopic procedures.

A1.6 The information given in this Annex describes the position at the time of publication. This will be kept under review and is subject to change as further information becomes available.

Table A1 – Distribution of TSE infectivity in human tissues and body fluids

Key: **+ve** = tested positive **-ve** = tested negative
NT = not tested **P** = infectivity proven in experimental transmission studies

Tissue	Presence of abnormal prion protein and level of infectivity			
	CJD other than vCJD		vCJD	
	PrP^{TSE} detected	Assumed level of infectivity	PrP^{TSE} detected	Assumed level of infectivity
Brain	**+ve**	High **P**	**+ve**	High **P**

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Spinal cord	**+ve**	High **P**	**+ve**	High **P**
Cranial nerves, specifically the entire optic nerve and only the intracranial components of the other cranial nerves	**+ve**	High	**+ve**	High
Cranial ganglia	**+ve**	High	**+ve**	High **P**
Posterior eye, specifically the posterior hyaloid face, retina, retinal pigment epithelium, choroid, subretinal fluid, optic nerve	**+ve**	High **P**	**+ve**	High
Pituitary gland	**+ve**	High (?)	**+ve**	High (?)
Spinal ganglia[1]	**+ve**	Medium	**+ve**	Medium **P**
Olfactory epithelium	**+ve**	Medium	**NT**	Medium
Dura mater[2]	**-ve**	Low	**+ve**[4]	Low
Tonsil	**-ve**	Low	**+ve**	Medium **P**
Lymph nodes and other organised lymphoid tissues containing follicular structures	**-ve**	Low **P**	**+ve**	Medium **P**
Gut-associated lymphoid tissue	**-ve**	Low	**+ve**	Medium
Appendix	**-ve**	Low	**+ve**	Medium
Adrenal gland	**-ve**	Low	**+ve**	Medium
Spleen	**+ve**	Low **P**	**+ve**	Medium **P**
Thymus	**-ve**	Low	**+ve**	Medium
Anterior eye and cornea	**-ve**	Low	**-ve**	Low
Peripheral nerve	**+ve**	Low	**+ve**	Low
Skeletal muscle	**+ve**	Low	**+ve**	Low
Dental Pulp	**-ve**	Low	**-ve**	Low
Gingival Tissue	**NT**	Low	**-ve**	Low
Blood and bone marrow	**NT**	Low	**-ve**	Low
CSF[3]	**-ve**	Low **P**	**-ve**	Low
Placenta	**-ve**	Low	**-ve**	Low
Urine	**-ve**	Low	**-ve**	Low
Other tissues	**-ve**	Low **P**	**+ve**[4]	Low

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[1]Spinal ganglia have a high assumed level of infectivity in the WHO Guidelines. However, unpublished results on the infectivity of spinal ganglia indicate that this tissue is of medium infectivity.

[2]Dura mater is designated low infectivity as virtually no detectable abnormal prion protein has been found in cases of CJD; however, as grafts of these tissues are associated with CJD transmission, probably as a result of contamination by brain and because of the lengthy period of implantation in the CNS, procedures conducted on intradural tissues (i.e. brain , spinal cord and intracranial sections of cranial nerves) or procedures in which human dura mater was implanted in a patient prior to 1992, remain high risk.

[3]Although PrP^{TSE} has not been detected in the CSF in either sporadic or variant CJD (15), experimental transmission of infectivity has been achieved from CSF in sporadic CJD in 4 of 27 primates by intracerebral inoculation (9) indicating that levels of infectivity are likely to be much lower than in the central nervous system.

[4]PrPTSE has been detected in dura mater, skin, kidney, liver, pancreas, ovary and uterus in a case of vCJD in USA with a lengthy duration of illness (16). Earlier studies of these tissues in UK vCJD cases gave negative results (2,8,17).

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A comprehensive list of references is given in the WHO Guidelines which should be consulted when further detail is required:

WHO – Guidelines on tissue infectivity distribution in transmissible spongiform encephalopathies; updated 2010
http://www.who.int/bloodproducts/tablestissueinfectivity.pdf

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