# Annex A.2

## Distribution of infectivity in animal tissue and body fluids

### Introduction

A.2.1 The following table (Table A2) presents a guide to the possible presence of TSE infectivity in various tissues and body fluids of cattle (exposed naturally or experimentally and orally to first passage BSE agent), sheep and goats (exposed naturally to scrapie agents and potentially to the BSE agent) irrespective of the stage of incubation. Table A2 has been updated in June 2010 taking account of the updated WHO Guidelines published in 2010 (WHO, 2010).

A.2.2 This is the first time that the WHO Guidelines include tissues from Cervidae affected with Chronic Wasting Disease (CWD). CWD has not been reported in Europe despite some surveillance for it and there are no specific regulations in force. Should information on TSE infectivity in CWD be required, for example in regard to Cervidae in zoos or in animals in transit through our ports, please see updated 2010 WHO Guidelines.

A.2.3 Throughout this document the term $PrP^{TSE}$ is used to denote the disease-specific, partially protease resistant form of PrP. In the previous version the term PrP-res was used but for practical purposes $PrP^{TSE}$ and PrP-res are the same.

A.2.4 Additional notes are ascribed to certain entries to explain the differences (sometimes of interpretation) between the equivalent WHO table and Table A2, or to take account of new information. In case of doubt, please refer to the WHO Guidelines.

A.2.5 Specified risk material (SRM) from cattle, sheep and goats in the UK and most other EU Member States, as at February 2007, is listed in a new table – Table A3 in this document. Please refer to the FSA website for up-to-date information and definitions.

A.2.6 The list of tissues in Table A2 is divided into three categories;

- High infectivity tissues: Central nervous system (CNS) tissues and other tissues anatomically closely associated with them (in italics in the attached table). These become detectably infected in the later stages of all TSEs and into the clinical phase of disease.
- Lower infectivity tissues: A range of peripheral tissues including some or all (depending on species) lymphoreticular system (LRS) tissues that may be infected from shortly after exposure.
- Tissues that have either been bioassayed with no infectivity being detected, and/or tested for $PrP^{TSE}$ and found negative.

Published: 2 June 2003
Updated: 19 July 2010

A.2.7 A fourth category of tissues has not been tested in any of the species and therefore must remain as of uncertain infectivity. However, no tissue in this category is likely to have high infectivity but could become cross-contaminated in certain circumstances.

A.2.8 The following notes are of considerable importance when the table data are used in risk assessments:

- 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 the absence of infectivity. Conversely, detection of small amounts of $PrP^{TSE}$ in a tissue does not necessarily mean that it would transmit disease in all circumstances.
- No account has been taken of the fact that a tissue having no detectable infectivity could become contaminated by inadequate care being taken at the point of collection. Such contamination could be direct (from other infected tissues) or indirect (from contaminated instruments). Furthermore, certain methods of stunning animals (such as those involving penetration of the cranium or use of a pithing rod) prior to killing by bleeding out may cause infected brain emboli to be dispersed into the blood stream and thence also to the heart, lungs and possibly to other organs and tissues.
- In the EU and some other countries certain tissues of ruminant species are categorised as SRM on the basis of a judgment that in an infected animal they would be, or might be infected. The list of tissues classed as SRM may be varied depending on the geographical BSE risk (GBR) ascribed to the host country. Some tissues in the current EC SRM list may not have demonstrated either infectivity or $PrP^{TSE}$, nevertheless any requirements of the law must be followed.
- In research laboratories, tissues from every challenged animal potentially present a risk. However, in diagnostic laboratories in the UK, tissues listed in Table A.2 and the WHO table will present a risk less frequently unless they come from a suspect case of TSE or from a high-risk group.

A.2.9 Extensive data on the distribution of infectivity, additional information and references can be found in the WHO guidelines at the WHO website:

http://www.who.int/bloodproducts/tse/WHO%20TSE%20Guidelines%20FINAL-22%20JuneupdatedNL.pdf. The WHO tables have copious notes which are not included in this ANNEX so the WHO tables should be consulted to aid interpretation of the indicated result, in any case of doubt or to extend knowledge.

The 2010 WHO update can be found at:

http://www.who.int/bloodproducts/tablestissueinfectivity.pdf

Published: 2 June 2003
Updated: 19 July 2010

**TABLE A2: Distribution of TSE infectivity in animal tissues and body fluids**

| | CATTLE | | SHEEP AND GOATS | |
|---|---|---|---|---|
| **TISSUE** | **INFECTIVITY** | **$PrP^{TSE}$** | **INFECTIVITY** | **$PrP^{TSE}$** |
| **HIGH INFECTIVITY** | | | | |
| Brain | + | + | + | + |
| Spinal ganglia (dorsal root ganglia) | + | + | + | + |
| Spinal cord | + | + | + | + |
| Trigeminal ganglia | + | + | NT | + |
| Retina | + | NT | NT | + |
| *Optic nerve* | + | NT | NT | + |
| Pituitary gland | - | NT | + | + |
| **LOWER INFECTIVITY** | | | | |
| **Peripheral nervous system** | | | | |
| Cauda equina | - | NT | NT | NT |
| Peripheral nerves | [+] | + | + | + |
| Autonomic ganglia | NT | + | NT | + |
| **Lymphoreticular tissues** | | | | |
| Spleen | - | - | + | + |
| Lymph nodes | - | - | + | + |
| Nictitating Membrane | + | - | [+] | + |
| Thymus | - | NT | + | + |
| Tonsil | + | - | + | + |
| **Alimentary tract** | | | | |
| Oesophagus | - | NT | [+] | + |
| Fore-stomachs | - | NT | [+] | + |
| Abomasum | - | NT | [+] | + |
| Duodenum | - | - | [+] | + |

Published: 2 June 2003
Updated: 19 July 2010

| | | | | |
|---|---|---|---|---|
| Jejunum | - | + | [+] | + |
| Ileum | + | + | + | + |
| Colon/caecum | - | - | + | + |
| Rectum | NT | NT | NT | + |
| **Reproductive tissues** | | | | |
| Placenta | - | NT | + | + |
| Ovary | - | NT | - | - |
| Uterus | - | NT | - | - |
| **Body fluids, secretions and excretions** | | | | |
| CSF | - | NT | + | - |
| Blood | - | ? | + | ? |
| Saliva | NT | NT | - | NT |
| Milk | - | - | + | [+] |
| Urine | - | NT | - | - |
| Faeces | - | NT | - | NT |
| **Other tissues**** | | | | |
| Adrenal | [+] | + | + | - |
| Liver | - | NT | + | - |
| Pancreas | - | NT | + | NT |
| Nasal mucosa | - | NT | + | + |
| Blood vessels | - | NT | NT | + |
| Skeletal Muscle* | [+] | NT | [+] | + |
| Salivary gland | - | NT | + | NT |
| Mammary gland/udder | - | NT | - | + |
| Skin | - | NT | - | + |
| Adipose tissue | - | NT | NT | NT |
| Heart/pericardium | - | NT | - | NT |
| Lung | - | NT | - | - |
| Kidney | - | - | [+] | + |
| Bone marrow | (+) | NT | + | NT |
| Tongue | - | NT | [+] | + |

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**NO DETECTABLE INFECTIVITY**

Published: 2 June 2003
Updated: 19 July 2010

| | | | | |
|---|---|---|---|---|
| **Reproductive tissues** | | | | |
| Testis | - | NT | - | - |
| Prostate/Epididymis/ | | | | |
| Seminal vesicle | - | NT | - | - |
| Semen | - | NT | - | - |
| Placenta fluids | - | NT | NT | NT |
| Fetus | - | NT | - | - |
| Embryos | - | NT | ? | NT |
| **Musculo-skeletal tissues** | | | | |
| Bone | - | NT | NT | NT |
| Tendon | - | NT | NT | NT |
| **Other tissues**** | | | | |
| Trachea | - | NT | NT | NT |
| Thyroid gland | NT | NT | - | NT |
| **Body fluids, secretions and excretions**** | | | | |
| Colostrum | (-) | - | (?) | NT |
| Cord blood | - | NT | NT | NT |

**Key:**

| | |
|---|---|
| *Italic type* | Tissues included due to close anatomical proximity to high infectivity tissues |
| + | Positive transmission or presence of $PrP^{TSE}$ detected |
| - | Bioassay negative or $PrP^{TSE}$ not detected |
| NT | Bioassay not undertaken or $PrP^{TSE}$ not tested for |
| NA | Not applicable |
| No detectable infectivity | Tissues not included in other parts of the table but bioassayed and /or tested for $PrP^{TSE}$ with negative result. |
| ( ) | Limited or preliminary data |
| ? | Uncertain interpretation |
| [] | Infectivity or $PrP^{TSE}$ data based exclusively on bioassays in transgenic (Tg)mouse over-expressing the PrP-encoding gene, or $PrP^{TSE}$ amplification methods |

* In cattle, preliminary data indicate a low level of infectivity in the *M. semitendinosus* from one cow with clinical BSE. A homogenate of this muscle was inoculated i/c-i/p into ten highly BSE-sensitive transgenic mice and $PrP^{TSE}$ was detected in one mouse (Buschmann and Groschup, 2005). No transmissions have been reported when various bovine tissues have been inoculated into either susceptible mice or cattle by the i/c-i/p or i/c routes respectively. Concern has been expressed about possible infectivity in lingual tonsillar

tissue at the root of the tongue, though the tongue itself shows no detectable infectivity (Wells *et al*., 2005).

** Some tissues tested in humans have not been tested in animals such as cornea, some dental tissues, sweat, tears, mucus and bile.

## SPECIFIED RISK MATERIAL

A.2.10 Specified Risk material (SRM) includes those tissues of cattle, sheep and goats which are known to, or might potentially, harbour detectable BSE infectivity in infected animals. SRM is excluded from the human food and animal feed chains and cannot be used for any other purpose. The tissues which fall within the current definition of SRM are listed on the UK Food Standards Agency website http://www.food.gov.uk/safereating/animaldiseases/bse/what/beef/controls and are given below in Table A3.

## TABLE A3 Specified risk material in the EU (as at November 2006)

| **Specified Risk Material in all Member States from 25 May 2006** | |
|---|---|
| **Cattle** | **All ages**<br>▪ The tonsils, the intestines, from the duodenum to the rectum, and the mesentery<br>**Over 12 months**<br>▪ Skull excluding the mandible but including the brains and eyes, and spinal cord<br>**Over 24 months**<br>▪ Vertebral column, excluding the vertebrae of the tail the spinous and transverse processes of the cervical, thoracic and lumbar vertebrae, the median sacral crest and the wings of the sacrum, but including the dorsal root ganglia |
| **Sheep and goats** | **All ages**<br>▪ The spleen and the ileum<br>**Over 12 months (or permanent incisor erupted)**<br>▪ Skull including the brains and eyes, tonsils, spinal cord |

## REFERENCES

A comprehensive list of references is given in the WHO Guidelines which should be consulted when further detail is required. The following are selected, relatively recent, publications of relevance to the Tables above.

### General

WHO. *Guidelines on tissue infectivity distribution in transmissible spongiform encephalopathies;* June 2006.
http://www.who.int/bloodproducts/tse/WHO%20TSE%20Guidelines%20FINAL-22%20JuneupdatedNL.pdf

WHO. *Guidelines on tissue infectivity distribution in transmissible spongiform encephalopathies;* Updated 2010.

Published: 2 June 2003
Updated: 19 July 2010

http://www.who.int/bloodproducts/tablestissueinfectivity.pdf

## Bovine Spongiform Encephalopathy

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Hoffmann C, Ziegler U, Buschmann A, Weber A, Kupfer L, Oelschlegel A, Hammerschmidtand B, Groschup MH. Prions spread via the autonomic nervous system from the gut to the central nervous system in cattle incubating bovine spongiform encephalopathy. *J Gen Virol* 2007; **88**: 1048–55

Iwamaru Y, Okubo Y, Ikeda T, Hayashi H, Imamura M, Yokoyama T, Shinagawa M.
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Wells GAH, Spiropoulos J, Hawkins SAC, Ryder SJ. Pathogenesis of experimental bovine spongiform encephalopathy (BSE): pre-clinical infectivity in tonsil and observations on lingual tonsil in slaughtered cattle. *Vet Rec* 2005; **156**: 401-7.

## Scrapie

Andreoletti O, Lacroux C, Chabert A, Monnereau L, Tabouret G, Lantier F, Berthon P, Eyenne F, Lafond-Benestad S, Elsen J-M, Schelcher F. PrP(Sc) accumulation in placentas of ewes exposed to natural scrapie: influence of foetal *PrP* genotype and effect on ewe-to-lamb transmission. *J Gen Virol* 2002; **83**: 2607-16.

Casalone C, Corona C, Crescio MI, Martucci F, Mazza M, Ru G, Bozzetta E, Acutis PL, Caramelli M. Pathological prion protein in the tongues of sheep infected with naturally occurring scrapie. *J Virol* 2005; **79**: 5847-9.

## Specified Risk Material

FSA (Food Standards Agency UK). List of tissues which fall within the current definition of Specified Risk Material. 2006:
http://www.food.gov.uk/safereating/animaldiseases/bse/what/beef/controls

Published: 2 June 2003
Updated: 19 July 2010