

WHO Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies

Updated 2010



**World Health
Organization**

WHO/EMP/QSM/2010.1

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INTRODUCTION

The data reported in the “WHO Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies” were originally assembled by an expert group appointed during a WHO Consultation held in 2003 and subsequently updated during a WHO Consultation held in 2005 (see References section). As new information became available, the group updated the tables and they now reflect the current status of knowledge about infectivity in body tissues, secretions, and excretions of humans with sporadic or variant Creutzfeldt-Jakob disease (CJD); cattle with typical or atypical bovine spongiform encephalopathy (BSE); sheep with scrapie; and (for the first time), deer or elk with Chronic Wasting Disease (CWD). It is not the purpose of this document to revise the current “WHO Guidelines on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies” published in 2006, which remain valid, but the new information on tissue infectivity distribution reported here is important in the context of potential transmission of variant CJD through human blood and blood products, as well as through medicinal products prepared with bovine-derived materials, and may have implications for future recommendations.

Since the publication in 2006 of Annex 1 (Major Categories of Infectivity) in the “WHO Guidelines on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies”, some tissues (ovary, uterus, mammary glands/udder, skin, adipose tissue, and heart/pericardium) and body fluids (saliva, milk, urine, and feces) in which infectivity had not been detected, have since been found to contain infectivity or PrP^{TSE} and therefore have there been moved from the category of “tissues with no detectable infectivity” to the category of “lower-infectivity tissues.”

The inclusion of infectivity data in CWD in these Tables was considered important for three reasons: 1) CWD is continuing its spread to new regions of North America, 2) infectivity has been convincingly demonstrated in several bodily secretions and excretions of infected deer and 3) CWD is the only form of animal Transmissible Spongiform Encephalopathies (TSE) that exists in the wild and, although not presently considered to be an important concern for human, could pose serious problems of control in the future, especially as a potential source of infection in other animal species.

MAJOR CATEGORIES OF INFECTIVITY: TABLES IA, IB, IC

The assignment of tissues to high, low, and undetected infectivity categories is based exclusively upon observations of naturally occurring disease, or primary experimental infection by the oral route (in ruminants). The Tables do not include results from disease models using strains of TSE that have been adapted to experimental animals, because passaged strain phenotypes can differ significantly and unpredictably from those of naturally occurring disease. However, for tissues and fluids of exceptional public health interest, such as muscle, intestine, skin, secretions and excretions, experimental results have been indicated in footnotes.

Because the detection of misfolded prion protein (PrP^{TSE}) broadly parallels infectivity titers in various tissues [Beekes et al 1996; Andreoletti et al 2004], PrP^{TSE} testing results are presented in parallel with bioassay data.

Although a given tissue may be positive or negative in different varieties of TSE, the expert group considered a tissue to be potentially infectious even if a positive result occurred in only a single disease. The categorical assignment of tissues will almost certainly undergo further revision as new data accumulate from increasingly sensitive tests.

IA: High-infectivity tissues: CNS tissues that attain a high titer of infectivity in the later stages of all TSEs, and certain tissues that are anatomically associated with the CNS.

IB: Lower-infectivity tissues: peripheral tissues that have tested positive for infectivity and/or PrP^{TSE} in at least one form of TSE.

IC: Tissues with no detectable infectivity: tissues that have been examined for infectivity and/or PrP^{TSE} with negative results.

Data entries are shown as follows:

- + Presence of infectivity or PrP^{TSE}
- Absence of detectable infectivity or PrP^{TSE}
- NT Not tested
- NA Not applicable
- ? Uncertain interpretation
- () Limited or preliminary data
- [] Infectivity or PrP^{TSE} data based exclusively on bioassays in transgenic

(Tg)mice over-expressing the PrP-encoding gene or PrP^{TSE} amplification methods.

A word of caution is offered about tissues in Table IB for which positive results are so far limited to either detection of PrP^{TSE} using amplification techniques (PMCA), or infectivity bioassays in Tg mice that over-express PrP. The amounts of pathological protein or infectious agent detected by these exquisitely sensitive assays may well fall below the threshold of transmissibility for normal animals and humans.

A good example is illustrated in the studies of urine and feces from deer infected with CWD: bioassays using normal deer as recipient subjects were negative; subsequent bioassays performed in Tg mice were positive. A similar discordance was observed for BSE muscle inoculated into cattle and Tgmice. Until more evidence is compiled showing that positive results in experimental PMCA and Tg mouse assays equate to a risk of transmitting disease under natural conditions, it cannot be assumed that such results imply the existence of a substantial risk to the health of animals or humans.

Considering the succession of updated Tables of the past few years, and the fact that inflammation has been shown to result in PrP^{TSE} deposition in tissues that are not normally involved in TSE pathogenesis, it is evident that as testing continues, more tissues will find their way from Table IC into Table IB (but probably not from either Table IC or IB into Table IA). It is also evident that the data generated to date are far from complete, and that a great deal more work needs to be done if conclusions about the tissue distribution and significance of infectivity in a given TSE are to be based on direct measurements rather than by analogy to other forms of the disease.

Finally, it is critically important to understand that categories of infectivity are not the same as categories of risk, which require consideration not only of the level of infectivity in tissue, but also of the amount of tissue to which a person or animal is exposed, and the route by which infection is transmitted. For example, although the level of tissue infectivity is the most important factor in estimating the risk of transmission by instrument cross-contamination during surgical procedures (e.g., neurosurgery versus general surgery), it will be only one determinant of the risk of transmission by blood transfusions, in which a large amount of low-infectivity blood is administered intravenously, or the risk of transmission by foodstuffs that, irrespective of high or low infectivity, involve a comparatively inefficient oral route of infection.

Table IA: High-infectivity tissues

Tissues	Humans				Cattle		Sheep & goats		Elk & deer	
	vCJD		Other TSEs		BSE		Scrapie		CWD	
	Infectivity ¹	PrP ^{TSE}	Infectivity ¹	PrP ^{TSE}	Infectivity ¹	PrP ^{TSE}	Infectivity ¹	PrP ^{TSE}	Infectivity ¹	PrP ^{TSE}
Brain	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	NT	+
Retina	NT	+	+	+	+	NT	NT	+	NT	+
Optic nerve ²	NT	+	NT	+	+	NT	NT	+	NT	+
Spinal ganglia	+	+	NT	+	+	+	+	+	NT	+
Trigeminal ganglia	+	+	NT	+	+	+	NT	+	NT	-
Pituitary gland ³	NT	+	+	+	-	NT	+	+	NT	+
Dura mater ³	NT	(+)	+	-	NT	NT	NT	NT	NT	NT

Table IB: Lower-infectivity tissues

Tissues	Humans				Cattle		Sheep & goats		Elk & deer		
	vCJD		Other TSEs		BSE		Scrapie		CWD		
	Infectivity ¹	PrP ^{TSE}	Infectivity ¹	PrP ^{TSE}	Infectivity ¹	PrP ^{TSE}	Infectivity ¹	PrP ^{TSE}	Infectivity ¹	PrP ^{TSE}	
Peripheral Nervous system											
Peripheral nerves	+	+	(-)	+	[+]	+	+	+	+	NT	+
Autonomic ganglia ⁴	NT	+	NT	(-)	NT	+	NT	+	+	NT	+
Lymphoreticular tissues											
Spleen	+	+	+	+	-	-	+	+	+	NT	+
Lymph nodes	+	+	+	-	-	-	+	+	+	NT	+
Tonsil	+	+	NT	-	+	-	+	+	+	NT	+
Nictitating membrane	NA	NA	NA	NA	+	-	[+]	+	+	NT	+
Thymus	NT	+	NT	-	-	NT	+	+	+	NT	-
Alimentary tract⁵											
Esophagus	NT	-	NT	-	-	NT	[+]	+	+	NT	+
Fore-stomach ⁶ (ruminants only)	NA	NA	NA	NA	-	NT	[+]	+	+	NT	+
Stomach/ abomasum	NT	-	NT	-	-	NT	[+]	+	+	NT	+
Duodenum	NT	-	NT	-	-	-	[+]	+	+	NT	+
Jejunum ⁷	NT	+	NT	-	-	+	[+]	+	+	NT	NT
Ileum ⁷	NT	+	NT	-	+	+	+	+	+	NT	+
Appendix	(-)	+	NT	-	NA	NA	NA	NA	NA	NA	NA
Colon/caecum ⁷	NT	+	NT	-	-	-	+	+	+	NT	+
Rectum	[+]	+	NT	NT	NT	NT	NT	+	+	NT	+
Reproductive tissues											
Placenta ⁸	NT	-	(+)	-	-	NT	+	+	+	NT	-
Ovary ³	NT	-(+)	NT	-	-	NT	-	-	-	NT	-
Uterus ³	NT	-(+)	NT	-	-	NT	-	-	-	NT	-
Other tissues											
Mammary gland/udder ⁹	NT	-	NT	-	-	NT	-	+	+	NT	NT
Skin ^{3,10}	NT	-(+)	NT	-	-	NT	-	+	+	[+]	[+]
Adipose tissue	NT	-	(-)	-	-	NT	NT	NT	NT	[+]	NT
Heart/pericardium	NT	-	-	-	-	NT	-	NT	NT	NT	+
Lung	NT	-	+	-	-	NT	-	-	-	NT	+
Liver ³	NT	-(+)	+	-	-	NT	+	-	-	NT	-
Kidney ^{3,11}	NT	-(+)	+	-	-	-	[+]	+	+	NT	+
Adrenal	NT	+	-	-	[+]	+	+	-	-	NT	+
Pancreas ³	NT	-(+)	NT	-	-	NT	+	NT	NT	NT	+
Bone marrow ¹²	-	-	(-)	-	(+)	NT	+	NT	NT	NT	-
Skeletal muscle ¹³	NT	+	(-)	+	[+]	NT	[+]	+	+	[+]	-
Tongue ¹⁴	NT	-	NT	-	-	NT	[+]	+	+	NT	-
Blood vessels	NT	+	NT	+	-	NT	NT	+	+	NT	-
Nasal mucosa ¹⁵	NT	NT	NT	+	-	NT	+	+	+	NT	+
Salivary gland	NT	-	NT	-	-	NT	+	NT	NT	-	-
Cornea ¹⁶	NT	-	+	-	NT	NT	NT	NT	NT	NT	NT
Body fluids, secretions and excretions											
CSF	-	-	+	-	-	NT	+	-	-	NT	NT
Blood ¹⁷	+	?	-	?	-	?	+	?	?	+	?
Saliva	NT	-	-	NT	NT	NT	-	NT	+	+	[-]
Milk ¹⁸	NT	NT	(-)	NT	-	-	+	[+]	+	NT	NT
Urine ¹⁹	NT	-	-	-	-	NT	-	-	-	- [+]	[+]
Feces ¹⁹	NT	NT	-	NT	-	NT	-	NT	-	- [+]	NT

Table IC: Tissues with no detected infectivity or PrP^{TSE}

Tissues	Humans				Cattle		Sheep & goats		Elk & deer	
	vCJD		Other TSEs		BSE		Scrapie		CWD	
	Infectivity ¹	PrP ^{TSE}	Infectivity ¹	PrP ^{TSE}	Infectivity ¹	PrP ^{TSE}	Infectivity ¹	PrP ^{TSE}	Infectivity ¹	PrP ^{TSE}
Reproductive tissues										
Testis	NT	-	(-)	-	-	NT	-	-	NT	-
Prostate/Epididymis/ Seminal vesicle	NT	-	(-)	-	-	NT	-	-	NT	-
Semen	NT	-	(-)	-	-	NT	-	-	NT	NT
Placenta fluids	NT	NT	(-)	(-)	-	NT	NT	NT	NT	NT
Fetus ²⁰	NT	NT	NT	NT	-	NT	-	-	NT	(-)
Embryos ²⁰	NT	NT	NT	NT	-	NT	?	NT	NT	NT
Musculo-skeletal tissues										
Bone	NT	-	NT	-	-	NT	NT	NT	NT	NT
Tendon	NT	-	NT	-	-	NT	NT	NT	NT	NT
Other tissues										
Gingival tissue	NT	-	-	-	NT	NT	NT	NT	NT	NT
Dental pulp	NT	-	NT	-	NT	NT	NT	NT	NT	NT
Trachea	NT	-	NT	-	-	NT	NT	NT	NT	-
Thyroid gland	NT	-	(-)	-	NT	NT	-	NT	NT	-
Body fluids, secretions and excretions										
Colostrum ²¹	NT	NT	(-)	NT	(-)	-	(?)	NT	NT	NT
Cord blood ²¹	NT	NT	(-)	NT	-	NT	NT	NT	NT	NT
Sweat	NT	NT	-	NT	NT	NT	NT	NT	NT	NT
Tears	NT	NT	-	NT	NT	NT	NT	NT	NT	NT
Nasal mucus	NT	-	-	NT	NT	NT	NT	NT	NT	NT
Bile	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT

Footnotes

1. Infectivity bioassays of human tissues have been conducted in either primates or mice (or both); bioassays of cattle tissues have been conducted in either cattle or mice (or both); and most bioassays of sheep and/or goat tissues have been conducted only in mice. In regard to sheep and goats not all results are consistent for both species; for example, two goats (but no sheep) have contracted BSE naturally [Eurosurveillance, 2005, Jeffrey et al., 2006]. Similarly, most of the results described for CWD were derived from studies in deer, and findings may not be identical in elk or other cervids.
2. In experimental models of TSE, the optic nerve has been shown to be a route of neuroinvasion, and contains high titers of infectivity.
3. No experimental data about infectivity in pituitary gland or dura mater in humans with all forms of human TSE have been reported, but cadaveric dura mater patches, and growth hormone derived from cadaveric pituitaries have transmitted disease to hundreds of people and therefore must be included in the category of high-risk tissues. PrP^{TSE} was detected by immunoblot in the dura mater of a vCJD patient who died in the US after an unusually long incubation period (see also Table IB for other positive tissues: skin, kidney, liver, pancreas, ovary and uterus) [Notari et al., 2010]. It must be mentioned that earlier studies of numerous cases examined in the UK reported all of these tissues to be negative [Ironsides et al., 2002; Head et al., 2004].
4. In cattle, PrP^{TSE} is reported to be inconsistently present in the enteric plexus in the distal ileum, but immunohistochemical examination of tissues from a single 'fallen stock' case of BSE in Japan suggested (albeit equivocally) involvement of myenteric plexuses throughout the small and large intestine [Kimura and Haritani, 2008].
5. In vCJD, PrP^{TSE} is limited to gut-associated lymphoid and nervous tissue (mucosa, muscle, and serosa are negative).
6. Ruminant forestomachs (reticulum, rumen, and omasum) are widely consumed, as is the true stomach (abomasum). The abomasum of cattle (and sometimes sheep) is also a source of rennet.
7. When a large BSE oral dose was used to infect cattle experimentally, infectivity was detected in the jejunum and the ileo-caecum junction in Tg mice overexpressing PrP [courtesy of Dr. M Groschup]. PrP^{TSE} was detected at low incidence in lymphoid tissue of ileum [Terry et al., 2003] and has been detected at an even lower frequency in jejunal lymphoid tissue of cattle similarly infected by the oral route [EFSA, 2009].
8. A single report of transmission of sporadic CJD infectivity from human placenta has never been confirmed and is considered improbable.
9. PrP^{TSE} has been detected in scrapie-infected sheep with chronic mastitis, but not from infected sheep without mastitis [Ligios et al., 2005].
10. Studies in hamsters orally infected with scrapie revealed that PrP^{TSE} deposition in skin was primarily located within small nerve fibers. Also, apical skin 'velvet' from the antlers of CWD-infected deer are reported to contain PrP^{TSE} and infectivity [Angers et al., 2009].

11. PrP^{TSE} detected by immunocytochemistry in the renal pelvis of scrapie-infected heep [Siso et al., 2006]; and in lymphoid follicles within connective tissue adjacent to the renal pelvis in CWD-infected mule deer [Fox et al., 2006].
12. A single positive marrow in multiple transmission attempts from cattle orally dosed with BSE-infected brain [Wells et al., 1999; Wells et al., 2005; Sohn et al., 2009].
13. Muscle homogenates have not transmitted disease to primates from humans with sporadic CJD, or to cattle from cattle with BSE. However, intracerebral inoculation of a semitendinosus muscle homogenate (including nervous and lymphatic elements) from a single cow with clinical BSE has transmitted disease to transgenic mice that over-express PrP at a rate indicative of trace levels of infectivity [Buschmann and Groschup, 2005]. Also, recent published and unpublished studies have reported the presence of PrP^{TSE} in skeletal muscle in experimental rodent models of scrapie and vCJD [Beekes et al., 2005], in experimental and natural scrapie infections of sheep and goats [Andreoletti et al., 2004], in sheep orally dosed with BSE [Andreoletti, unpublished data], and in humans with sporadic, iatrogenic, and variant forms of CJD [Glatzel et al., 2003; Kovacs et al., 2004; Peden et al., 2006]. Bioassays of muscle in transgenic mice expressing cervid PrP have documented infectivity in CWD-infected mule deer [Angers et al., 2006], and experiments are underway to determine whether detectable PrP^{TSE} in other forms of TSE is also associated with infectivity.
14. In cattle, bioassay of infectivity in the tongue was negative, but the presence of infectivity in palatine tonsil has raised concern about possible infectivity in lingual tonsillar tissue at the base of the tongue that may not be removed at slaughter [Wells et al., 2005; EFSA, 2008]. In sheep naturally infected with scrapie, 7 of 10 animals had detectable PrP^{TSE} in the tongue [Casalone et al., 2005; Corona et al., 2006].
15. Limited chiefly to regions involved in olfactory sensory reception.
16. Because only one case of iatrogenic CJD has been certainly attributed to a corneal transplant among hundreds of thousands of recipients (one additional case is considered probable, and another case only possible), cornea has been categorized as a lower-risk tissue; other anterior chamber tissues (lens, aqueous humor, iris, conjunctiva) have been tested with a negative result both in vCJD and other human TSEs, and there is no epidemiological evidence that they have been associated with iatrogenic disease transmission.
17. A wealth of data from studies of blood infectivity in experimental rodent models of TSE have been extended by recent studies documenting infectivity in the blood of sheep with naturally occurring scrapie and in sheep transfused with blood from BSE-infected cattle [Houston et al., 2008]; of deer with naturally occurring CWD [Mathiason et al., 2006]; and (from epidemiological observations) in the red cell fraction (which includes significant amounts of both plasma and leukocytes) of four blood donors in the pre-clinical phase of vCJD infections [reviewed in Brown, 2006; Hewitt et al., 2006]. Plasma Factor VIII administration has also been potentially implicated in a subclinical case of vCJD in a hemophilia patient [Peden et al., 2010]. Blood has not been shown to transmit disease from humans with any form of 'classical' TSE [Dorsey et al., 2009], or from cattle with BSE (including fetal calf blood). A

number of laboratories using new, highly sensitive methods to detect PrP^{TSE} are reporting success in a variety of animal and human TSEs. However, several have experienced difficulty obtaining reproducible results in plasma, and it is not yet clear that positive results imply a potential for disease transmissibility, either because of false positives, or of 'true' positives that are due to sub-transmissible concentrations of PrP^{TSE}. Because of these considerations (and the fact that no data are yet available on blinded testing of specimens from naturally infected humans or animals) the expert group felt that it was still too early to evaluate the validity of these tests with sufficient confidence to permit either a negative or positive conclusion.

18. Evidence that infectivity is not present in milk from BSE-infected bovines includes temporo-spatial epidemiologic observations failing to detect maternal transmission to calves suckled for long periods; clinical observations of over a hundred calves suckled by infected cows that have not developed BSE; and experimental observations that milk from infected cows reared to an age exceeding the minimum incubation period has not transmitted disease when administered intracerebrally or orally to mice [Middleton and Barlow, 1993; Taylor et al., 1995]. Also, PrP^{TSE} has not been detected in milk from cattle incubating BSE following experimental oral challenge [SEAC, 2005]. However, low levels (μg to ng/L) of normal PrP have been detected in milk from both animals and humans [Francini et al., 2006]. PrP^{TSE} has been detected in the mammary glands of scrapie-infected sheep with chronic mastitis [Ligios et al., 2005], and very recently it has been reported that milk (which in some cases also contained colostrum) from scrapie-infected sheep transmitted disease to healthy animals [Konold et al., 2008; Lacroux et al., 2008].
19. A mixed inoculum of urine and feces from naturally infected CWD deer did not transmit disease during an 18 month observation period after inoculation of healthy deer with a heterozygous (96 G/S) *PRNP* genotype [Mathiason et al., 2006]. However, recent bioassays in Tg mice have transmitted disease from both urine [Haley et al., 2009] and feces [Tamgüney et al., 2009]. In addition, mice with lymphocytic nephritis that were experimentally infected with scrapie shed both PrP^{TSE} and infectivity in urine, when bioassayed in Tg mice [Seeger et al., 2005]. Very low levels of infectivity have also been detected in the urine

(and histologically normal kidneys) of hamsters experimentally infected with scrapie [Gregori and Rohwer, 2007; Gonzalez-Romero et al., 2008]. Finally, in an experimental scrapie-hamster model, oral dosing resulted in infectious feces when bioassayed in Tg mice over-expressing PrP [Safar et al., 2008].
20. Embryos from BSE-affected cattle have not transmitted disease to mice, but no infectivity measurements have been made on fetal calf tissues other than blood (negative mouse bioassay) [Fraser and Foster, 1994]. Calves born of dams that received embryos from BSE-affected cattle have survived for observations periods of up to seven years, and examination of the brains of both the unaffected dams and their offspring revealed no spongiform encephalopathy or PrP^{TSE} [Wrathall et al., 2002].

21. Early reports of transmission of sporadic CJD infectivity from human cord blood and colostrum have never been confirmed and are considered improbable. A bioassay from a cow with BSE in transgenic mice over-expressing bovine PrP gave a negative result [Buschmann and Groschup, 2005]; and PrP^{TSE} has not been detected in colostrum from cattle incubating BSE following experimental oral challenge [SEAC, 2005].

References

The references are updated from those published in 2003 and 2006: WHO Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products, 2003; and WHO Guidelines on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies, 2006 ISBN 92 4 154701 4 (<http://www.who.int/blood/products/tse/en>). The update was compiled by an expert group composed of Dr. O. Andreoletti, Mr R. Bradley; Dr P. Brown; Prof. Dr H. Budka; Dr. JP Deslys, Dr. M Groschup, Prof. J.W. Ironside; Prof. M. Pocchiari, Dr. C. Sigurdson, Mr G.A.H. Wells, and Prof. R. Will. Dr Brown coordinated and consolidated the information for review by the group. Sincere thanks are also due to Dr D.M. Asher for the overall editing of the document.

Most of the observations that form the basis for the Tables have been published in the previous WHO Guidelines or cited in scientific reviews. Studies published since the Tables were first created in 2003 have been listed, but no attempt has been made to include the many earlier reports in which only one or two tissues were examined unless they concerned tissues of exceptional current interest. Also, some observations made by, or known to, members of the expert group have not yet been published.

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The 2010 updated version of the WHO Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies provide evidence based information on the tissue infectivity distribution in humans with variant Creutzfeldt-Jakob disease (vCJD), the human disease caused by infection with the bovine spongiform encephalopathy (BSE) agent as well as for other human and animal Transmissible Spongiform Encephalopathies (TSEs).

These tables were first published in 2006 with the WHO Guidelines on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies (see <http://www.who.int/bloodproducts/cs/TSEPUBLISHEDREPORT.pdf>).

Blood Products and Related Biologicals
Quality and Safety: Medicines
Essential Medicines and Pharmaceutical Policies
Health Systems and Services
World Health Organization
20, Avenue Appia
CH-1211 Geneva 27, Switzerland

Telephone 41 22 791 3892/3667
Fax 41 22 791 4730
<http://www.who.int/bloodproducts>
<http://www.who.int/medicines>

