

**FDA TSE Advisory Committee Meeting**  
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**Infectivity of Tissues and Fluids of Humans with Transmissible Spongiform Encephalopathies**

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**NIH Series of 300 Cases of Human Spongiform Encephalopathies Transmitted to Primates: 1963 to present**  
[Brown P, Gibbs CJr, Rodgers-Johnson P, Asher DM, Sulima MP, Bacote A, Goldfarb LG, Gajdusek DC. Ann Neurol 1994;35:513-529]

- Creutzfeldt-Jakob Disease and GSS Variant 282
  - Sporadic CJD 234
  - Iatrogenic CJD 8
  - Familial CJD 36
  - Gerstmann-Sträussler-Scheinker Syndrome 4
- Kuru 18

**NIH Series of 300 Cases of Human Spongiform Encephalopathies Transmitted to Animals: Infectivity Assays**

- Tissue preparation: saline suspensions 1% to 20%
- Assay Animals:
  - Primates
    - Chimpanzee
    - New-world monkeys (squirrel, spider, capuchin)
    - Old-world monkeys (less sensitive, longer incubation)
  - Other (small number, much less sensitive)
    - Rodents, cat, ruminants
- Inoculation: intracerebral route, 0.05 to 0.1 ml vol

**NIH Series of 300 Cases of Human Spongiform Encephalopathies Transmitted to Primates: Interpretation of Infectivity Assays**

- Positive:
  - Animal ill or found dead; histopathology showed typical spongiform change in brain. (Later, Western immunoblot positive for protease-resistant prion protein [PrP-res].)
- Negative:
  - Animal survived for at least one SD longer than the mean incubation period of positive animals of the same species (24 to 70 mo); if dead, histopathology did not show typical spongiform change in brain. (Later, Western immunoblot negative for PrP-res.)
- Inconclusive: Neither.

**Infectivity of Neural Tissues and Fluids from Humans with TSEs**

Tissue or Fluid Tested	Positive/ Total Tested	% Positive
Brain	234/259	90
Eye*	4/5	80
Spinal cord	4/6	67
CSF	3/26	26

\* Specimens of retina, vitreous, lens, cornea

**Infectivity Detected in Non-neural Tissues from Humans with TSEs**

Tissue Tested	Positive/ Total Tested	% Positive
Lung	2/4	50
Lymph node	3/15	20
Kidney*	5/28	18
Liver	4/35	11
Spleen*	3/31	10

\* Two pooled specimens of kidney plus spleen also transmitted disease.

### Estimated Amounts of Infectivity in Tissues of Persons Dying with TSEs

- Human TSE brains usually contained  $\geq 10,000$  primate intracerebral lethal doses per gram of tissue ("pooled" data  $10^{4.8}$  LD<sub>50</sub> per gm).
  - 27 positive brains tested in dilutions  $> 1\%$  (sCJD 21, kuru 3, GSS 2, rCJD 1)
  - 73 % (19/26) of brains were positive at 1:10,000
  - 43 % (6/13) were positive at 1:1,000,000
  - 13 % (1/8) were positive at 1:100,000,000
  - None of 6 was positive at 1:1,000,000,000
- Primate brains contained  $10^5$  to  $10^7$  LD<sub>50</sub>/gm
- Other human tissues probably contained  $\leq 1000$  LD<sub>50</sub>/gm

### Tissues from Humans with TSEs Not Transmitting Disease to Primates

- Blood 0/12
- Bone marrow 0/3
- Peripheral nerve 0/5
- Muscle 0/9
  - Skeletal 0/5
  - Heart 0/4
- Adrenal 0/3
- Adipose tissue 0/1
- Gingiva 0/1
- Intestine 0/1
- Placenta/amnion 0/1
- Prostate 0/1
- Testis 0/1
- Thyroid 0/1

### Fluids, Secretions, Excretions from Humans with TSEs Not Transmitting Disease to Primates

- Urine 0/11
- Feces 0/7
- Saliva 0/6
- Tears 0/4
- Nasal secretion 0/3
- Sputum 0/3
- Milk 0/2
- Vaginal secretion 0/2
- Semen 0/1

### Infectivity of Materials from Humans with TSEs: Limitations of Negative Transmission Attempts

- **Small sample sizes were studied.**
  - Small numbers of specimens
  - Small volumes of tissues and fluids
- **Species barriers reduce sensitivity of infectivity assays.** (Incubation periods in primates drop on first primate-to-primate serial passage, then remain stable on subsequent passages. That suggests the presence of some species barriers between non-human primates and humans.)
- **Limits of detection in primates for human infectivity present in human materials are unknown.**
- **There may be variation in distribution of infectivity in tissues of humans with TSEs**
  - Clinical illness
  - Asymptomatic incubation periods (not amenable to study)

### Infectivity of Tissues from Humans with TSEs: Conclusions

- Infectivity was consistently detected ( $\geq 50\%$  of attempts) in brain, eye, spinal cord, and lung of persons with TSEs.
- Infectivity was detected less often ( $\geq 10\%$  but  $< 50\%$  of attempts) in cerebrospinal fluid, lymph node, kidney, liver, and spleen.
- Infectivity was not detected in a variety of other tissues, fluids, secretions and excretions of persons dying with TSEs, but the number of samples tested was small.

### Infectivity of Tissues from Humans with TSEs: Conclusions

- It remains possible that infectivity might be present inconsistently or in small amounts in those negative tissues, fluids, secretions or excretions of persons with TSEs or incubating TSEs.  
(No evidence--anecdotal or epidemiological--suggests transmission from person to person by ordinary contact with those materials.)