

## Chapter 1 Prion

### 1.1 General overview of prion and prion diseases

Scrapie is a prion agent. Prions are 'self-replicating' basic proteins of small molecular weight. Prions form a new class of infectious agents responsible for a number of slow degenerative central nervous system diseases of humans and other animal species. The transmissible spongiform encephalopathies (TSEs) are a group of progressive neurological prion diseases, including scrapie in sheep and goats, bovine spongiform encephalopathy (BSE) in cattle and Creutzfeldt-Jakob disease (CJD) in humans (Gale 2006). Public awareness of prion diseases have been raised after an outbreak of BSE occurred among cattle in many European countries and scientific evidence indicated the foodborne transmission of BSE to humans (Will et al. 1996; Smith and Bradley 2003).

The disease is most easily transmitted to humans via consuming food contaminated with the brain or spinal cord of infected carcasses.

### 1.2 Summary Data

Diringer et al. (1998) inoculated outbred Syrian hamsters orally with graded doses of scrapie agent. The infectious agent was prepared from the brains of scrapied hamsters at the terminal stage of disease.

Jacquemot et al. (2005) exposed C57BL/6 mice to mouse-adapted scrapie strain C506M3 via the intraperitoneal route. The inoculum was a brain homogenate at 10% (wt/vol) in 5% glucose solution from a mouse with scrapie at the terminal stage of disease

Taylor et al. (1995) injected Weanling RIII/FaDk-ro mice with pooled BSE-infected brain. They measured the titer of infectivity by bioassay in mice. The infectious agent was prepared from the brains of 861 cattle with suspected BSE obtained between August and November 1990 from five veterinary centers throughout England.

**Table 1.1. Summary of the prion data and best fits**

Experiment Number	Reference	Host Type/Pathogen Strain	Route/# of Doses	Dose Units	Response	Best Fit Model	Optimized Parameter(s)	LD <sub>50</sub>
1	Diringer et al. 1998	hamsters/scrapie strain 263K	oral /5	LD50 i.c.	Death	beta-Poisson	$\alpha = 1.76$ $N_{50} = 1.04E+05$	1.04E+05
2	Jacquemot et al. 2005	mice/scrapie strain C506M3	intraperitoneal /3	LD50 i.c.	Death	exponential	$k = 2.40E-05$	2.89E+04
3	Taylor et al. 1995	mice/BSE agent	Unknown type of injection/4	ID50 unit	Infection	exponential	$k = 0.69$	1.00

**The data were not able to be statistically pooled.**

### 1.3 Optimized Models and Fitting Analyses

#### 1.3.1 Optimization Output for experiment 1

**Table 1.2. Hamsters/scrapie strain 263K Strain model data**

Dose	Dead	Survived	Total
200	0	40	40
2000	1	79	80
20000	9	71	80
200000	58	22	80
2000000	29	1	30

Diringer et al. 1998

**Table 1.3. Goodness of Fit and Model Selection**

Model	Deviance	$\Delta$	DF	$\chi^2_{0.95,1}$ p-value	$\chi^2_{0.95,m-k}$ p-value
Exponential	14.54	12.62	4	3.84	9.49
Beta Poisson	1.92		3	4.00E-04	7.81

**Beta Poisson is best fitting model**

**Table 1.4 Optimized parameters for the best fitting (beta Poisson), obtained from 10,000 bootstrap iterations**

Parameter	MLE Estimate	Percentiles					
		0.5%	2.5%	5%	95%	97.5%	99.5%
$\alpha$	1.76	--	--	--	--	--	--
$N_{50}$	1.04E+05	--	--	--	--	--	--
LD <sub>50</sub> (spores)	1.04E+05	7.06E+04	7.83E+04	8.21E+04	1.33E+05	1.41E+05	1.54E+05

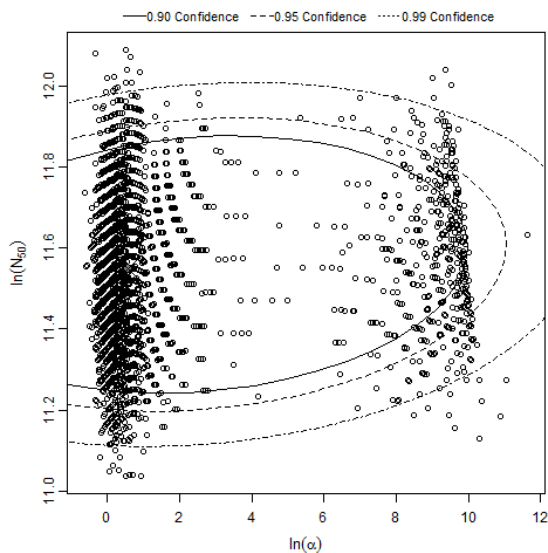


Figure 1.1 Parameter scatter plot for beta Poisson model ellipses signify the 0.9, 0.95 and 0.99 confidence of the parameters.

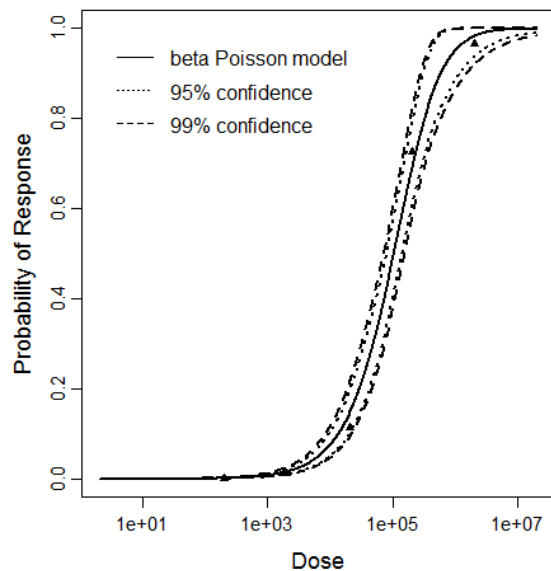


Figure 1.2 beta Poisson model plot, with confidence bounds around optimized model

### 1.3 Optimized Models and Fitting Analyses

#### 1.3.2 Optimization Output for experiment 2

**Table 1.5 Mice/ scrapie strain C506M3 model data**

Dose	Dead	Survived	Total
125	0	11	11
1250	1	9	10
12500	2	8	10

Jacquemot et al. 2005

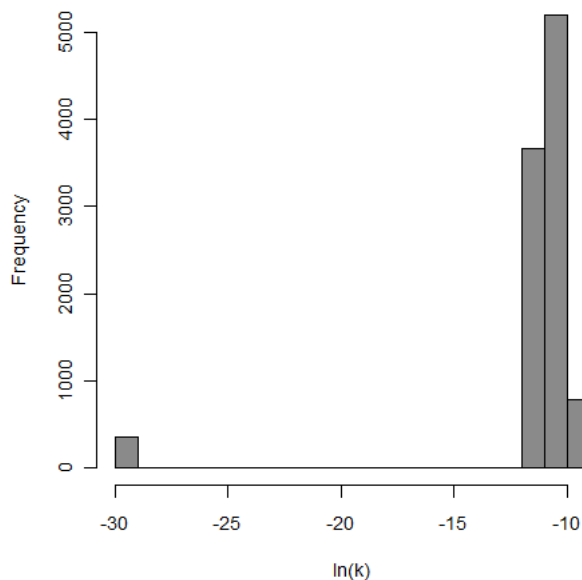
**Table 1.6. Goodness of Fit and Model Selection**

Model	Deviance	$\Delta$	DF	$\chi^2_{0.95,1}$ p-value	$\chi^2_{0.95,m-k}$ p-value
Exponential	1.34	0.99	2	3.84	5.99
Beta Poisson	0.35		1		3.84

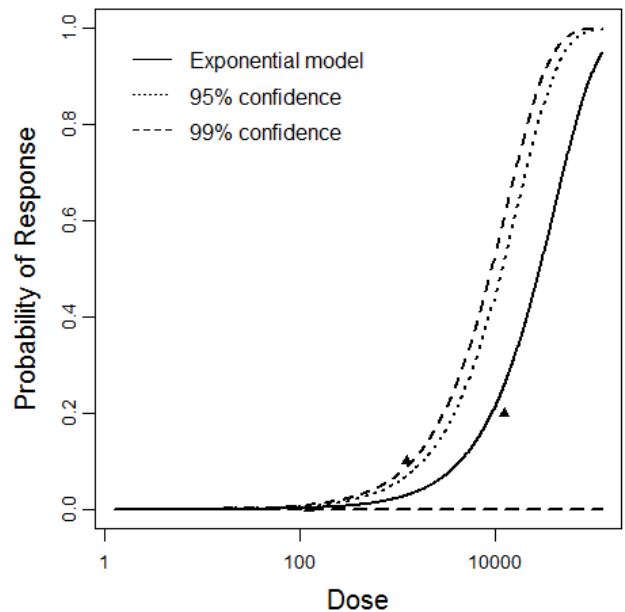
**Exponential is best fitting model**

**Table 1.7 Optimized parameters for the best fitting (exponential), obtained from 10,000 bootstrap iterations**

Parameter	MLE Estimate	Percentiles					
		0.5%	2.5%	5%	95%	97.5%	99.5%
k	2.40E-05	1.00E-13	1.00E-13	7.23E-06	5.47E-05	5.81E-05	7.44E-05
LD <sub>50</sub> (spores)	2.89E+04	9.32E+03	1.19E+04	1.27E+04	9.58E+04	6.92E+12	6.92E+12



**Figure 1.3 Parameter histogram for exponential model (uncertainty of the parameter)**



**Figure 1.4 Exponential model plot, with confidence bounds around optimized model**

### 1.3 Optimized Models and Fitting Analyses

#### 1.3.3 Optimization Output for experiment 3

Dose	Infected	Non-infected	Total
0.0186	0	13	13
0.186	4	12	16
1.856	9	5	14
18.56	13	0	13

Taylor et al. 1995

Model	Deviance	$\Delta$	DF	$\chi^2_{0.95,1}$ p-value	$\chi^2_{0.95,m-k}$ p-value
Exponential	2.77	0.76	3	3.84 0.384	7.81 0.429
Beta Poisson	2.01		2		5.99 0.366

**Exponential is best fitting model**

Parameter	MLE Estimate	Percentiles					
		0.5%	2.5%	5%	95%	97.5%	99.5%
k	0.69	0.30	0.36	0.40	1.16	1.32	1.64
LD <sub>50</sub> (Spores)	1.00	0.42	0.53	0.60	1.73	1.95	2.28

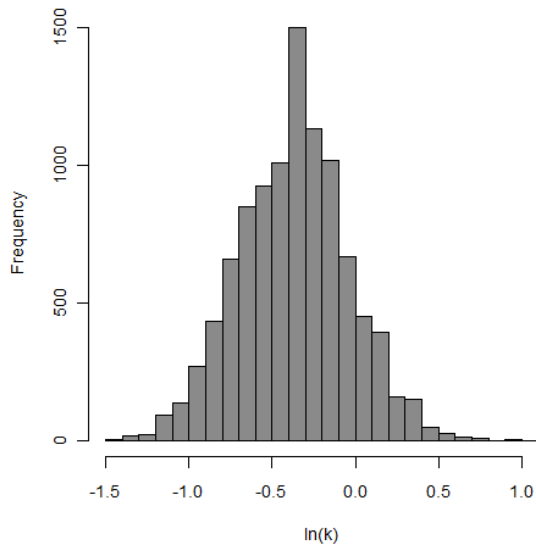


Figure 1.5 Parameter histogram for exponential model (uncertainty of the parameter)

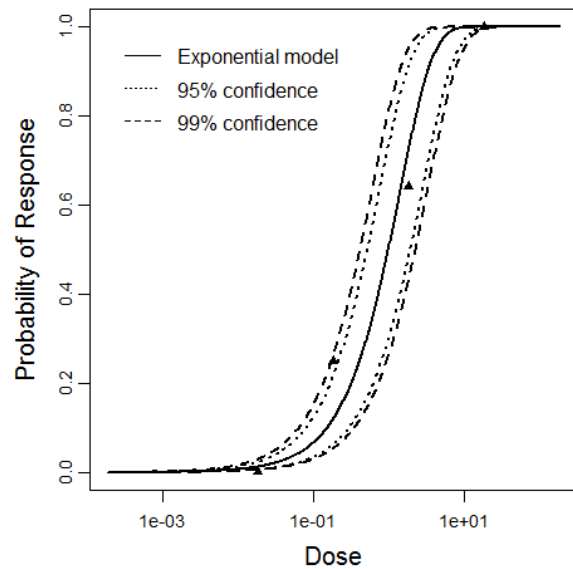


Figure 1.6 Exponential model plot, with confidence bounds around optimized model

#### **1.4. Summary**

One should note that the dose unit in the literature was not given as organism number or cfu/pfu, so the relative units were presented.

#### **References**

Diringer, H., roehmel, J. and Beekes, M. (1998) Effect of repeated oral infection of hamsters with scrapie. *Journal of General Virology* **79**, 609-612.

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