Paper GM2.3 - 55th Annual Meeting of the EAAP, 5-9 September, 2004. Bled, Slovenia. Corresponding author's e-mail: cdiaz@inia.es

FIRST RESULTS ON MODELLING LEVEL OF INFECTION TO DETECT A POLYGENIC EFFECT ASSOCIATED TO SUSCEPTIBILITY TO SCRAPIE IN A ROMANOV FLOCK.

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ECOLE NATIONALE VETERINAIRE TOULOUSE

INTRODUCTION

- ***Scrapie*** **is one TSE affecting sheep and goats.**
- **Susceptibility to *scrapie* is mainly controlled by polymorphisms at codons 136, 154 and 171 of the PrP gene.**
- **In general, the incidence of infectious diseases is strongly influenced by environmental factors (Soller and Andersson, 1998). In natural scrapie some non genetic factors associated to vertical and horizontal transmission have been described (ej. Elsen at al., 1999; Díaz et al., 2004).**

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INTRODUCTION

- **Level of exposure (LEX) and PrP genotype have a large effect on the risk of animals to show scrapie signs.**

- **Increasing level of exposure to prion agent increases risk of infection and affect variation of IP of TSE affected animals (Gravenor et al., 2003).**

- **Artificial challenge is used to study genetic basis of susceptibility: doses of infection and timing are known. However, in naturally infected populations doses, timing etc are unknown.**

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OBJECTIVE

The goal of this preliminary study was to compare:

- **Measurements of infection**
- **Mechanisms of action**

to explain differences in risk of animals to show scrapie signs .

DATA

- **Data from Langlade experimental INRA farm. This flock is naturally infected with *scrapie*. First outbreak in April 1993.**

- **Data of 4049 Romanov animal alive between the 1st of April 1993 and the 4th of March of 2002. Animals were born between 1983 and 2002.**

- **447 died of *scrapie*.**

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MEASUREMENTS OF INFECTION

- **Positive Placentas: infectious placenta from scrapie-affected ewes carrying foetus with susceptible genotypes (Tuo et al., 2002; Andreoletti et al., 2002).**

- **Infected animals: animals showing signs of scrapie confirmed by positive histology.**

ASSUMPTIONS

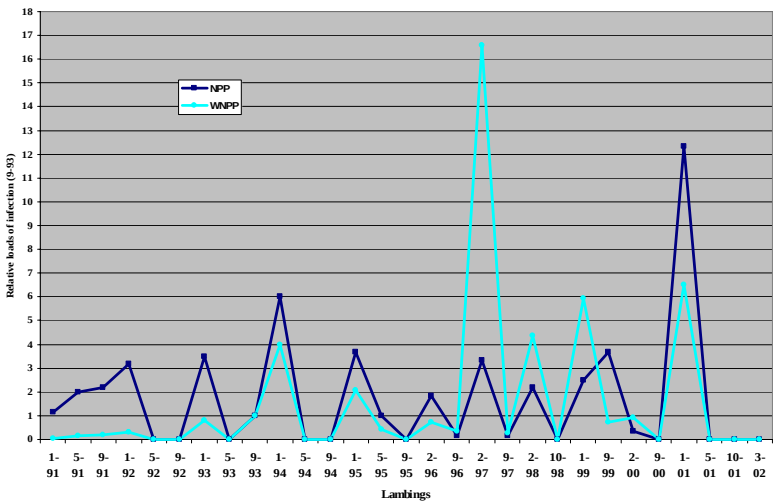
- All animals become exposed from the very first moment they have the opportunity to.
- Infected animals are assumed to become infectious when they have the first contact with the flock (birth, arrival, beginning).
- All infected individuals contribute to infection regardless their genotype.
- The infectiousness of an individual increases during the incubation period.
- Infection loads change from lambing to lambing.

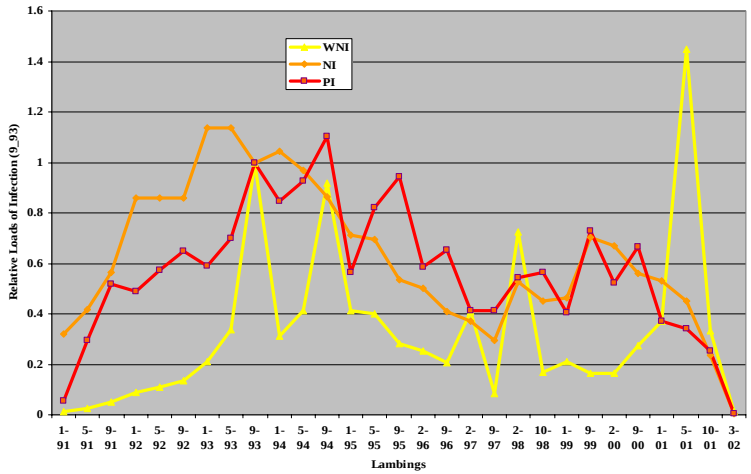
INFECTION LOADS

- **NPP (π) : number of placenta positive units.**
- **WNPP (π)** $= \sum_{i=1}^{NPP} 1/d_i$
- **NI (π) = number of infected animals**
- **WNI (π) =** $= \sum_{i=1}^{NI} 1/d_i$
- **PI (π) = NI (π) /NS (π)**

MECHANISMS OF ACTION OR LEVEL OF EXPOSURE (1)

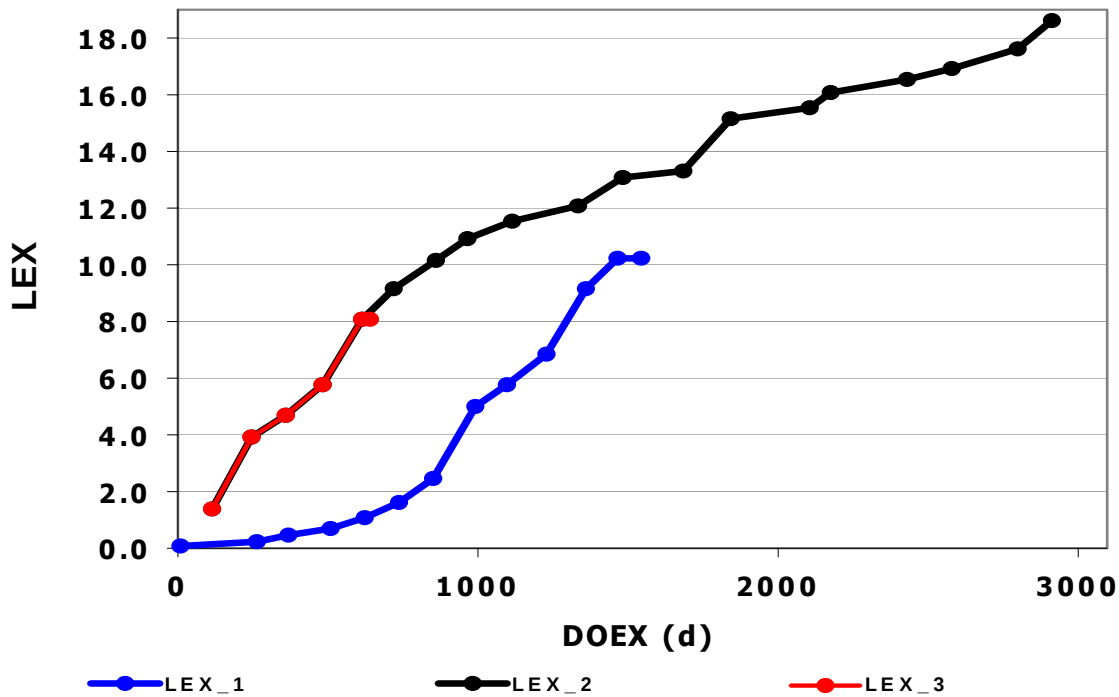
- **ME: animals have Multiple Exposures each with a corresponding infection load at each lambing.**





MECHANISMS OF ACTION OR LEVEL OF EXPOSURE (2)

- **ILE: animals have an Increasing Level of Exposure from lambing to lambing.**



Survival Analysis (1)

$$\lambda_i(t) = \lambda_0(t)exp\{X\beta\}$$

Failure time: the period between the first exposure to infection and the date they left the flock with *scrapie* signs (DOEX):

Beginning of infection was assumed in January, 1991.

First exposure:

- **In 1991: born before.**
- **Date of birth: born after .**
- **Entry date: born outside.**

Survival Analysis (2)

$$\lambda_i(t) = \lambda_0(t)exp\{X\beta\}$$

- **Uncensored data:**

  Clinical signs + Positive histology.

- **Censored data:**

  - animal still alive on March, 2002

  or

  - "naturally dead".

- **Survival Analysis was performed using Survival Kit (Ducrocq and Sölkner, 1998).**

Model of Analysis

$$\lambda_i(t) = \lambda_0(t)\exp\{F_j + AFE_k + Sx_l + PrP_m + f(LEX)_n(\pi) + Rt\_dds_o + Ls_p\}$$

$\lambda_0(t)$ **Baseline function**

F = Experimental Group
Sx = Sex of the animal.
AFE= Age at firts exposure
PrP= Genptype
f (LEX)= Polynomial function of level of infection.
RT_dds= Interation between rearing type and dam scrapie status
Ls= Litter sire

Comparisons of Models:

- **AIC= –2 log L + 2 p**
- **BIC= -2 log L + p log γ**

Table 1. Polynomial degree (p.d.), -2LogL, number of parameters (p), AIC BIC for all models left after LRT.

LI	LEX	p.d	-2LogL	p	AIC	BIC
NPP	ME	4	5178.08694	23	5224.08694	5318.44577
	ILE	2	5181.76381	21	5223.76381	5309.91753
WNPP	ME	2	5223.42023	21	5265.42023	5351.57395
	ILE	4	5102.04362	23	5148.04362	5242.40245
NI	ME	4	5172.40219	23	5218.40219	5312.76103
	ILE	2	5178.40149	21	5220.40149	5306.55521
WNI	ME	3	5030.55926	22	5074.55926	5164.81554
	ILE	2	4907.98176	21	4949.98176	5036.13548
PI	ME	4	5067.28503	23	5113.28503	5207.64387
	ILE	3	5028.87419	22	5072.87419	5163.13047

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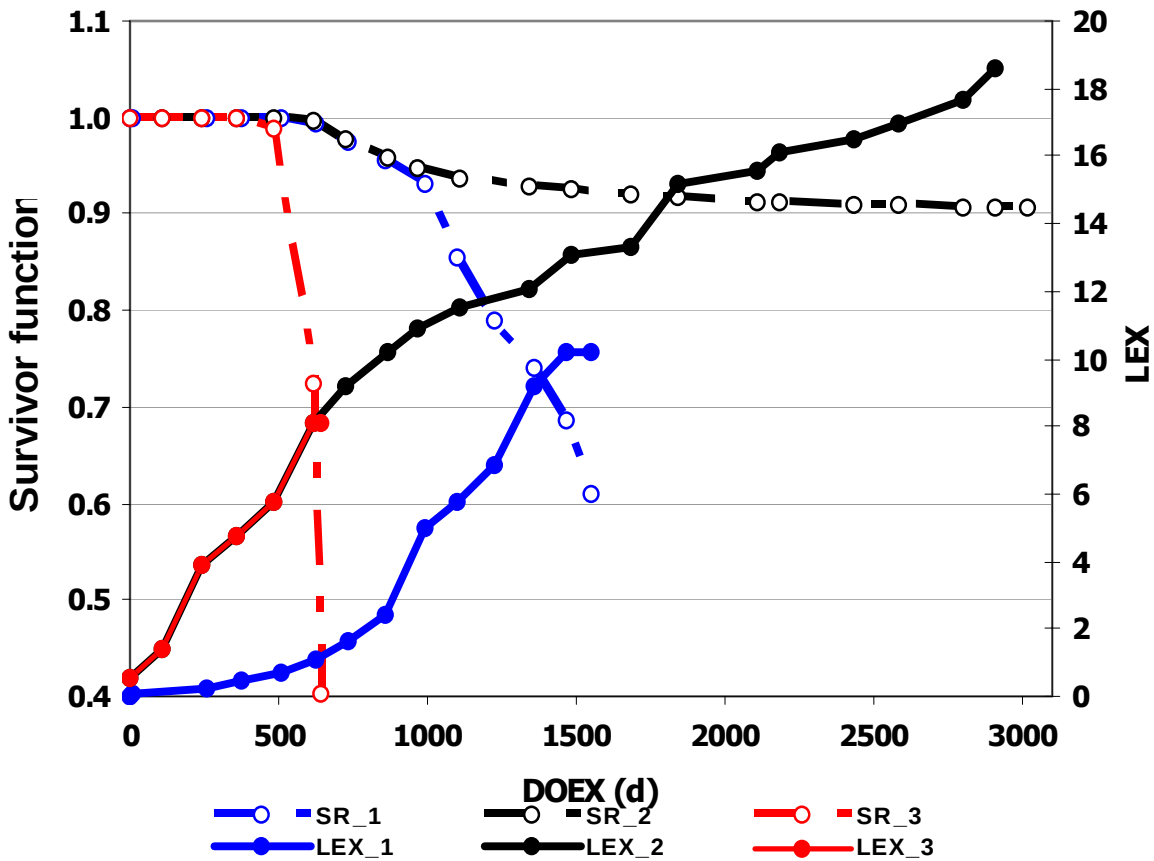
Table 2. Number of scrapie cases, Risks relative to ARQ-ARQ, incidence of scrapie cases among all individual exposed at least 365 days per PrP genotype

Genotypes	Num. of scrapie	Range of Relative Risk	Num. of Animals	% of Scrapie animals
VRQ/VRQ	112	3.35	169	66.2
ARQ/VRQ	227	1.0	439	52.0
ARQ/ARQ	86	0.56	228	37.7
AHQ/AHQ	1	0.035	13	7.7
ARR/VRQ	6	0.035	160	3.8
AHQ/ARQ	6	0.030	99	6.0
AHQ/VRQ	2	0.014	105	1.9
ARR/ARQ	2	0.013	108	1.8
ARR/AHQ	0	0.000	75	0
ARR/ARR	0	0.000	145	0

Survival Rate and Level of Exposure of three different animals



Conclusions

BASED ON THE ASSUMPTIONS MADE:

- **WNI as a measurement of infection and ILE as hypothesis of action seem to describe better the risk of animals to show scrapie signs.**
- **LEX_F seems to have more biological interpretation.**
- **Polygenic variance may not be a negligible part of the total genetic variances associated to susceptibility.**