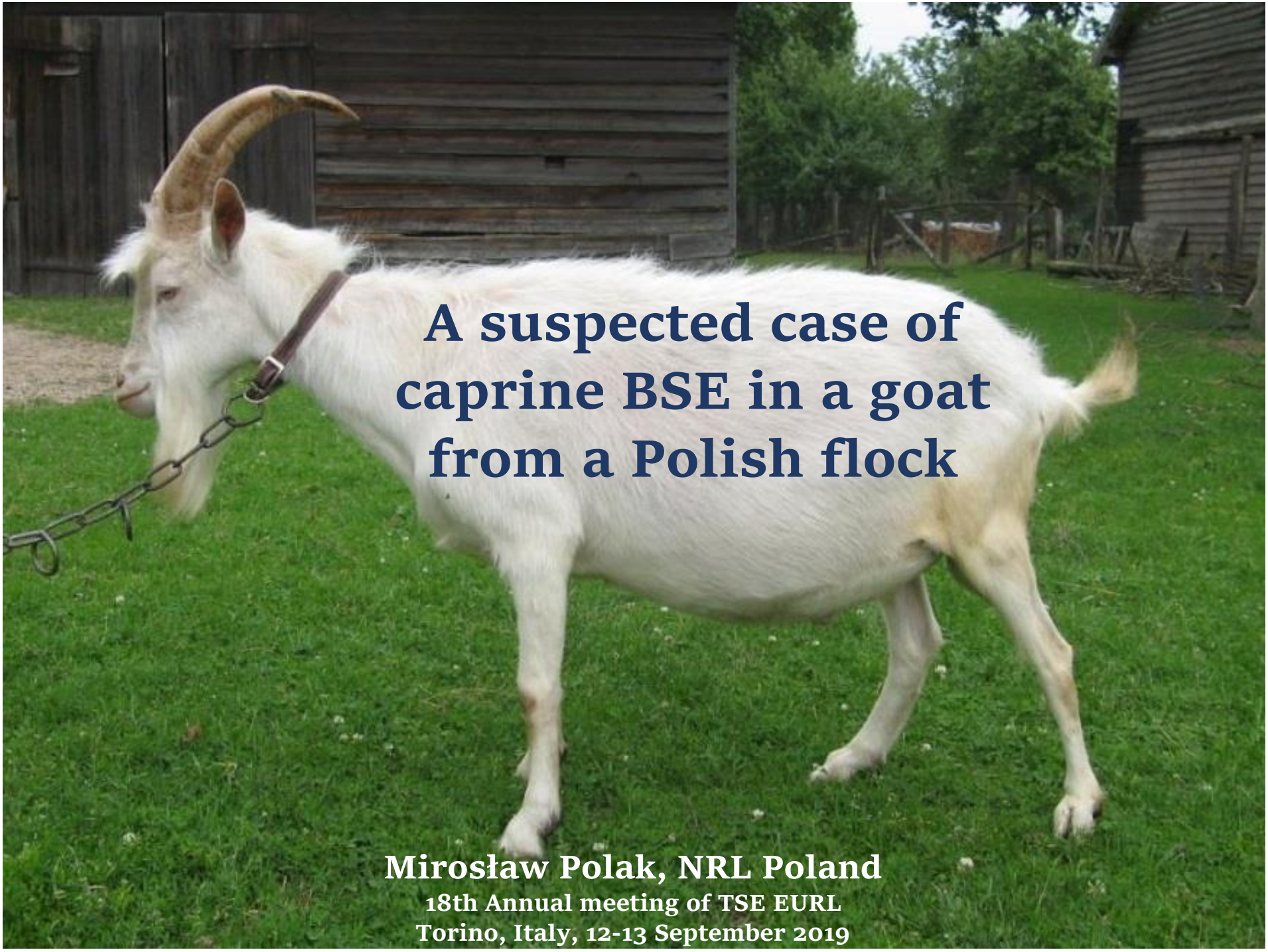


A suspected case of caprine BSE in a goat from a Polish flock

Mirosław Polak, NRL Poland

18th Annual meeting of TSE EURL
Torino, Italy, 12-13 September 2019

TSE discriminatory testing background

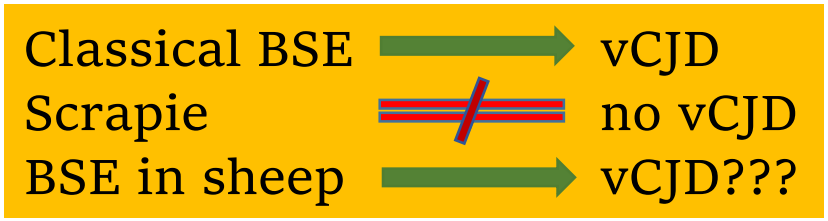
BSE – a wolf in sheep's clothing?

Matthew Baylis, Fiona Houston, Rowland R. Kao, Angela R. McLean, Nora Hunter and Mike B. Gravenor

The entire sheep flock in the UK has been threatened with slaughter if BSE is found in farmed sheep, largely on the grounds that an epidemic of BSE in sheep could be harder to contain than was the case for cattle, and that lamb could present a greater risk to consumers than beef. However, identifying BSE in a sheep is not straightforward, because of its similarities to the related disease, scrapie. Here, we review the likelihood that any UK sheep have BSE, how they might have got it, how a case could be identified and what the Government is doing in terms of surveillance and possible control methods.

Published online: 31 October 2002

In September 2001, the UK government published its



The relative economics of cattle versus sheep have probably contributed to the difference in the policies for cattle and sheep BSE but the different nature of the diseases and the absence of precise data on sheep BSE have played an even greater part. Encouragingly, sheep themselves could have an alternative solution encoded in their genes, and the UK government is earnestly pursuing this possibility by instigating a policy of selective breeding for resistance.

'...there are reasonable grounds for believing that up to several thousand farmed sheep could have been infected with BSE...'

Cause for concern

There have been no proven or even putative cases of BSE identified in farmed sheep. To date, all known cases of the disease have been induced under laboratory conditions by the experimental infection of sheep with tissue from infected animals (Fig. 1). Nevertheless, there are reasonable grounds for believing that up to several thousand farmed sheep

'...the similar tissue tropisms of the infectious agents of BSE and scrapie in sheep suggest that BSE could, potentially, be transmissible from sheep to sheep.'

Fig. 1. Cheviot sheep showing early clinical signs of experimental BSE. The signs included ataxia, altered behaviour and rubbing (note loss of hair on face).

Marc Eloit, Karim Adjou, Muriel Coulpier, Jean Jacques Fontaine, Rodolphe Hamel, Thomas Lilin, Sebastien Messiaen, *UMR 1161 INRA/AFSSA/ENVA, 7 avenue de Général de Gaulle, 94704 Maisons Alfort, France*
Olivier Andreoletti, *UMR INRA/ENVT 1225, École Nationale Vétérinaire de Toulouse, 23 Chemin des Capelles, 31076 Toulouse, France*
Thierry Baron, Anna Bencsik, Anne Gaelle Biacabe, *AFSSA Lyon, avenue Tony Garnier, 69007 Lyon, France*
Vincent Beringue, Hubert Laude, Annick Le Dur, Jean Luc Vilotte, *INRA, VIM, Domaine de Vilvert, 78352 Jouy-en-Josas Cedex, France*
Emmanuel Comoy, Jean Philippe Deslys, *CEA, Neurovirologie, 92265 Fontenay-aux-Roses, France*
Jacques Grassi, Stephanie Simon, *Service de Pharmacologie et d'Immunologie, CEA/Saclay, 91191 Gif-Sur-Yvette, France*
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BSE agent signatures in a goat

SIR, – One of the concerns about BSE is the potential presence of the agent in small ruminants, sheep and goats, as well as cattle. With the objective of documenting this, seven French laboratories have analysed 438 brain samples from confirmed cases of TSE in sheep and goats. These comprised clinical cases recorded from 1990 (216), and samples collected in the framework of active surveillance in 2002 (135 positive cases among 27,085 goats tested) and 2003 (87 positive cases among 22,835 goats tested) at slaughterhouses or from fallen stock.

The samples were first screened by four biochemical tests which all detect a common, albeit not completely specific, feature of the BSE strain, that is, an increased sensitivity to proteinase K digestion of the N-terminal part of PrP^{res} as compared with most scrapie strains (Stack and others 2002). Three different Western blot tests and one ELISA were conducted independently in four different laboratories (Lezmi and others 2004). Each sample was tested by at least three of the four tests. For one goat sample (CH636), the four tests provided convergent results, which were indistinguishable from those obtained with a control sample from a sheep and/or a goat experimentally infected with BSE (Fig 1a). Based on these criteria, CH636 was classified as a BSE suspect. Sequence analysis of the DNA extracted from this sample evidenced only goat sequences. The goat had been identified at an abattoir during the 2002 survey and belonged to a flock comprising 310 other goats. No PrP^{res} was detected in the brain or lymphoid organs of all remaining goats, whose carcases were destroyed.

The same CH636 brain extract was inoculated by the intracerebral route into four strains of wild-type mice (RIII and C57BL/6) and transgenic mice (tga20 [Fischer and others 1996] or tg540 [J. L. Vilotte, unpublished data]) overexpressing the murine or bovine gene of PrP, respectively, in four different laboratories. Incubation times were all compatible with those recorded for experimental ovine BSE. A characteristic feature of BSE is the specific lesion profile, which has been described in RIII mice (Bruce and others

Isolation of Prion with BSE Properties from Farmed Goat

John Spiropoulos, Richard Lockey, Rosemary E. Sallis, Linda A. Terry, Leigh Thorne, Thomas M. Holder, Katy E. Beck, and Marion M. Simmons

Transmissible spongiform encephalopathies are fatal neurodegenerative diseases that include variant Creutzfeldt-Jakob disease in humans, scrapie in small ruminants, and bovine spongiform encephalopathy (BSE) in cattle. Scrapie is not considered a public health risk, but BSE has been linked to variant Creutzfeldt-Jakob disease. Small ruminants are susceptible to BSE, and in 2005 BSE was identified in a farmed goat in France. We confirm another BSE case in a goat in which scrapie was originally diagnosed and retrospectively identified as suspected BSE. The prion strain in this case was further characterized by mouse bioassay after extraction from formaldehyde-fixed brain tissue embedded in paraffin blocks. Our data show that BSE can infect small ruminants under natural conditions and could be misdiagnosed as scrapie. Surveillance should continue so that another outbreak of this zoonotic transmissible spongiform encephalopathy can be prevented and public health safeguarded.

Transmissible spongiform encephalopathies (TSEs) are fatal diseases characterized by neurodegenerative changes in the central nervous system that include vacuolation, gliosis, and accumulation of an abnormal isoform (PrP^{Sc}) of a naturally occurring host-encoded protein (PrP^{C}) (*1*). According to the prion hypothesis, PrP^{Sc} is the major or the sole infectious agent (*1*). Although this hypothesis has not received universal acceptance, PrP^{Sc} is ubiquitous in all known naturally occurring TSEs, and its detection is widely used for their diagnosis.

Bovine spongiform encephalopathy (BSE), a TSE of cattle, was first detected in 1986 (*2*) and has since been linked with emerging TSEs in other species (*3,4*) including humans (*5,6*). Because of its ability to cross species barriers and particularly its zoonotic potential, BSE is considered a public health risk, and extensive measures have been established to detect and eliminate the disease.

Scrapie, a naturally occurring TSE affecting small ruminants, has been known for centuries (*7*) and is not considered to pose a public health risk (*8*). Under experimental conditions, however, small ruminants are susceptible to BSE, with pathogenesis and clinical signs that are not readily distinguishable from scrapie (*9–12*). Additionally, the fact that small ruminants were exposed to BSE-contaminated food before the exclusion of meat and bone meal from ruminant feedstuffs led to the possibility that sheep and goats on commercial farms could be affected by BSE that could be misdiagnosed as scrapie (*13,14*). The response to this potential risk was the implementation of extensive statutory active surveillance, elimination, and breeding for resistance programs in the European Union (EU).

In 2005, as part of a review of historical TSE-positive cases of sheep and goats in France, a specimen from a goat slaughtered for human consumption in 2002 was reported to be "indistinguishable from a BSE isolate on the basis of all identification criteria available." (*15*). In response to this report, 2 retrospective studies were initiated in the United Kingdom to analyze archived samples from goat cases that were initially diagnosed as scrapie (*16,17*). Because only fixed material was available, both studies had to use differential immunohistochemical analysis (D-IHC), a technique that can discriminate scrapie from experimentally induced BSE in sheep (*18*). These studies identified a single case, originally diagnosed in 1990 as scrapie, that had a D-IHC signature indistinguishable from BSE (*16*).

Given the wide phenotypic variance of scrapie in sheep and our limited knowledge of this variance in goats, the

Author affiliation: Animal Health and Veterinary Laboratories Agency, Weybridge, Surrey, UK

DOI: http://dx.doi.org/10.3201/eid1712.110333

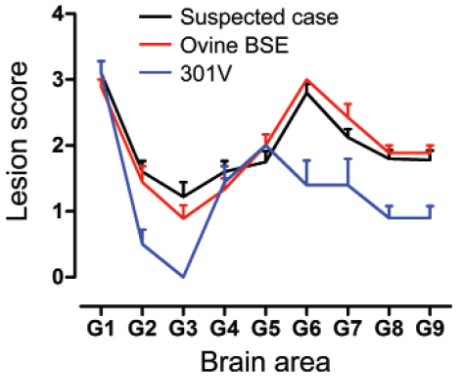

Figure 5. Lesion profiles from VM mice after second passage of the suspected case, serial passage of an ovine bovine spongiform encephalopathy (BSE) source, and a 301V control. Profiles were made on the basis of the lesion score, which is the quantification of transmissible spongiform encephalopathy–specific vacuolation in 9 neuroanatomical gray matter areas: G1, dorsal medulla nuclei; G2, cerebellar cortex of the folia including the granular layer, adjacent to the fourth ventricle; G3, cortex of the superior colliculus; G4, hypothalamus; G5, thalamus; G6, hippocampus; G7, septal nuclei of the paraterminal body; G8, cerebral cortex (at the level of G4 and G5); G9, cerebral cortex (at the level of G7). At least 9 clinically and histopathologically positive mice contributed to each profile. Error bars indicate SEM.

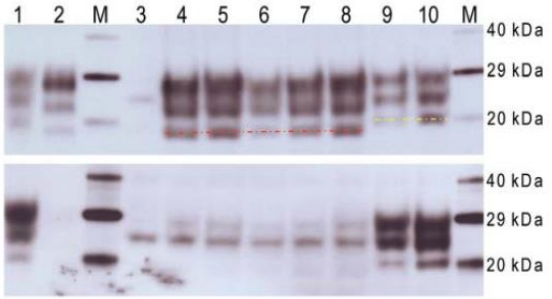

Figure 4. Western blot analysis of a range of murine transmissible spongiform encephalopathy–affected brain homogenates in host-encoded prion protein (PrP)–a (RIII) mice. A) Western blot probed with SHA31, 15-s exposure time. B) Western blot probed with 12B2, 5-min exposure time. M, biotinylated marker; lane 1, ovine scrapie field case; lane 2, bovine spongiform encephalopathy (BSE) field case; lane 3, unchallenged mouse; lane 4, bovine BSE-challenged mouse; lane 5, ovine BSE-challenged mouse; lane 6, caprine BSE-challenged mouse; lanes 7 and 8, mice challenged with suspected case; lane 9, caprine scrapie-challenged mouse; lane 10, ovine scrapie-challenged mouse. Molecular weights are indicated kDa. Red line indicates 19 kDa unglycosylated band; yellow line indicates 20 kDa unglycosylated band. Identical results were also obtained with C57/BL6 mice.

Molecular Typing of Protease-Resistant Prion Protein in Transmissible Spongiform Encephalopathies of Small Ruminants, France, 2002–2009

Johann Vulin, Anne-Gaëlle Biacabe, Géraldine Cazeau, Didier Calavas, and Thierry Baron

The agent that causes bovine spongiform encephalopathy (BSE) may be infecting small ruminants, which could have serious implications for human health. To distinguish BSE from scrapie and to examine the molecular characteristics of the protease-resistant prion protein (PrP^{res}), we used a specifically designed Western blot method to test isolates from 648 sheep and 53 goats. During 2002–2009, classical non-Nor98 transmissible spongiform encephalopathy had been confirmed among ≈1.7 million small ruminants in France. Five sheep and 2 goats that showed a PrP^{res} pattern consistent with BSE, or with the CH1641 experimental scrapie source, were identified. Later, bioassays confirmed infection by the BSE agent in 1 of the 2 goats. Western blot testing of the 6 other isolates showed an additional C-terminally cleaved PrP^{res} product, with an unglycosylated band at ≈14 kDa, similar to that found in the CH1641 experimental scrapie isolate and different from the BSE isolate.

Transmissible spongiform encephalopathies (TSEs) are a group of fatal neurodegenerative diseases that include scrapie in sheep and goats, bovine spongiform encephalopathy (BSE) in cattle, and Creutzfeldt-Jakob disease (CJD) in humans (*1*,*2*). TSEs are characterized by accumulation in the brain of a disease-associated isoform (PrP^{d}) of a host-encoded cellular prion protein (PrP^{c}) (*3*). PrP^{d}, in comparison with the normal prion protein PrP^{c}, clearly differs in secondary and tertiary structures (*4*,*5*) and in biochemical characteristics (*6*). Proteinase K (PK) digestion destroys PrP^{c}, but in PrP^{d} it generates a protease-resistant fragment known as PrP^{res}. Most TSE diagnostic methods (e.g., ELISA and Western blot tests) are based on detection of PrP^{res} (*7*).

The transmissible agent involved in BSE in cattle is known to cause prion diseases in other species under natural conditions (*8*). BSE can also be experimentally transmitted to sheep and goats, including after oral challenge to test for transmission (*9*). Because BSE-contaminated meat and bone meal may have been fed to small ruminants, BSE may have been transmitted to sheep or goats. Also, the Scientific Steering Committee of the European Commission has hypothesized that the BSE agent might have originated from a scrapie agent in sheep or goats and that these animals may represent a reservoir (*10*). In view of these data, the European Commission defined a strategy to investigate the possible presence of BSE in sheep and goats under natural conditions (*11*).

The standard for strain typing TSE agents is based on analysis of the phenotypic characteristics of the disease after transmission in laboratory rodents. Biological characterization of the BSE agent in inbred wild-type mice appeared to be reliable, because it showed uniform features in mice (*8*). However, this approach is time-consuming and costly. The identification of uniform molecular features of PrP^{res} by Western blot in human variant CJD paved the way to a similar approach for detecting possible BSE in small ruminants (*12*). The molecular criteria defined in these studies included electrophoretic mobilities, glyco-

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DOI: 10.3201/eid1701.100891

Testing volume of small ruminants

Charts SR1 and SR2: Evolution of TSE testing in sheep and goats in the EU 28 from 2002 to 2014

Chart SR1: sheep

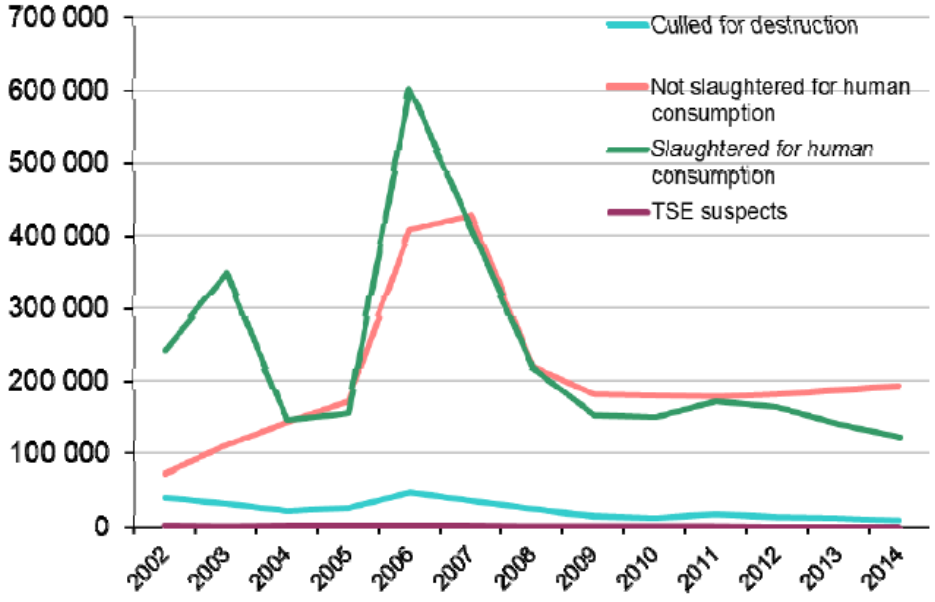
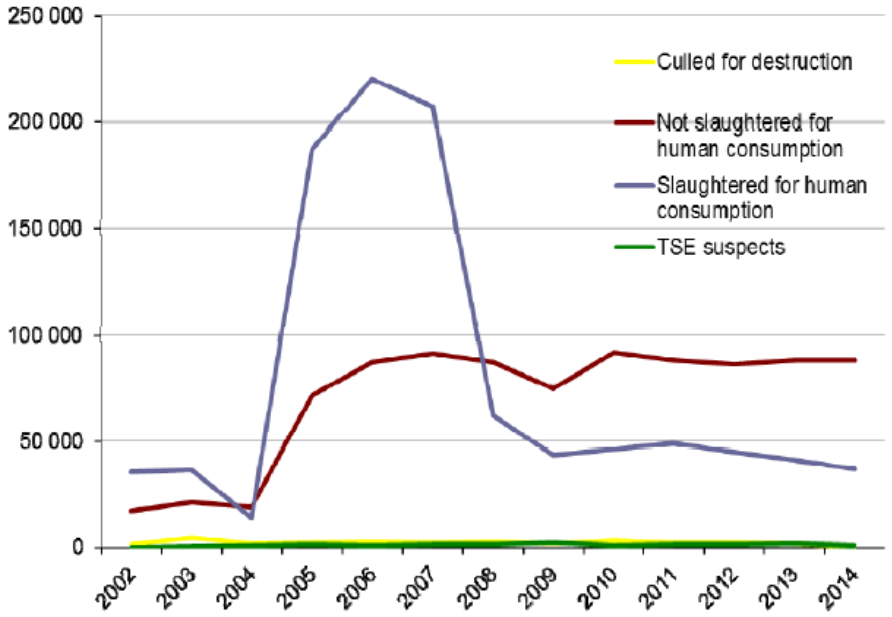


Chart SR2: goats



Testing volume of small ruminants

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Chart SR1: sheep

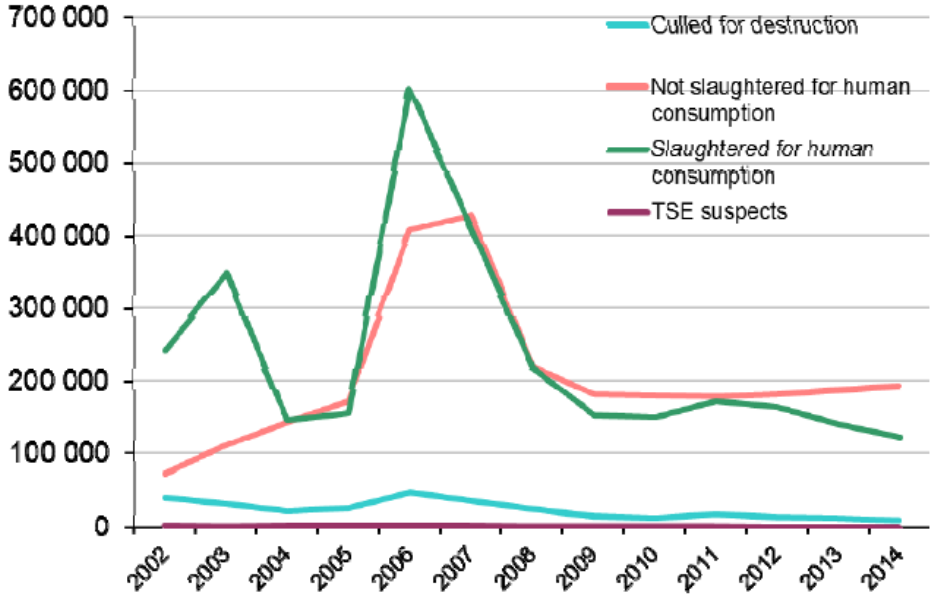
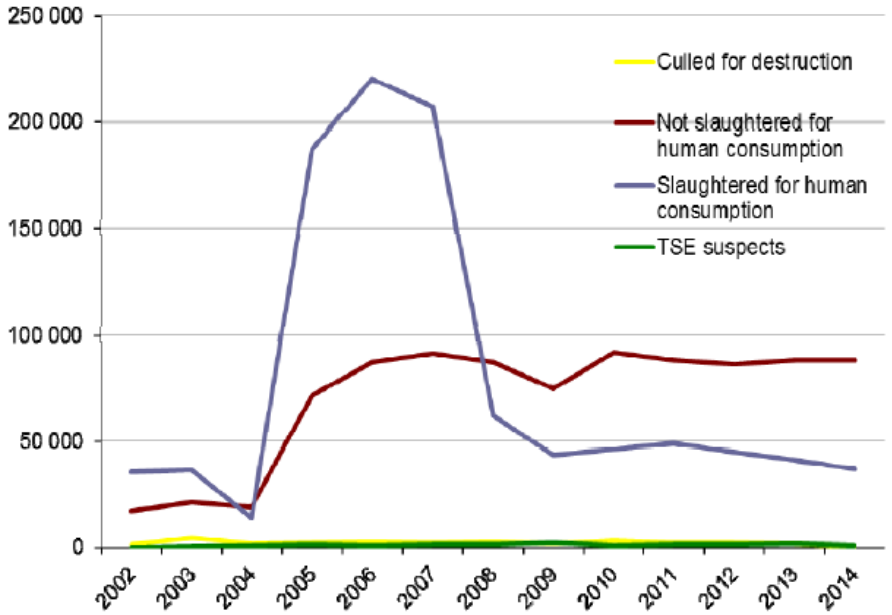


Chart SR2: goats



As in the previous years, the 2014 results provide, at this stage, no element suggesting the possible presence of BSE in sheep and goats. The 14 TSE cases in sheep which led to inconclusive results at BSE discriminatory testing came all from holdings under TSE control and eradication measures, for which the exclusion of BSE was confirmed for the index case as well for other secondary cases.

TSE STRAIN CHARACTERISATION IN SMALL RUMINANTS

A TECHNICAL HANDBOOK FOR NATIONAL REFERENCE LABORATORIES IN THE EU

Antibodies	Sequences Recognized in the Bovine PrP Protein
Group A	
SAF32	62 - QPHGGGW - 92
4F2	62 - QPHGGGW - 92
12B2	101 - WGQGG - 105
P4	101 - WGQGGSH - 107
Group B	
9A2	110 - WNK -112
RB1	110 - WNKP - 113
F89/160.1.5	148 - PLIHFGSD - 155
Bar233	152 - FGSDYEDRYYRE - 163
L42	156 - YEDRYY - 161
Sha31	156 - YEDRYYRE - 163
6H4	156 - YEDRYYREN - 164
Group C	
12F10	154 - SDYEDRYYRE - 163
SAF84	175 - RPVDQY - 180
94B4	198 - HTVTTTTK - 205
F99/97.6.1	229 - YQRE - 232
R524	233 - SQAY - 236

N

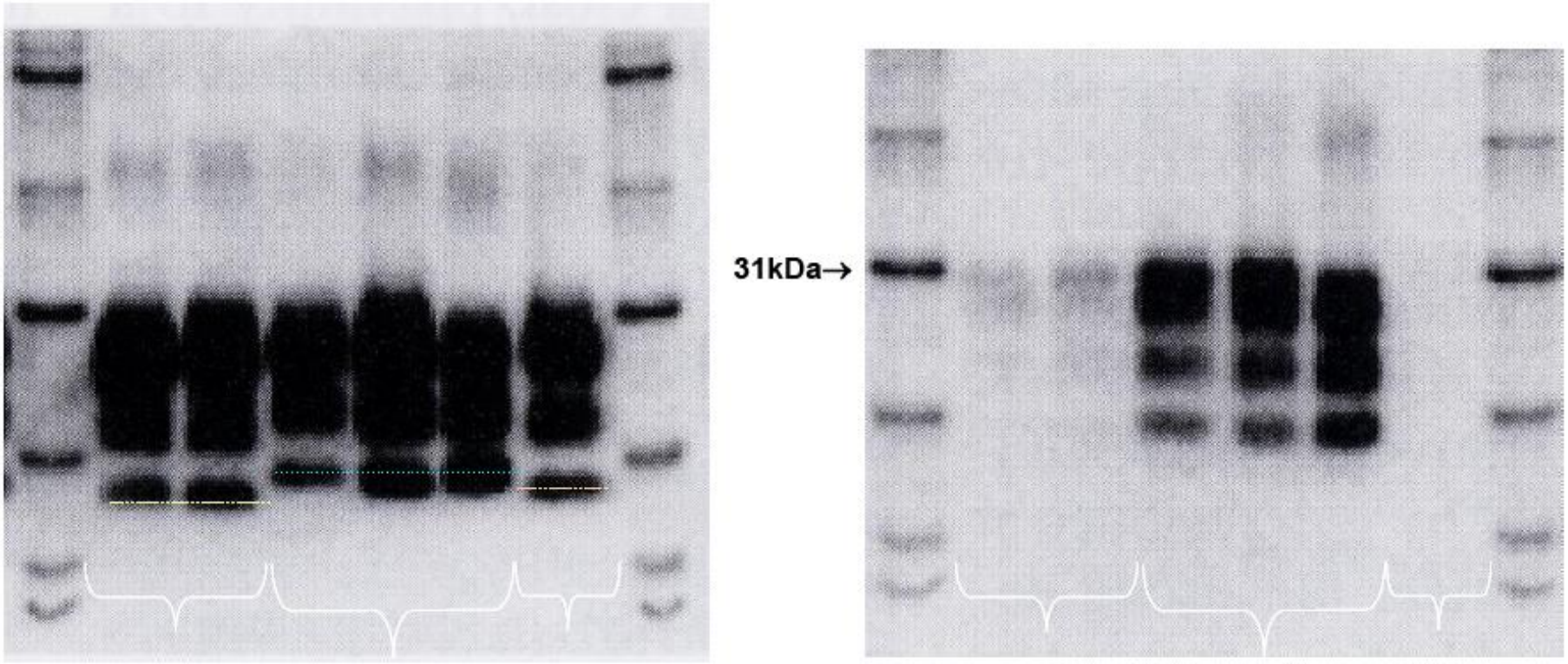
Core

C

Biacabe AG, Jacobs JG, Bencsik A, Langeveld JP, Baron TG. H-type bovine spongiform encephalopathy: complex molecular features and similarities with human prion diseases. Prion. 2007 Jan-Mar;1(1):61-8. Epub 2007 Jan 11.

Mab 6H4

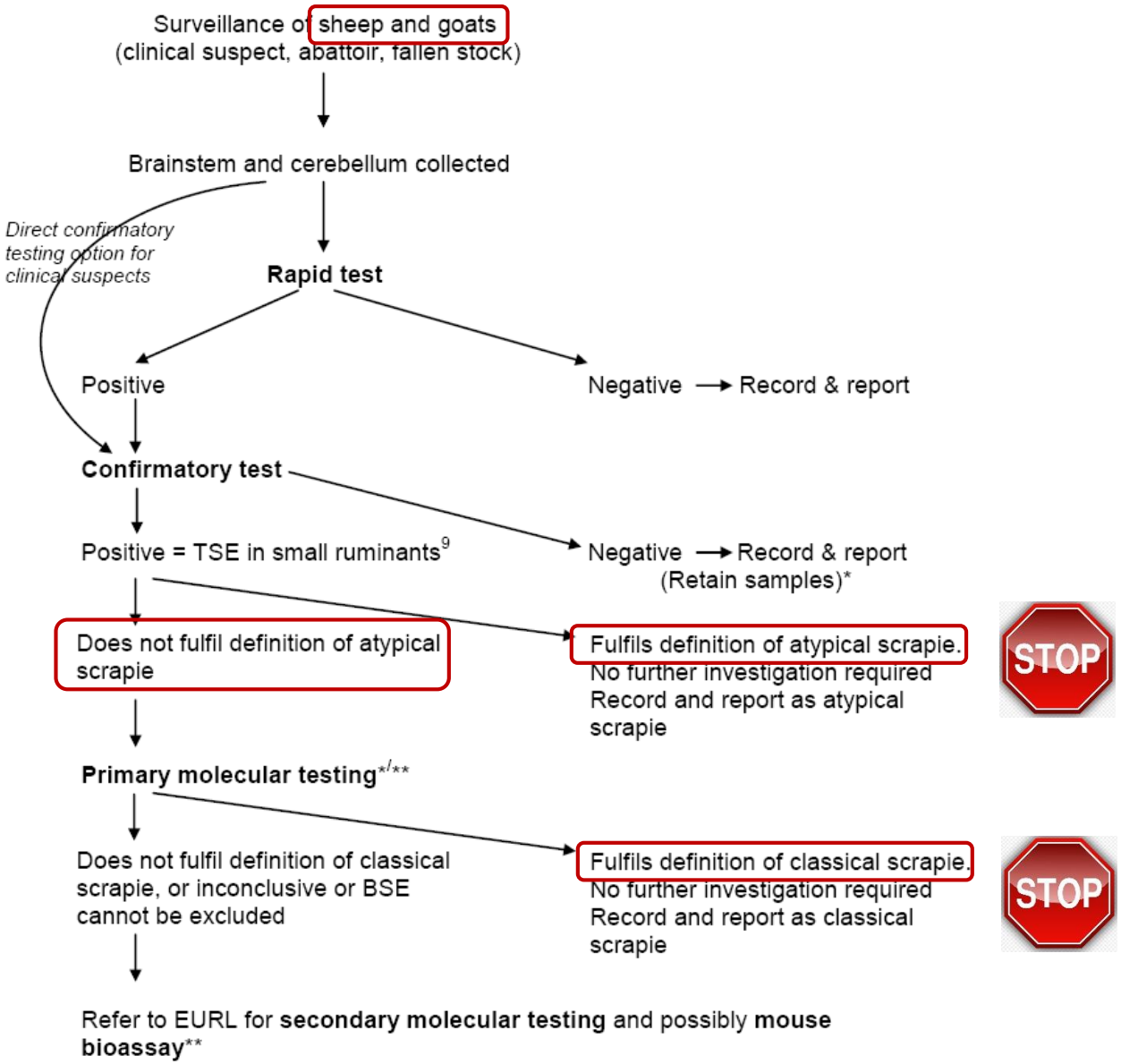
Mab P4



Experimental BSE in sheep:

- Strong signal and lower molecular mass migration (compared to ovine classical scrapie) with mAb 6H4.
- Much reduced signal with mAb P4.

APPENDIX 1: TESTING STRATEGY FLOWCHART



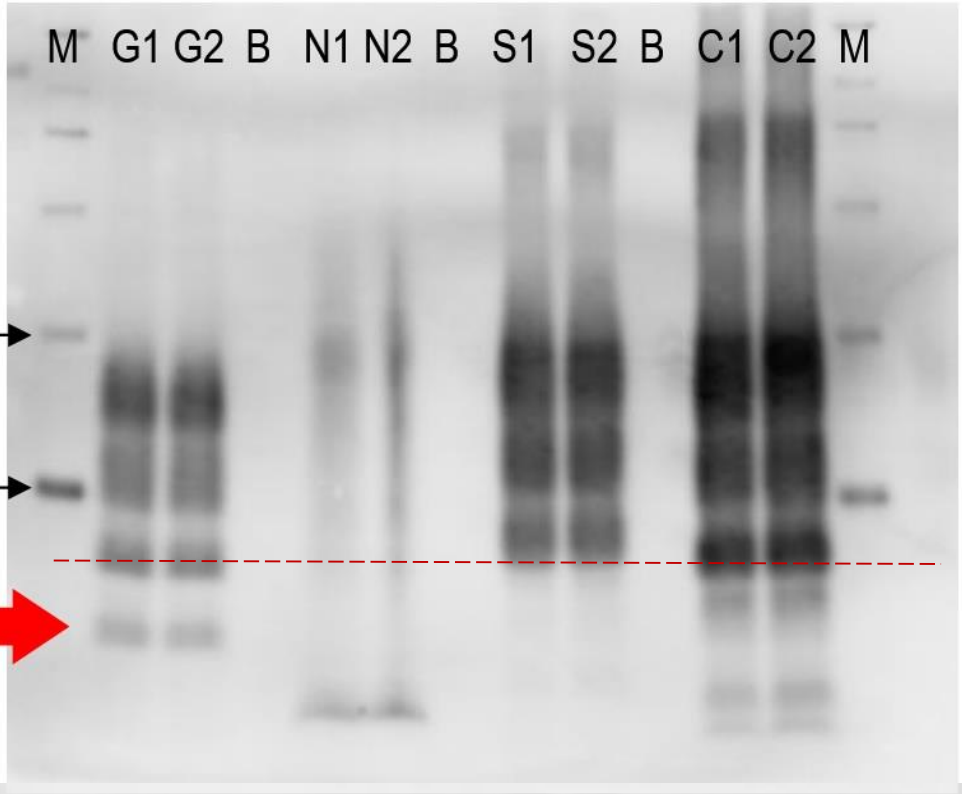
These steps conducted by the NRL
*** All discriminatory testing to be QA'ed by EURL*

A suspected case of caprine BSE in a goat from a Polish flock

Male goat, fallen stock, age 107 months

Idexx O.D. values 1st test: 2.109

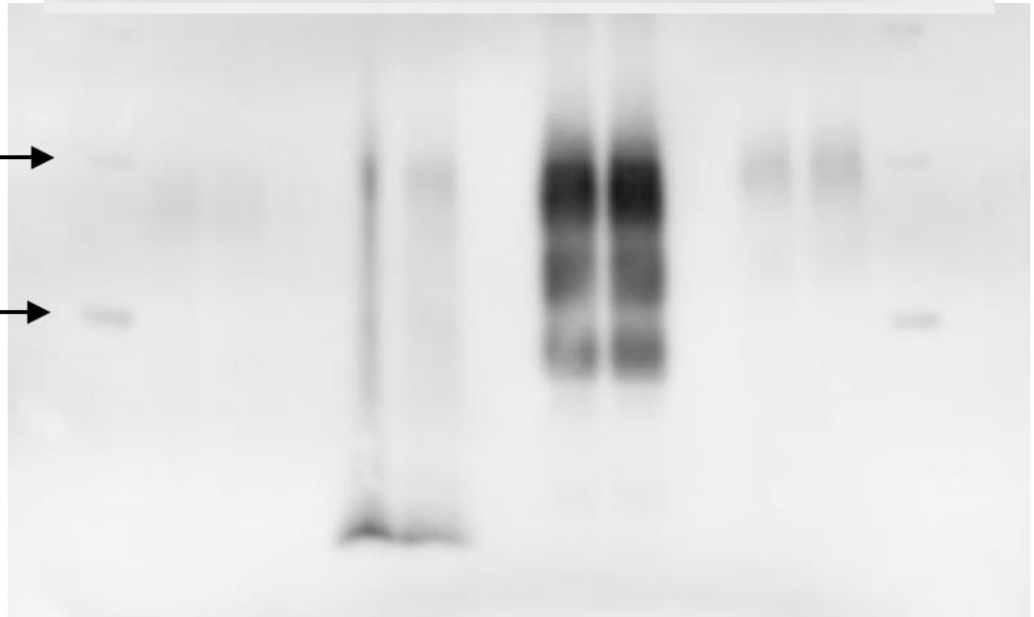
2nd test:: 1.916; 1.939; 3.321; 3.634



M	MM XP marker
G1,G2	goat sample
B	blank well
N1,N2	Nor98 ctrl
S1,S2	classical scrapie ctrl
C1,C2	classical BSE ctrl
Arrows	30kDa, 20kDa

10 min exposure time

SHA31



classical BSE like

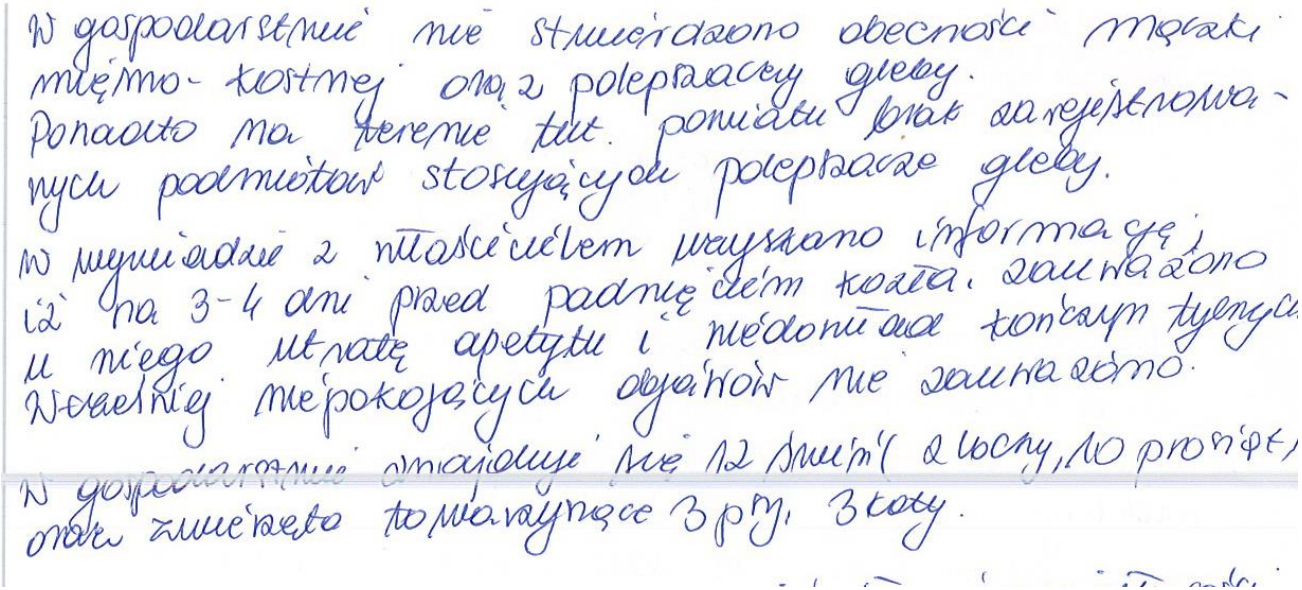
10 min exposure time

P4

Epizootic investigation of this case:

No MBM or soil improvers on the farm

3-4 days before death: loss of appetite and hind limb paresis
No other signs were observed



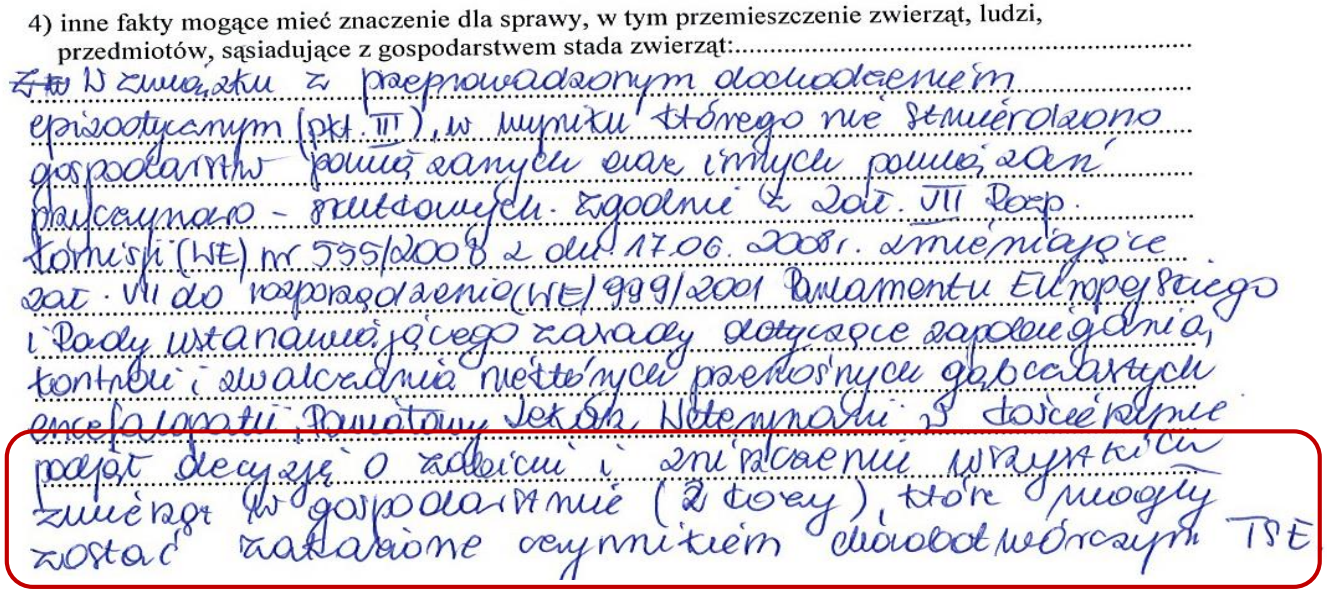
Epizootic investigation of this case:

GATUNEK ZWIERZĄT	Ogółem zwierząt w danej miejscowości	Ogółem zwierząt	OGNISKO PIERWOTNE / WTÓRNE [1]												
			Liczba zwierząt							Liczba zwierząt Zabitych Lub ubitych Z nakazu organu Inspekcji Weterynaryjnej			Liczba zwierząt pozostałych po wygaszeniu ogniska choroby	UWAGI
			Chorych	Podejrzanych		Padłych		Dobitych			Podejrzanych			
				O chorobę	O zakażenie	Ogółem	Z tego skierowano do badania	Ogółem	Z tego skierowano do badania	Chorych	O chorobę	O zakażenie		
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Koniowate														
Bydło														
Owce														
Kozy				2		1	1				2		0	
Świnie		12												
Drób														
Pszczoły														
Ryby														
Psy		3												
Koty		3												
Zwierzęta dzikie														

[1] Niepotrzebne skreślić

Epizootic investigation of this case:

2 remaining goats were killed and destroyed – TSE negative

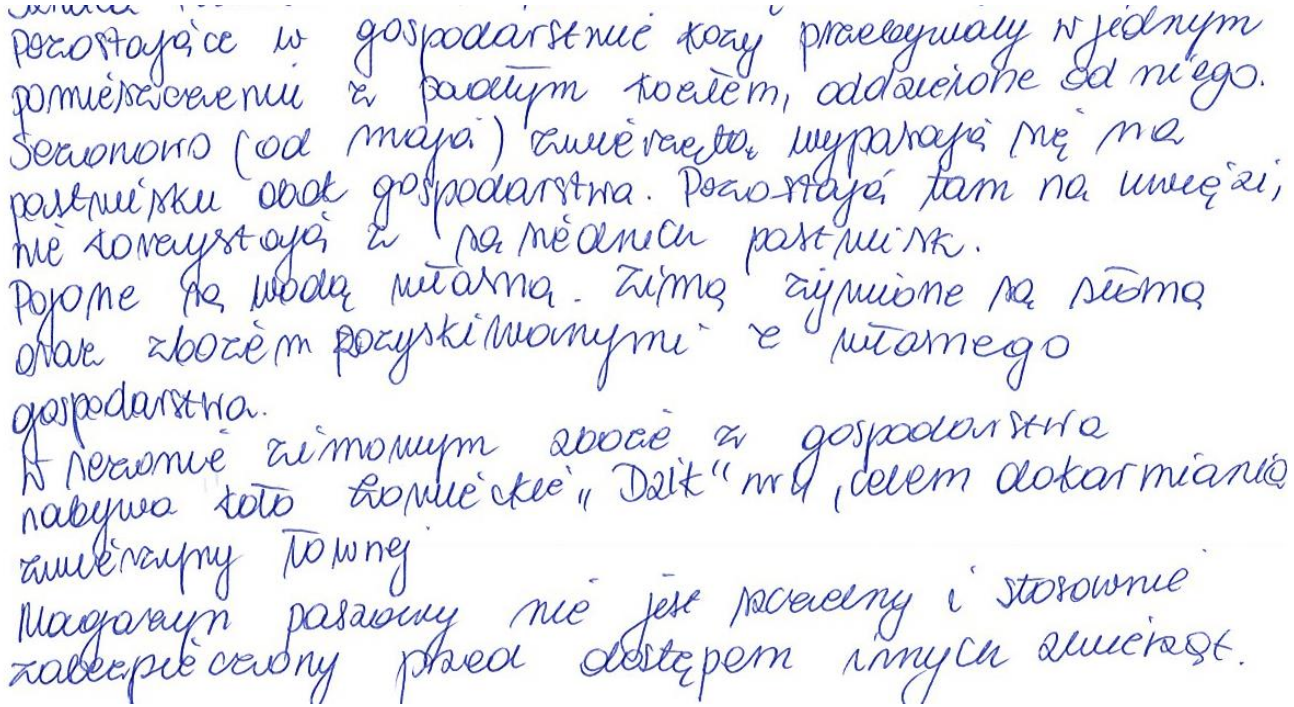


4) inne fakty mogące mieć znaczenie dla sprawy, w tym przemieszczenie zwierząt, ludzi, przedmiotów, sąsiadujące z gospodarstwem stada zwierząt:

W związku z przeprowadzonym dochodzeniem epizootycznym (pkt. III), w wyniku którego nie stwierdzono gospodarstw powiązanych epidemiologicznie z innych powiązań pochodzenia - rozchodowych. Zgodnie z Zał. III Rozp. Komisji (WE) nr 595/2008 z dn. 17.06.2008 r. zmieniające Zał. VII do rozporządzenia (WE) 999/2001 Parlamentu Europejskiego i Rady ustanawiającego zasady dotyczące zapobiegania, kontroli i zwalczania niektórych przenośnych gąbczastych encefalopatii. Powiatowy Lekarz Weterynarii w Łosicach podjął decyzję o zabiciu i zniszczeniu wszystkich zwierząt w gospodarstwie (2 owce), które mogły zostać zakażone czynnikiem chorobotwórczym TSE

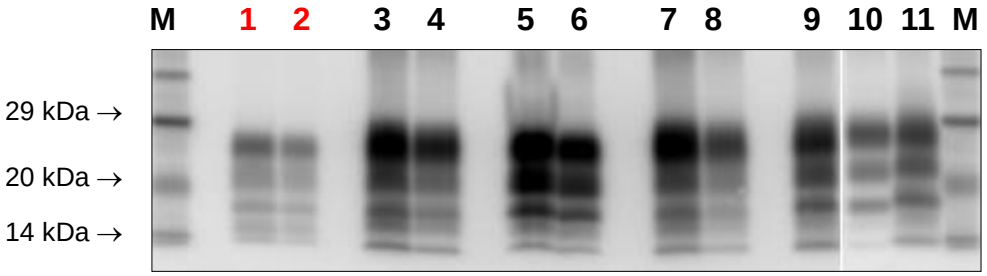
Epizootic investigation of this case:

Pasture feeding since May. Winter feeding: home-made hay and grain

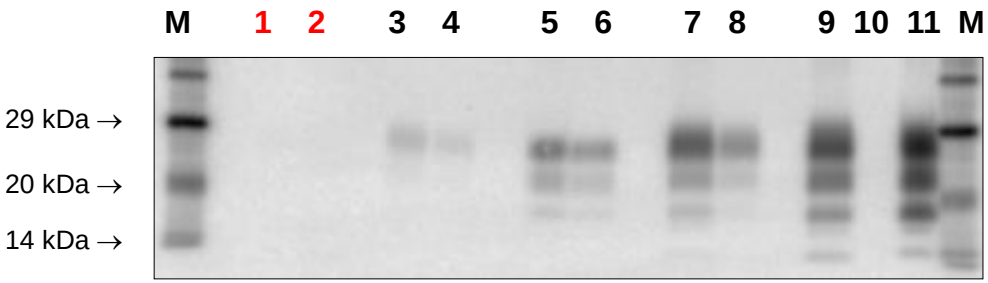


TSE discriminatory testing at EURL/AHVLA/UK

Analysis of Polish caprine sample (NVRI ref: 358 - AHVLA ref: V6773B)
AHVLA Bio-Rad Hybrid Discriminatory WB following detection with mAbs SHA31 & P4



mAb SHA31

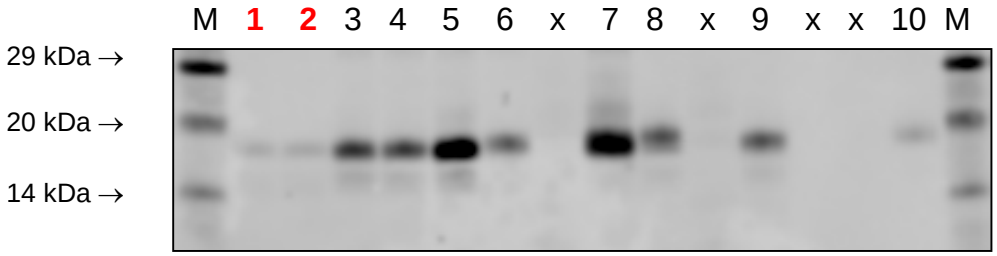


mAb P4

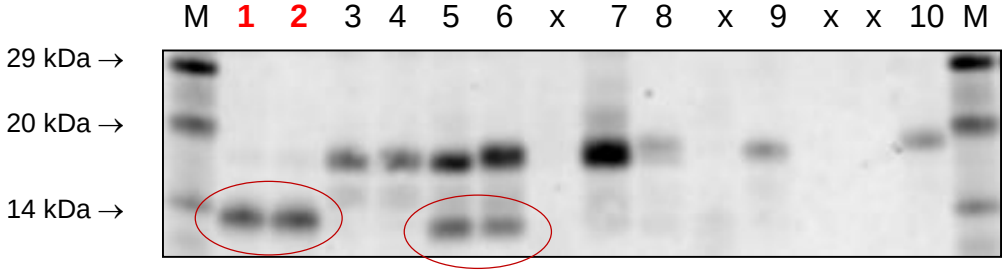
Lane	Animal No.
1	V6773B - (Neat) Biorad Homogenate prepared by NVRI.
2	V6773B - (Dil 1:2) Biorad Homogenate prepared by NVRI.
Controls	
M	Biotinylated Markers
3 & 4	BSE/Sheep (Dil 1:2 & 1:4)
5 & 6	CH1641 (Neat & Dil 1:2)
7 & 8	BSE/Goat (Dil 1:10 & 1:40)
9	Scrapie/Goat (Dil 1:10)
10	BSE/Bovine (Dil 1:10)
11	Scrapie/Ovine (Dil 1:2)

AHVLA studies

Analysis of Polish caprine sample (NVRI ref: 358 - AHVLA ref: V6773B)
after PNGase deglycosylation and detection with
mAb SHA31 and HRP labelled SAF84 antibody



mAb SHA31



SAF84HRP

Lane	Animal No.
1	V6773B Sample 358
2	V6773B Sample 358
Controls	
M	Biotinylated Markers
3 & 4	AHVLA Exp BSE/Sheep
5 & 6	AHVLA CH1641
7	AHVLA Exp BSE/Goat
8	Caprine scrapie
9	Bovine BSE
10	Ovine scrapie

CH1641-like scrapie strain identified from a natural case of scrapie (1970) in a Cheviot sheep by passage in sheep and goats

(drawback: lack of CH1641-goat samples for comparison)

AHVLA studies

Final conclusions from STEG:

Categories of possible classification:

1. NOT BSE
2. BSE NOT EXCLUDED
3. INCONCLUSIVE

NOT BSE/INCONCLUSIVE – unusual case requiring further investigation by bioassay (2013)

Final conclusions from STEG:

Bioassay studies:

tg338 (overexpressing **ovine** VRQ PrP transgene)

tg110 (overexpressing **bovine** PrP transgene)

No propagation in **tg110** – not BSE

Inefficient propagation in **tg338** (3/10 TSE positive)

Disease phenotype was different from the BSE phenotype observed in this mouse line

Conclusion from the studies: uncharacterised classical scrapie strain, which may represent a novel strain – serial passages recommended to fully characterise the properties of this strain

Caution
For The Future

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Sheep and Goat BSE Propagate More Efficiently than Cattle BSE in Human PrP Transgenic Mice

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Abstract

A new variant of Creutzfeldt Jacob Disease (vCJD) was identified in humans and linked to the consumption of Bovine Spongiform Encephalopathy (BSE)-infected meat products. Recycling of ruminant tissue in meat and bone meal (MBM) has been proposed as origin of the BSE epidemic. During this epidemic, sheep and goats have been exposed to BSE-contaminated MBM. It is well known that sheep can be experimentally infected with BSE and two field BSE-like cases have been reported in goats. In this work we evaluated the human susceptibility to small ruminants-passaged BSE prions by inoculating two different transgenic mouse lines expressing the methionine (Met) allele of human PrP at codon 129 (tg650 and tg340) with several sheep and goat BSE isolates and compared their transmission characteristics with those of cattle BSE. While the molecular and neuropathological transmission features were undistinguishable and similar to those obtained after transmission of vCJD in both transgenic mouse lines, sheep and goat BSE isolates showed higher transmission efficiency on serial passaging compared to cattle BSE. We found that this higher transmission efficiency was strongly influenced by the ovine PrP sequence, rather than by other host species-specific factors. Although extrapolation of results from prion transmission studies by using transgenic mice has to be done very carefully, especially when human susceptibility to prions is analyzed, our results clearly indicate that Met129 homozygous individuals might be susceptible to a sheep or goat BSE agent at a higher degree than to cattle BSE, and that these agents might transmit with molecular and neuropathological properties indistinguishable from those of vCJD. Our results suggest that the possibility of a small ruminant BSE prion as vCJD causal agent could not be ruled out, and that the risk for humans of a potential goat and/or sheep BSE agent should not be underestimated.

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Experimental sheep BSE prions generate the vCJD phenotype when serially passaged in transgenic mice expressing human prion protein.

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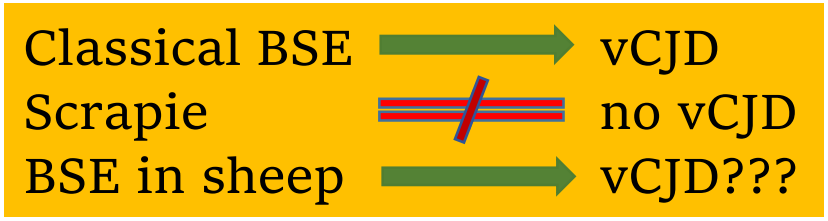
Abstract

The epizootic prion disease of cattle, bovine spongiform encephalopathy (BSE), causes variant Creutzfeldt-Jakob disease (vCJD) in humans following dietary exposure. While it is assumed that all cases of vCJD attributed to a dietary aetiology are related to cattle BSE, sheep and goats are susceptible to experimental oral challenge with cattle BSE prions and farmed animals in the UK were undoubtedly exposed to BSE-contaminated meat and bone meal during the late 1980s and early 1990s. Although no natural field cases of sheep BSE have been identified, it cannot be excluded that some BSE-infected sheep might have entered the European human food chain. Evaluation of the zoonotic potential of sheep BSE prions has been addressed by examining the transmission properties of experimental brain isolates in transgenic mice that express human prion protein, however to-date there have been relatively few studies. Here we report that serial passage of experimental sheep BSE prions in transgenic mice expressing human prion protein with methionine at residue 129 produces the vCJD phenotype that mirrors that seen when the same mice are challenged with vCJD prions from patient brain. These findings are congruent with those reported previously by another laboratory, and thereby strongly reinforce the view that sheep BSE prions could have acted as a causal agent of vCJD within Europe.



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Thank you for your attention