Sheep feed and scrapie, France.
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Scrapie is a small ruminant, transmissible spongiform encephalopathy (TSE). Although in the past scrapie has not been considered a zoonosis, the emergence of bovine spongiform encephalopathy, transmissible to humans and experimentally to sheep, indicates that risk exists for small ruminant TSEs in humans. To identify the risk factors for introducing scrapie into sheep flocks, a case-control study was conducted in France from 1999 to 2000. Ninety-four case and 350 control flocks were matched by location and main breed. Three main hypotheses were tested: direct contact between flocks, indirect environmental contact, and foodborne risk. Statistical analysis was performed by using adjusted generalized linear models with the complementary log-log link function, considering flock size as an offset. A notable effect of using proprietary concentrates and milk replacers was observed. The risk was heterogeneous among feed factories. Contacts between flocks were not shown to be a risk factor.

Scrapie is a transmissible spongiform encephalopathy (TSE) affecting sheep and goats (1), as is Creutzfeldt-Jakob disease (CJD) in humans or bovine spongiform encephalopathy (BSE) in cattle. Moreover, scrapie is contagious in natural conditions (2). Though genetic determinism is a major feature of scrapie, the infectious agent is nonetheless needed for the disease to develop (3,4).

Known to exist for centuries, scrapie was thought to be a possible origin of BSE, although this hypothesis has not yet been verified. Sheep and goats can be experimentally infected with BSE, resulting in a disease that is impossible to distinguish from natural scrapie (5). Since BSE is implicated in the emergence of variant CJD (6,7), the existence of BSE in small ruminants poses a further risk for human health. Scrapie has become a public health challenge, and its propagation must be stopped; therefore, the risk factors for the introduction of scrapie in sheep must be understood.

In sheep infected with scrapie, the infectious agent is widely distributed in the organism. In particular, the gut-associated lymphoid tissues and the placenta are considered highly important in spreading the disease (8) and can contaminate the environment (9). Because feed is considered to be the main, if not the only, contamination source of BSE in cattle (10,11), it can also be presumed to be a potential risk factor for scrapie in sheep.

A case-control study of infected and scrapie-free flocks was conducted to identify risk factors for scrapie in sheep flocks in France. Various risk factors hypotheses were tested from the most plausible to the weakest.

Materials and Methods

Study Design

A case-control study of infected and scrapie–free flocks was designed (see online appendix for details; http://www.cdc.gov/ncidod/EID/vol11no08/04-1223_app.htm). A flock was defined as having at least 20 adult ewes. To consider the heterogeneity of exposure to scrapie risk, cases and controls were matched according to main sheep breed and location. A “case” was any flock having >1 animal that had been shown as scrapie-positive by the French surveillance network from January 1996 to July 2000 (12).

Four frequency-matched control flocks were randomly selected from the sheep flocks in which scrapie had never been reported. Flocks that did not meet this criterion were excluded.

The suspected risk factors were grouped into 3 categories corresponding to the main working hypotheses of scrapie dissemination. The first category covered risks for transmission by direct contact between flocks and indirectly through the environment. The second category covered foodborne risks. The third category covered other environmental dissemination risks such as equipment sharing between farms or transmission through hay mites. Table 1 describes the 22 potential risk factors studied.

Data Collection

Information was collected by using a preestablished questionnaire to interview farmers and analyzing farm records. Questions related to potential risk factors covered...
the 4-year period preceding detection of the first clinical case of scrapie in case flocks and the 4-year period preceding the interview for controls. Additionally, information regarding potential confounding factors including flock size, production type (dairy, meat, or mixed), and intensification level of the flock production was recorded.

Table 1. Univariate analysis of potential risk factors

| Risk factors                                  | Modalities | No. controls (%) | No. cases (%) | OR* | 80% CI |
|-----------------------------------------------|------------|------------------|---------------|-----|--------|
| Direct contacts between flocks and indirect environmental contacts |            |                  |               |     |        |
| Purchase of ewes                              | No         | 227 (65)         | 55 (59)       | 1.0 | –      |
|                                               | Yes        | 123 (35)         | 39 (41)       | 1.3 | 1.0–1.8 |
| Purchase of rams                              | No         | 146 (42)         | 33 (35)       | 1.0 | –      |
|                                               | Yes        | 204 (58)         | 61 (65)       | 1.0 | 0.8–1.4 |
| Temporary direct contacts between flocks†     | No         | 230 (66)         | 66 (70)       | 1.0 | –      |
|                                               | Yes        | 120 (34)         | 28 (30)       | 0.7 | 0.5–1.1 |
| Stay of animals in other flocks with direct contacts | No     | 319 (91)         | 87 (93)       | 1.0 | –      |
|                                               | Yes        | 31 (9)           | 7 (7)         | 0.7 | 0.4–1.3 |
| Stay of animals from other flocks with direct contacts | No    | 332 (95)         | 91 (97)       | 1.0 | –      |
|                                               | Yes        | 18 (5)           | 3 (3)         | 0.8 | 0.4–1.9 |
| Presence of small ruminants in the vicinity of the farm | No     | 71 (20)          | 14 (15)       | 1.0 | –      |
|                                               | Yes        | 279 (80)         | 80 (85)       | 1.1 | 0.7–1.7 |
| Sharing paths                                 | No         | 149 (43)         | 39 (41)       | 1.0 | –      |
|                                               | Yes        | 201 (57)         | 55 (59)       | 0.9 | 0.7–1.2 |
| Other indirect environmental contacts‡        | No         | 311 (89)         | 85 (90)       | 1.0 | –      |
|                                               | Yes        | 39 (11)          | 9 (10)        | 0.7 | 0.4–1.2 |
| Feeding                                       |            |                  |               |     |        |
| Purchase of raw materials§                    | No         | 213 (61)         | 66 (70)       | 1.0 | –      |
|                                               | Yes        | 137 (39)         | 28 (30)       | 0.6 | 0.4–0.8 |
| Purchase of milk replacers¶                   | No         | 287 (82)         | 66 (70)       | 1.0 | –      |
|                                               | Yes        | 63 (18)          | 28 (30)       | 2.0 | 1.4–2.7 |
| Purchase of proprietary concentrates¶         | No         | 79 (23)          | 7 (7)         | 1.0 | –      |
|                                               | Yes        | 271 (77)         | 87 (93)       | 2.2 | 1.2–3.8 |
| Purchase of milk replacers from factory 1     | No         | 329 (94)         | 76 (81)       | 1.0 | –      |
|                                               | Yes        | 21 (6)           | 18 (19)       | 3.1 | 2.1–4.6 |
| Purchase of milk replacers from other factories | No    | 317 (91)         | 87 (93)       | 1.0 | –      |
|                                               | Yes        | 33 (9)           | 7 (7)         | 0.9 | 0.5–1.6 |
| Purchase of proprietary concentrates from factory 1 | No  | 271 (77)         | 48 (51)       | 1.0 | –      |
|                                               | Yes        | 79 (23)          | 46 (49)       | 2.6 | 1.9–3.5 |
| Purchase of proprietary concentrates from factory 2 | No  | 292 (83)         | 85 (90)       | 1.0 | –      |
|                                               | Yes        | 58 (17)          | 9 (10)        | 0.4 | 0.2–0.7 |
| Purchase of proprietary concentrates from other factories | No  | 228 (65)         | 54 (57)       | 1.0 | –      |
|                                               | Yes        | 122 (35)         | 40 (43)       | 1.2 | 0.8–1.7 |
| Other indirect contacts                       |            |                  |               |     |        |
| Artificial insemination                       | No         | 247 (71)         | 57 (61)       | 1.0 | –      |
|                                               | Yes        | 103 (29)         | 37 (39)       | 1.0 | 0.7–1.5 |
| Cesarean section performed by veterinarian    | No         | 163 (47)         | 28 (30)       | 1.0 | –      |
|                                               | Yes        | 187 (53)         | 66 (70)       | 1.9 | 1.3–2.7 |
| Ear-tagging                                   | No         | 236 (67)         | 55 (59)       | 1.0 | –      |
|                                               | Yes        | 114 (33)         | 39 (41)       | 1.1 | 0.8–1.6 |
| Sharing of farming devices                    | No         | 85 (24)          | 22 (23)       | 1.0 | –      |
|                                               | Yes        | 265 (76)         | 72 (77)       | 0.7 | 0.5–1.0 |
| Presence of dogs on the farm                  | No         | 325 (93)         | 84 (89)       | 1.0 | –      |
|                                               | Yes        | 25 (7)           | 10 (11)       | 1.1 | 0.7–1.7 |
| Purchase of hay                               | No         | 247 (71)         | 70 (74)       | 1.0 | –      |
|                                               | Yes        | 103 (29)         | 24 (26)       | 0.7 | 0.5–1.0 |

*OR, odds ratio; CI, confidence interval.
†Contacts by transhumance or common pastures with contacts between animals.
‡Independently of the factories.
§Purchase of hay excluded because considered in other indirect contacts.
¶Purchase of milk replacers without direct contacts between animals.
Interviews were conducted from May 1999 to July 2000 with 453 flock owners (98 cases and 355 controls). Nine flocks were excluded because they did not meet the inclusion criteria. A total of 444 flocks (94 cases and 350 controls) were included in the study. Data were encoded and then stored in an Access database (Microsoft Access 97 SR-2, Microsoft Corporation, Redmond, WA, USA).

**Analysis**

Data analysis was conducted in 2 steps by using statistical models adjusted for the 2 matching factors through the corresponding cross-variable “strata” (main breed and location) treated as a stratification variable (13). First, to identify the confounding factors to be further analyzed (14), a log-linear model considered 5 factors, including flock size (number of ewes), production type, intensification level of the flock production as potential confounding factors, flock status, and strata. The model introduced the main effect of these 5 factors with all second interaction terms. Flock size was the only potential confounding factor notably associated with the flock status (Table 2).

Second, to assess associations between flock status and risk factors, a generalized linear model for binary outcome was set up with the complementary log-log link function (Clog-log model) (14) (see online Appendix, available at http://www.cdc.gov/ncidod/EID/vol11no08/04-1223_app.htm). This model considered the flock size by using the logarithm of the flock size as an offset (15,16).

**Results**

According to the univariate analysis, 8 potential risk factors were selected (Table 1). Six risk factors were related to foodborne risk; the other 2 were related to purchasing ewes, and cesarean sections performed by the veterinarian. The subsequent multivariate model (multivariate Clog-log 1) (Table 3) showed a significant association between the flock status and using milk replacers. In addition, using the multivariate Clog-log 2 model milk replacers and proprietary concentrates from factory 1 were significantly associated with the flock status (Table 3).

**Discussion**

The main finding of the study was the role of feed as a risk factor for scrapie. This is consistent with what has been shown for BSE in cattle. The use of proprietary concentrates, and more precisely the use of feed containing

### Table 2. Multivariate analysis of potential confounding factors

| Factors                        | Modalities* | No. controls (%) | No. cases (%) | Log-linear model |
|--------------------------------|-------------|------------------|---------------|------------------|
|                                |             |                  |               | OR† 95% CI       |
| Flock size                     | <133*       | 100 (29)         | 11 (12)       | 1.0 –            |
|                                | 133–236     | 87 (25)          | 24 (25)       | 2.5 1.1 – 5.5    |
|                                | 237–366     | 77 (22)          | 33 (35)       | 4.0 1.8 – 8.6    |
|                                | >366        | 86 (25)          | 26 (28)       | 3.0 1.3 – 7.0    |
| Type of flock                   | Dairy*      | 229 (65)         | 64 (68)       | 1.0 –            |
|                                | Meat        | 113 (32)         | 27 (29)       | 1.0 0.3 – 3.2    |
|                                | Mixed       | 8 (2)            | 3 (3)         | 1.2 0.3 – 5.5    |
| Intensification criteria        | None*       | 241 (69)         | 56 (60)       | 1.0 –            |
|                                | Production monitoring | 38 (11) | 16 (17) | 1.8 0.8 – 3.8    |

*Reference modality.
†OR, odds ratio; CI, confidence interval.
meat and bone meal (MBM), was shown to have a major role in BSE infection of cattle (11). The agent of BSE is not inactivated by MBM processing methods, which were put into place by the industry in the late 1970s (17).

In France, MBM was authorized for small ruminants until July 1994. Moreover, the MBM ban proved to be <100% efficient; hundreds of BSE cases were observed in cattle in France born after the MBM ban of feed for cattle. The exposure period that was investigated in the current study was from 1991 to June 2000, depending on the case. It occurred before the French MBM ban in feed for all farmed animals in November 2000; furthermore, the period investigated was before the MBM ban for small ruminants in France for more than half of the cases. It is, therefore, plausible that sheep may have been contaminated by MBM in feed throughout the 1990s, despite control measures. The results showed that 1 feed company was at risk for proprietary concentrates when others were not. This finding is in agreement with the fact that risk might depend on the type of raw materials used in the factory, as well as the way they were processed and used.

The risk attributable to milk replacers is the first evidence of such a TSE risk in animals. Milk replacers for all farmed species are made of skimmed cow milk enriched with vegetable or animal fats. Milk has not been shown to be at risk for scrapie transmission (18–20). Even if animal fat is not infectious, the animal fats that were incorporated in milk replacers may have been contaminated. Contamination could have occurred during collection at the slaughterhouse by contact with infectious material such as central nervous system or paravertebral ganglia. In France, these fats were prohibited for use in farm animal feed in November 2000.

The same factory was identified as selling both the milk replacers and the proprietary concentrates at risk for scrapie. Most farmers buy both their feed concentrates and milk replacers from the same wholesaler (which, in turn, buys from the same factory). Even if the effect of the 2 factors remained in the multivariate analysis, a confounding effect between these 2 factors cannot be excluded.

The main concern raised by this study is the nature of the infectious agent that was transmitted to sheep by means of feed. It might be scrapie, but it could be also BSE, since cattle were infected by feed during the same period in France. In 2005, BSE in a goat was first reported in France (21); in the United Kingdom, a goat that was thought to have scrapie in 1990 is being reexamined because it is now suspected to have had BSE (http://www.defra.gov.uk/news/2005/050208a.htm). In France, every index case animal from infected small ruminant flocks that has been reported since the surveillance began in 1990 has been biochemically tested to distinguish natural scrapie isolates

| Table 3. Multivariate analysis of risk factors |
|-----------------------------------------------|
| Risk factors | Modalities* | No. cases (%) | No. controls (%) | Multivariate Clog-log 1 | Multivariate Clog-log 2 |
|------------------------------------------------|-------------|---------------|------------------|------------------|------------------|
| Direct contacts between flocks and indirect environmental contacts | | | | OR† | 95% CI | OR | 95% CI |
| Purchase of ewes | No | 39 (41) | 123 (35) | 1 | – | 1 | – |
| | Yes | | | 1.3 | 0.9–2.0 | 1.3 | 0.6–2.0 |
| Feeding | | | | | | | |
| Purchase of raw materials (hay excluded) | No | 28 (30) | 137 (39) | 1 | – | 1 | – |
| | Yes | | | 0.6 | 0.4–1.0 | 0.7 | 0.4–1.0 |
| Purchase of milk replacers | No | 28 (30) | 63 (18) | 1 | – | 1.9 | 1.2–3.0 |
| | Yes | | | | | NI | |
| Purchase of proprietary concentrates | No | 87 (93) | 271 (77) | 1 | – | 1.5 | 0.7–3.4 |
| | Yes | | | | | NI | |
| Purchase of milk replacers from factory 1 | No | 18 (19) | 21 (6) | 1 | – | | |
| | Yes | | | | | NI | |
| Purchase of proprietary concentrates from factory 1 | No | 46 (49) | 79 (23) | 1 | – | 1.9 | 1.0–3.5 |
| | Yes | | | | | 1 | – |
| Purchase of proprietary concentrates from factory 2 | No | 9 (10) | 56 (17) | 1 | – | 1 | – |
| | Yes | | | | | NI | 0.7 | 0.3–1.5 |
| Other indirect contacts | Cesarean section performed by veterinarian | No | 66 (70) | 187 (53) | 1 | – | 1 | – |
| | Yes | | | | | 1.6 | 0.9–2.8 |
| | | | | | | | 1.4 | 0.8–2.5 |

*Reference modality = No.
†OR, odds ratio; CI, confidence interval; NI, not in model.
from isolates sharing common biochemical features with experimental ovine BSE (validated by the TSEs Community Reference Laboratory of Weybridge, UK [unpub. data]). Among >400 small ruminant field isolates tested in France, only 1 isolate from a goat was indistinguishable from BSE. These arguments suggest that the agent transmitted to sheep by food was scrapie rather than BSE. Moreover, BSE is thought to have been transmitted and amplified by recycling contaminated carcasses into MBM on a regional basis (22). It follows that if the sheep identified as having scrapie did in fact have BSE, this misconception would have occurred in the same regions as BSE in cattle. That the areas of France most at risk for BSE in cattle (23) were different from those where scrapie occurred during the study does not suggest that the infectious agent for sheep was BSE.

Unexpectedly, the other hypotheses concerning the contamination of flocks with scrapie were not confirmed by the present study. In Norway, a matched case-control study showed 3 risk factors, though at a 10% \( \alpha \) level: purchasing females, sharing rams, and sharing pastures between flocks (24). However, in a recent Irish study, purchasing breeding sheep through markets was not a risk factor for scrapie at a 5% \( \alpha \) level (25). In the Norwegian study, feed did not appear to be a risk factor, whereas in the Irish study, feeding proprietary concentrates to lambs appeared to be protective. In the present study, purchasing ewes may not have emerged as a risk factor merely because of the lack of power of the study. The link between cesarean sections and scrapie occurrence that was observed in the univariate analysis was likely due to a confounding effect with the real risk factors and so became nonsignificant in the multivariate analyses.

Beyond the limits of the study, our results clearly show that in France, and more precisely in southwest France where most of the studied farms were located, the major risk for the introduction of scrapie in a flock during the 1990s was feeding certain proprietary concentrates and, possibly, milk replacers to sheep. Exposing sheep to TSE risk by feeding has certainly decreased since that time because of the complementary control measures taken in 1996 (ban on specified risk materials and cadavers in the processing of MBM) and 2000 (complete ban of MBM and certain animal fats for all farmed animals). However, it is essential to monitor these risk factors over time in France and to extend this kind of study to other countries in which the disease occurs.

The study results show strong evidence that TSEs can spread to sheep through feeding in field conditions, as is the case for cattle. Given the potential risk for humans, the possibility of BSE spreading to sheep must be taken seriously, even though the horizontal transmission of BSE in sheep would occur and stay at a low level (26), should such contamination occur (27). In any case, such findings support the need for a more comprehensive surveillance of TSEs in sheep, as well as the need to systematically examine all scrapie cases for their resemblance to BSE.

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