Annex: Questions and answers before the first meeting

The following are brief ‘answers’ to the questions tabled by Sir Richard Southwood at the preliminary meeting held on 19 May 1988.

Animal health

i) Scrapie

1. What happens to the carcass of scrapie infected sheep – do they enter the human food chain, go for rendering etc?

[MAFF]

Owners and flockmasters of flocks with endemic scrapie are capable of identifying affected sheep in the early clinical stages. In such cases, affected sheep are likely to be sent to market as culled ewes and therefore go for slaughter for human consumption. Infected sheep, in the pre-clinical stage, are undoubtedly also likely to enter the food chain.

Sheep in the more advanced stages of the disease could also enter the human food chain if the carcass ‘sets out’. Otherwise, the carcass of such animals and clinically affected animals dying from scrapie or inter-current disease are most likely to go for rendering: subclinically infected animals dying from other diseases or the casualties of road traffic accidents will also go for rendering.

2. What is the incidence of scrapie in this country and worldwide?

[MAFF]

a. Great Britain

The precise prevalence of flocks infected by scrapie in Great Britain remains unknown. However, in infected flocks an annual incidence of 10% is not uncommon.

There is some evidence that the prevalence of affected flocks has declined since the 18th century. The only statistics on the current prevalence of infected/affected flocks are from the Veterinary Investigation Diagnosis Analysis database (MAFF, 1987: Epidemiology Unit, CVL, unpublished observations). This database provides somewhat biased statistics on disease incidence, but the number of incidents of scrapie recorded are likely to represent new incidents. Once scrapie is confirmed in a flock the attendant veterinary surgeon and owner/flockmaster will not resort to a laboratory diagnosis, but rely on clinical signs.

b. Worldwide

As in Great Britain, the true prevalence of infected flocks is not known for the majority of countries. The exceptions are Australia and New Zealand where the disease has not been diagnosed in the national flocks. The only available statistics on the worldwide prevalence are from the OIE returns (FAO, WHO, OIE 1986).
A low sporadic incidence was reported in Senegal, Brazil, Canada, USA, Afghanistan, Cyprus, Japan, Turkey, France, Iceland, Ireland, The Netherlands, Norway, United Kingdom and Yugoslavia. Scrapie has been suspected, but not confirmed in Zaire, Bahrain and Sweden. In addition, scrapie has occurred in South Africa, but the last case was recorded in 1972 and there is now a ‘stamping out’ policy. In the other countries, scrapie has never been recorded or no information is available. It should be noted that there is considerable variation in the intensity of disease surveillance between countries.

3. Which tissues from scrapie infected sheep have been found to be infectious to other animals a) sheep/goats b) rodents c) carnivores?

[MAFF]

a. Sheep/goats

Sheep to sheep: foetal membranes, spleen, lymph nodes, CSF and brain (Gordon 1957, Stamp and others 1959, Pattison and others 1972).

Sheep to goat: foetal membranes and brain (Pattison, Gordon and Millson 1959, Pattison and others 1972).


b. Rodents


Goats to rats: brain (Chandler and Fisher 1963).

Goats to mice: brain, CSF, spinal cord, sciatic nerve, tonsil, lymph nodes, spleen, ileum, colon, adrenal gland, thymus nasal, septum and lung (Hadlow and others 1980).

Mouse (or rat) adapted sheep scrapie to golden hamsters, Chinese hamsters, voles and gerbils: brain (Zlotnik 1963, Chandler and Turfrey 1972).

c. Carnivores

Sheep to mink: brain (Hanson and others 1971).

4. How infective are different tissues and animals with different levels of scrapie symptoms?

[MAFF]

In subclinically infected scrapie sheep, primary multiplication occurs in the spleen and lymphoreticular system (Eklund, Kennedy and Hadlow 1967). Quantitative assays of the agent during the course of infection are restricted to experimental infection of laboratory animals, particularly mice. In the case of the latter, the concentration of the agent in brain when mice develop clinical signs is always the same, irrespective of the age of the mouse at the time of inoculation, the dose of agent and route of inoculation (Kimberlin and Walker 1978); the concentration of the agent in brain and spinal cord also always exceeds that of other tissues. The replication of the scrapie agent in the spinal cord of experimentally infected mice occurred after 25 to 42 per cent of the incubation period had elapsed and always preceded the onset of replication in brain after 41 to 55 per cent of the incubation period (Kimberlin and Walker 1979). These authors noted that this sequence is consistent with the spread of agent from spleen to spinal cord and thence to the brain, possibly along neural pathways. (Evidence for the latter hypothesis was subsequently produced by Kimberlin and Walker in 1986). After interacerebral inoculation, replication of the agent in brain started much sooner, after 13 to
Peripheral, experimental infection of hamsters and mice with scrapie has resulted in maximum titres of the agent in the brain being achieved very rapidly and before the onset of clinical signs of scrapie (Eklund, Kennedy and Hadlow 1967, Baringer, Bowman and Prusiner 1983, Collis and Kimberlin 1985).

In the case of mink, after subcutaneous inoculation of the TME agent, there would appear to be an extremely limited replication of the agent in the LRS as a prelude to infection of the CNS (Hadlow, Race and Kennedy 1987). These authors found that, during the first 12 weeks post infection, TME agent probably replicated to some extent in lymph nodes draining the inoculation site, but not in other lymphatic organs except the thymus at 8 weeks. There was a complete absence of the TME agent from all extraneural sites at between 16 and 20 weeks, but after 4 weeks after its apparent disappearance from the peripheral lymph nodes, the agent appeared in the CNS, some 4 weeks before the onset of clinical signs. Similar findings have been reported following interaperitoneal infection of mink (Eckroade, Zu Rhein and Hanson 1979).

The pattern of extraneural replication in the goat resembles that in goats inoculated subcutaneously (Hadlow and others 1974).

5. What do we know about the transmission (vertical/lateral) of scrapie in sheep?

[MAFF]

Definitive studies to determine whether prenatal infection occurs and to quantify the incidence of this method of transmission have not been conducted. There is indirect evidence for this mode of transmission:

i. Ewes injected subcutaneously with SSBP/1 scrapie shortly before or soon after conception resulted in scrapie in the offspring and in a proportion of cases at the unusually young age of 7 months (Gordon 1996). Natural cases of scrapie have not been seen at this age.

ii. As a result of the development of laboratory animal transmission models in mice, so-called maternal transmission has not been reported in mice. The explanation for this is that for an animal to become infected by a natural route it must be immunologically competent (Outram et al. 1973). Sheep are immunologically competent before birth (Schinkel and Ferguson 1953), but mice do not develop this competence until some days after birth.

There is rather more direct evidence that prenatal and/or perinatal transmission occurs at a relatively high incidence and is important in the maintenance of infection in a flock:

i. There is a preponderance of twin lambs with both affected or both unaffected and a deficiency where only one twin is affected. Lambs are equally at risk of infection from their dams whether they are born a year before or contemporary with their dams being clinically affected.

ii. The incidence in progeny from reciprocal crosses between infected and unaffected sheep tends to follow the maternal incidence. The corollary to this is that the incidence of clinical disease has been reduced by the culling of female lines.

iii. The only confirmed natural portal of exit of the scrapie agent is via the placenta which contains high titres of the agent (Pattison and others 1974). Faeces, urine, blood, saliva, semen and milk have not been found to contain the agent or only at very low titres (Palmer 1959, Pattison and others 1972, Hourrigan and others 1979). There is however, the possibility that excretion of the agent may occur intermittently in some of these latter ‘body fluids’.

The occurrence of lateral transmission has been the subject of some contention. There is now acceptance and evidence that it does occur (Brotherston and others 1968, Haralambiev and others 1973, Dickinson and others 1974, Hourrigan and others 1979). Such transmission has apparently occurred in the absence of affected parturient ewes suggesting that excretion of the
scrapie agent does occur other than via the placenta. Although the agent has not been detected in the faeces, it has been detected in the intestine (Hadlow, Kennedy and Race 1982) and further examinations for the agent in faeces are probably required to dismiss excretion via this route. Similarly, although the agent has not been detected in semen there are a number reports that scrapie has been introduced into flocks by the purchase of a ram which subsequently developed clinical disease. Again excretion via faeces should perhaps not be ruled out to explain the infection of the flock by the purchased ram. The persistence of the agent on pastures remains unstudied, but in Iceland restocking of farms (following culling of whole scrapie affected flocks) which had been kept free of sheep for one to three years did result in scrapie occurring in the sheep which originated from flocks in which scrapie had never been recorded (Palsson and Sigurdsson 1959).

(These aspects of the disease in goats have not been studied to the same extent as in sheep. Although it was initially suggested that the goat was an end host, there is now evidence that vertical transmission (prenatal and/or post natal) does occur in the goat (Hourrigan and others 1979)).

6. What is meat and other material from scrapie–infected sheep used for – does it include pet food and material for biological products?

[MAFF]

Pet Food

As initial preclinical multiplication of the agent takes place in the spleen and other parts of the lympho-reticular system (LRS) there is obviously the possibility that scrapie infected material is used for pet food in addition to material from clinically affected sheep. Sheep spleens are used exclusively for pet foods and processed sheep heads are undoubtedly included.

Commercial canned pet food is subject to heat treatment. The following treatments are employed by . . .

[A table has been deleted here for commercial-in-confidence reasons.]

These time temperature processes are sufficient to reduce the titre of the scrapie agent to very low levels and in some cases may effectively reduce the titre to zero. The bulk of the meat used . . . is imported. There are, however, a number of products which comprise raw sheep material, usually spleen and cheek trimmings plus other offal and meat offcuts. Presumably these products are fed to dogs in the raw state in some instances.

Biological Products

There has been one instance of inadvertent transmission of the scrapie agent to sheep through loping ill vaccine (Gordon, Brownlee and Wilson 1939). One of the three batches of vaccine made in 1935 at the Moredun Institute contained the scrapie agent resulting in 7% of the recipients of the 18,000 doses in the batch developing scrapie. This vaccine was made from formalin-inactivated sheep brain, and brought to the attention of research workers that formalin, at a concentration of 0.35% for at least 3 months, which inactivated conventional viruses, did not totally inactivate the scrapie agent.

It would appear that companies producing biological products take sensible precautions to exclude the use of tissues and fluids from scrapie infected animals.
ii) BSE

7. How do cattle become infected with BSE?

[MAFF]

The results of the initial epidemiological study provide strong circumstantial evidence that cattle have become infected with a scrapie-like agent through the consumption of commercial feedstuffs containing meat and bone meal. Other sources of a transmissible agent have been ruled out; all affected animals would appear to be index cases and the epidemic is assuming the typical form of an extended common source. There is as yet no evidence for cattle to cattle transmission via vertical or horizontal routes. This is the subject of the continuing epidemiological investigations.

The results of modelling indicate that the age specific incidences are consistent with exposure commencing in 1982 and continuing until at least 1984. The results of this year’s study of the epidemic are needed to determine whether exposure continued until 1985, but there is at present no reason to believe that exposure is not continuing (see below). Both calves and adults (> 2 years of age) would appear to have been exposed, but with an ‘effective exposure’ in calves of 30 times that for adults. ‘Effective exposure’ in this context could mean a variation in susceptibility or a variation in the dose; the former is most likely (Wilesmith, unpublished findings – further details are available from the author).

8. If the agent originates from cattle feed why has it only recently appeared in this material?

[MAFF]

Epidemiological studies have confirmed that the first clinically suspect case of BSE occurred in April 1985 in a herd in which BSE was subsequently confirmed. Without doubt, the current incidence of BSE has not been experienced prior to 1986. It is possible that sporadic cases have occurred in the past without being subject to a neuropathological examination. Such cases could have been diagnosed as brain tumours or other space-occupying lesions in the CNS. Transmission of a scrapie-like agent to cattle via feedstuffs may therefore have occurred in the past, but exposure must have increased since 1981. The reasons for this are not clear, but there have been a number of changes in the rendering industry during the late 1970s and early 1980s. These are:

a. Solvent extraction of tallow has almost disappeared, due to the increased cost of hydrocarbons. Only two plants still use this method.

b. Low temperature renderers have commenced operations.

c. There has been a move from batch cooking to continuous rendering in response to the needs for economy of scale to retain profit margins.

d. Stord Bartz systems have been introduced which operate at lower temperature than, say, Stork Duke systems.

e. The continuous rendering systems will probably reach lower temperatures than batch rendering due to continuous movement of material in the cooker and displacement with cold raw material.

In addition, the following factors have been identified which have altered the nature of the material being processed:

a. The sheep population has increased markedly since 1982.

b. There has been a reduction in the number of operations resulting in more waste material being processed in fewer plants.

c. The number of knackers yards has decreased resulting in more casualty and condemned animals entering the rendering industry.

d. The practice of skinning sheep heads and harvesting of sheep brains has almost ceased, resulting in more unsplit heads going for rendering.
There appears to have been an increase in the incidence of scrapie. The inclusion rate of meat and bone meal in proprietary cattle rations has not changed over the period of interest, e.g. that for winter dairy cow concentrates has remained at an average of 2% since 1980.

The higher incidence in the south of England may be due to a combination of a change in rendering processes and the disproportionate increase in the sheep population in this part of Britain. There is a notable high incidence of affected herds (10%) on Guernsey where milk quotas are not in operation. This may be indicative of a dose response relationship.

9. If a change in composition/processing is involved can it be reversed?

[MAFF]
Discussions with representatives of the rendering industry are in hand to determine whether ‘safe’ rendering processes can be introduced. It is possible that the time/temperature combinations known to inactivate the scrapie and CJD agent will be achievable in certain of the continuous rendering processes, but these cannot be achieved in the batch process. However, it may be that the resultant greaves from this latter process could be economically reprocessed through a continuous process as already occurs in the case of some plants. Other options such as the exclusion of sheep head and spinal cords (and spleens) will also be discussed together with means of recording and ensuring the necessary time/temperature combination has been achieved.

10. Is the infection self-sustaining among cattle either by the infection of the calf by the mother, ante or intra partum or laterally between cattle, or are the cases limited to those which have received the infected feed?

[MAFF]
Please see answer to question 7.

11. How long is the incubation period in cattle – what is the age of affected animals?

[MAFF]
From the modelling studies described above the age specific incidences are consistent with an incubation period of 3 to 8 years with a log normal distribution. The peak incidence is in 4 year olds and the age range of confirmed cases is 2 years 9 months to 10 years of age.

12. What is the difference in feeding or other treatment that leads to the infection being largely confined to dairy cattle?

[MAFF]
As the question suggests, there is considerably higher incidence of affected dairy herds compared with beef suckler herds. This is undoubtedly due to the difference in feeding practices in these two herd types. In the majority of beef suckler herds, calves receive their dam’s milk, and dependent on the time of birth have the opportunity to graze or receive conserved grass forage, if used, concentrates are fed to adults only during the ‘service season’, usually for 10 weeks.

13. Where does material from affected animals go – meat, meat products, biological products, etc?

[MAFF]
The proportion of animals going for normal slaughter or to knackers yards is unknown, but the majority would appear to be slaughtered in abattoirs. The fate of meat and meat products from affected animals is therefore similar to that for normal animals, i.e., human consumption and
rendering. The only difference is that in a high proportion of cases the heads will be excluded because of their submission for histopathological diagnosis.

The low incidence of affected animals must make the probability of the use of serum and pancreas for biological products very low, but there is no restriction to prevent such use at present.

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14. Are the carcasses of cattle suffering from BSE treated in any way?

[MAFF]

Please see answer to question 13.

15. What are the routes to man of parts/products of cattle, especially dairy cattle, before and after slaughter? (‘Ox brain’ is still available through local butchers, but not ‘sheep brains’, apparently.)

[MAFF]

There is a small, but apparently active, trade in sheep brains to Greece and France. There is a small trade/’production’ for domestic consumption; this is limited because of the cost of sheep brains.

The trade in bovine brains is much more restricted because in the majority of cases they are destroyed by the method of killing (captive bolt pistol). Nonetheless, small amounts are exported to France and some may be produced for domestic consumption.

The fate of spleens has been described above (ie pet foods), but there is a very low probability that spinal cord forms part of meat products, such as sausages, meat pies etc. Similarly, other parts (excluding hides and fleeces) of bovine and ovine carcass could be used either directly for human consumption or as raw ingredients in meat products. The lack of quantitative information on the fate of the organs and tissues of most interest is because their use is recorded under the umbrella heading of ‘offals’, without further distinction. Consumption of offal from all species by the UK human population is estimated by MAFF and has declined since 1982 from 2.2 kg per head to 1.7 kg per head in 1996 (MLC 1987).

[DHSS]

- surface contact with outer-hide: cowhands, vets, slaughtermen, tanners, leather workers
- surface contact with udders/milk: cowhands/dairymen
- surface contact with blood, flesh, brain: slaughtermen, butchers, cooks
- aerosol inhalation of blood: slaughtermen?
- inoculation of blood: vets during needlestick injuries
- surface contact with saliva, semen, placenta, blood and amniotic fluid during calving: cowhands, vets
- surface contact with misc products: workers in various industries eg rendering, some pharmaceuticals
- ingestion of milk, offal and meat; general public
- indirectly through another species; general public via pets
- inoculation/administration via licensed medicinal products or ‘food supplements’: bovine insulin in diabetics, perhaps in other pharmaceuticals too
16. Are there routes to other animals (farm or domestic) from products of infected cattle? What are the risks of a species jump?

[MAFF]

If BSE is a result of cattle becoming infected with the scrapie agent, it will be some time, if ever, before it is known whether only a particular strain, and possibly a new one, is involved. Similarly the effects of passage of the agent in cattle, in terms of altered risks for other species, will be difficult to ascertain.

These possibilities aside, and assuming that a straightforward analogy with scrapie can be made, the risk of transmission to pet animals would appear to be unchanged. There is however, the potential problem of an increase in exposure to all species receiving rendered products or ‘raw’ products of infected animals, because we now have scrapie infected sheep and BSE infected cattle entering the food chain. Hounds, at least, have been fed uncooked carcass of dead and diseased animals for some time without becoming a maintenance host of a scrapie-like agent. It could also be argued from an evolutionary and dietary standpoint that cats and dogs are unlikely to become infected.

[DHSS]

- ingestion of meat/milk/offal: domestic pets via pet food, perhaps wild animals such as foxes, zoo carnivores, milk to calves, pigs etc
- inoculation/administration via medicinal products
- from contamination of pastures, farm buildings and implements

17. In what organs and secretions is the agent present? (If the scrapie model is valid not only CNS but lymph glands and placenta will contain the agent but not muscle).

[MAFF]

The decision has been made in the R & D programme that the investigation of infectivity of tissues and body fluids (other than CNS tissues) should await the development and establishment of a suitable laboratory animal model.

18. As it will probably be some months before the answer to No. 17 is known, what steps if any would it be prudent to take in the meantime in clinically affected animals covering a) meat, offal and meat products for human consumption, b) milk, c) material used in the preparation of biologicals and d) pet food?

[MAFF]

The evidence from scrapie research indicates that milk from affected animals does not contain the agent. It could therefore be argued that there is no need to take measures to exclude the milk of affected cows from the supply to the human population. (There is a natural self-limitation in that cows tend to ‘dry themselves off’ or become impossible to milk because of their hyperaesthesia).

Given the difficulties in abattoirs of identifying parts of a given carcass it may be prudent to condemn, for any use, the whole carcass of affected animals. This would seem to be politic given the possible fears from the public of the risk of consuming products from affected animals and therefore unfairly bring all animal products into disrepute.

[DHSS]

a. meat, offal and meat products for human consumption
   - not acceptable
b. milk
• no action at present

c. material used in preparation of biologicals
  • at present material is accepted only from clinically well animals

d. pet food
  • not acceptable

19. Is there a national/international reporting system for CJD etc – what information is available about the incidence worldwide?

[DHSS]

No information obtained about any international reporting system. Various national surveys have taken place eg in the UK (see Matthews, J Neurol Neuosurg Rych 1975 enclosed) and in France (Brown et al Neurology 1987 enclosed which includes on page 900 a summary table of various surveys). It is not known what proportion of cases of this rare disease are not diagnosed, even after death.

20. What bovine materials are used in human medicines?

[DHSS]

There are licensed products containing bovine vasopressin, insulin, bone, immune globulins, fibrin, dermal collagen, albumin. The list may not be complete. In addition, bovine serum albumin and other bovine products may be used in the preparation of vaccines and other products.

21. What information is available about CJD and primates?

Transmission of CJD to a chimpanzee was achieved by intra-cerebral inoculation of human brain biopsy in 1968.

112 isolates of CJD have since been made in various primates with clear evidence of serial transmissibility.

CJD material has produced disease in guinea pigs. There are also ‘experimental models’ in cats, mice, rats, hamsters – not clear if this really means as a result of human tissue inoculation.

Iatrogenic transmission of CJD accepted – high titres of the agent in experimentally infected guinea pig corneas.

Kimberlin reports that there is evidence against CJD being the manifestation of scrapie in man – CJD is apparently rare in Iceland where there are very many sheep and endemic scrapie – occurrence of CJD in Australia – many many sheep but no scrapie (European immigration may complicate the picture here) – high incidence of CJD in Libyan Jews in Israel but no scrapie in sheep there (could there nevertheless be a subclinical strain in the sheep – has anyone looked hard enough? – is there a genetic factor in that ethnic group?).

Two major surveys – eating habits/environment/occupation – have failed to establish a link between scrapie and CJD.

15% of CJD cases show a familial pattern – ?genetic susceptibility – ? common exposure.

There is evidence that different strains of the CJD agent exist ? also random mutation of the agent leading to occasional pathogenic variants of a possibly widespread but subclinical infection.

Two cases of CJD recently reported in ex-laboratory workers having regular contact with neural tissues during their working lives.
22. What research is being undertaken and what further research is needed?

[DHSS]

The highest priority must be directed towards development of techniques that enable the identification of ‘BSE-agent’ in tissues of animals/humans who are subclinically infected. Without identification of the nucleic acids of the agent (assuming it might have some) this could be an impossible dream. Otherwise were there a hazard to humans, it could be 10 or more years before it is revealed by clinical disease, by which time thousands/millions might have been infected.

Questions concerning possible risk of BSE for humans

[DHSS]

1. If ‘BSE-agent’ can infect humans, how could infection be manifested?
   - almost certainly as disorder of CNS
   - probably, but not necessarily, as spongiform encephalopathy
   - likely to be similar to, or identical with, CJD
   - after a latent period of a few years (but might this be shorter in children?)

2. Who would be most at risk from infection with ‘BSE agent’
   - those receiving medicinal products of bovine origin or prepared using bovine material
   - slaughter/butchers handling bovine brain
   - cowmen/vets
   - ox brain eaters (do we know how common this is?)
   - beef-eaters
   - milk drinkers

Do we know what other potentially infectious bovine products are used, eg in the cosmetic industry?
Can we draw up a flow chart of the final destination of all bovine parts?

3. What would be the first evidence of human infections?

In the absence of tests for the ‘agent’, subclinical infection could not be detected. So the first evidence would be clinical disease, probably mimicking CJD.

4. How sensitive is present surveillance for CJD and how readily would an increase be detected?

At present, do we rely on death certification? Would it be sensible to institute national monitoring for CJD (for example through the MRC, or involving neurologists and neuropathologists as in Bryan Matthews’s study), so any change in the future could be detected? Would it be sensible to set up/ extended studies of groups at special ‘risk’, such as slaughtermen? (Maybe the HSE would have views).

5. If BSE is the manifestation of scrapie in cows, and this is evidence of a recent species jump, should we re-examine the possible risk of sheep scrapie for humans?

- no geographical links between scrapie-infected countries and human CJD
- no particular links with sheep handling/occupational exposure to sheep

but this evidence was secured following study of clinical cases where infection is presumed to have been acquired 10 or more years previously ie prior to the first infections of cows. So if this resulted
from a particularly virulent strain of ‘scrapie agent’ and the human incubation period is longer than
the bovine one, the lack of evidence of human risk may not be entirely reassuring.

**6. Might there be a human risk from other animals, eg domestic pets?**

If scrapie-infected sheep offal is the source of infection for cows, and similar material has gone into
pet food, what is the chance of dogs/cats also being infected? Even if they do not show symptoms of
disease (say because the incubation period is longer than the natural life span) might they still be
infectious? Would there be any chance of transmission to humans through scratches or bites?
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