Scientific Steering Committee

OPINION OF THE SCIENTIFIC STEERING COMMITTEE ON THE HUMAN EXPOSURE RISK (HER) VIA FOOD WITH RESPECT TO BSE

Adopted on 10 December 1999

Text subject to editorial changes

Opinion of the SSC on the Human Exposure Risk (HER) via food with respect to BSE

EXECUTIVE SUMMARY

THE QUESTION

The SSC has been requested to deliver an opinion on the risk that humans could be exposed to potentially infective doses of the BSE agent, via food and under a normal consumption pattern.

THE RESPONSE:

The SSC has not yet defined the precise concept of geographic BSE status, but considers that three elements need to be considered: incident risk, propagation risk and human exposure risk. Previous opinions of the SSC have provided an analysis for the first two of these elements. The present opinion addresses the third of these elements. Human Exposure Risk (HER) can be expressed as the expected number of people that could be exposed to the BSE agent from one infected bovine entering the human food chain and processed as an animal declared fit for human consumption**.**

The SSC accepts the strength of the epidemiological, pathological and molecular biological evidence linking BSE to vCJD.

The HER will depend on the amount and distribution of infectivity in that animal and of the ways in which the various tissues that could contain infectivity are used. Sources of infectivity arising from foods received from other regions or countries also affect the national HER.

The infectivity in a typical bovine BSE case was considered by the SSC in their opinions on specified risk material (SRM) of 9 December 1997 and of BSE-risk of 19 February 1998. These showed that the total infectivity in an animal with clinical BSE was about 8,000 Cattle Oral Infective $Dose_{50}$ ($CoID_{50}$). As the infectious dose to humans is currently not known, the Cattle Oral Infectious Dose, as defined by the SSC in its opinion of 26 March 1998, is used in this opinion as an indicator of potential infectivity.

In an attempt to develop a quantitative approach to the Human Exposure Risk, the SSC requested detailed information on the use made of different bovine tissues from the Member States. Only three responded but in rather global and qualitative terms. The SSC decided to illustrate how the HER could be assessed by means of 3 “scenarios” intended to provide realistic values for the human exposure risk.

The first scenario represents a worst case analysis for a very wide exposure (up-to 500,000 consumers) to a low level of infectivity (0.023 to 0.043 $CoID_{50}$). The

third scenario represents a worst case analysis for a narrow exposure (about 5 consumers) to a high level of infectivity (1,000 $CoID_{50}$) from one animal entering the food chain with late but pre-clinical BSE infection. The second scenario illustrates a given hypothetical situation between these two extremes.

Excluding SRM from the human food chain would effectively minimise this exposure. However, while no tissue from known BSE-cases (clinical or pre-clinical) should enter the human food chain, with regard to the infectivity of tissues other than SRM the SSC refers to its opinion of 29 October 1999. This opinion shows that there is no evidence that muscle tissue from infected bovines is infective and that also for lymphoid tissue no infectivity was found so far.

However, given the fact that no information on a possible threshold dose or the effect of repeated and very low doses of the BSE agent on human health is available, the actual Human Infection Risk in terms of expected cases of vCJD cannot be estimated. As a general guideline any exposure should be prevented and if this is not fully possible the dose should be minimised by all means.

The SSC therefore considers that the ideal level of protection of consumers from exposure to BSE-infectivity is the absence of infected animals from the human food chain. In the event that this cannot be reasonably guaranteed, the second level of protection of consumers from exposure to BSE infectivity is the removal of SRM, particularly CNS-based SRM which accounts for 95% of the infective load in a BSE-case approaching the end of the incubation period. Failure to remove SRMs is likely to expose a large number of consumers to an unnecessary risk[1].

[1] 7 Member States of the European Union are removing SRMs (BE, FR, IRE, LUX, NL, PT and UK). AT, DE; DK, HE; SF, and SW do not have an SRM-ban in place, Italy and Spain request removal of SRM from animals from Countries with BSE.

FULL OPINION

1. TERMS OF REFERENCE

In its opinion on "*the BSE risk for specified geographical areas*" (23 January 1998) the SSC stated that "in the context of the assessment of the risk of humans being exposed to the BSE agent, three interlinked risks appear to be of major importance: the incident risk, the propagation risk and the human exposure risk."

A method for assessing the incident risk and the propagation risk in order to estimate the geographical BSE-risk has been developed by the SSC.

A working group Human Exposure Risk (HER) has been created with the mandate to develop a method for assessing the probability that under "normal" consumption patterns, a consumer would be exposed to defined amounts of the BSE agent. The method should produce an output that would allow an assessment of the risk of vCJD, as soon as the minimal infective dose and the incubation time are known for humans.

This opinion addresses the issue of the Human Exposure Risk by responding to the following questions:

- What are the critical factors determining the human exposure risk?
- What is the rational for assessing the HER on the basis of these factors?
- What is the order of magnitude of exposure that could be expected to result from one fully infective animal entering the human food chain?

2. SCIENTIFIC CONTEXT OF THE QUESTION

Given the importance of this opinion in the protection of human health, the SSC feels that a clear recognition of the following points is essential to fully understand the context of the opinion.

BSE is a new disease that occurred for the first time in UK, probably sometime between 1980 and 1985, but was only recognised and described in November 1986. The incubation period of BSE in bovines is on average 5 years, with the vast majority of cases falling into the range of 4-6 years.

By 1 November 1999, 175,838 bovine BSE cases were confirmed in the UK. BSE was also reported in indigenous cattle in Belgium, France, Eire, Liechtenstein, Luxemburg, Netherlands, Portugal and Switzerland, and in imported cattle in Canada, Denmark, Falkland Islands, Germany, Italy and Oman. Updated worldwide BSE figures are available from the International Office for Epizootics (Office International de Epizooties OIE), website: http://inet.uni-c.dk/~iaotb/3bse.htm#OIE.

In March 1996, a new variant of CJD (vCJD) was reported in human beings by the UK National CJD Surveillance Unit (Will *et al*, 1996). It resembles classical sporadic CJD, but occurs in younger people (average age: 29 years, range: 16-53

years)[2] and does not show the typical EEG appearance of CJD. The development of the disease (13 months on average) is also longer than in CJD (4-6 months).

Scientific evidence collected over recent years indicates that CJD and vCJD are most likely, if not certainly, diseases that are caused by different agents and that BSE and vCJD are most likely caused by the same (BSE) agent. Humans, therefore, probably became infected as a result of the consumption of BSE contaminated material, most likely orally (*via* food)[3,4].

Four lines of evidence are available:

- first, epidemiological evidence of a new clinico-pathological disease phenotype of distinct temporo-spatial clustering in a country where high exposure to the BSE agent of the population occurred with a delay between the BSE epidemic and the first cases of vCJD which would be compatible with the incubation time of a TSE (Will *et al*, 1996);
- second, experimental evidence of similar if not identical clinico-pathological features when BSE was transmitted to non-human primates (Lasmézas *et al*., 1996);
- third, identical prion protein (PrP) glycotype profiles of vCJD, BSE in cattle, and BSE transmitted to other species (Collinge *et al*, 1996; Hill *et al*, 1997);
- and fourth, identical incubation times and histo-pathological brain lesion profiles in inbred mouse strains inoculated with BSE and vCJD (Bruce *et al*, 1997).

While the last three lines of evidence demonstrate the sharing of physico-chemical and biological properties between BSE and vCJD agents, they are unable to elucidate the way in which humans might have become infected.

By 31 October 1999, 48 definite or probable vCJD cases were reported in the UK, one definite in France, and one definite recently in the Republic of Ireland (the latter patient having also resided in the UK). So far all vCJD patients have had the 129M/M PrP gene *(PRNP)* genotype (Collinge, 1999). However, it is unknown whether other genotypes can develop the same phenotype as in previously diagnosed vCJD, and whether incubation times might be longer, or susceptibility might differ, in other PrP genotypes, as shown for iatrogenic CJD (Deslys *et al*, 1998).

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[2] At the time of adoption of the opinion, a vCJD suspect child aged 13 years had been reported.

[3] Investigation of the reported vCJD cases in UK has failed to suggest any iatrogenic source of infection by other routes (e.g., injection of bovine-derived hormones).

[4] An alternative hypothesis, that BSE in cattle and vCJD in humans are both linked to the use of organo-phosphates containing pesticides, has been considered by the EC's Scientific Steering Committee as missing sufficient scientific grounds.

The numbers of confirmed vCJD cases have been low so far. However, there are two important "unknowns" that justify precautionary measures to reduce or eliminate the risk of possible new infections:

- The length of the incubation period of vCJD is not known. Hypotheses vary from a few years to more than 25 years. Therefore, the number of cases so far could just be the start of an epidemic of which the extent and the end are not known.
- The minimal infective doses, as well as the effect on man of repeated very low doses, are unknown.

It is unclear how many people have been exposed to how much infectivity in the past or are possibly still being exposed by consuming infectious material from animals that are slaughtered while being infected but before showing clinical signs of the disease.

Combining the above unknowns, one may expect that, depending upon the hypothesis, less than one hundred to several hundred thousands of vCJD cases may appear in the coming years. Nevertheless, in view of a long incubation times of all TSEs, a very high degree of uncertainty in the future size of the epidemic remains for the next 3-5 years (Ghani *et al*, 1998).

In addition to the above unknowns, there are a number of other questions to which science has not provided a fully satisfactory answer so far:

- The exact nature of the infective agent is not known (Chesebro, 1999). Although most evidence points towards the prion-theory, alternative hypotheses have been advanced and have not all been refuted. One hypothesis is for example, that the agent may be an extremely small and difficult to detect virus (or "*virino*").
- The exact level of inactivation/elimination of the infectious agent by processing is uncertain. Scientific evidence shows that even harsh conditions such as treatment of infected material by 133°C at 3 bars for 20 minutes does not completely clear the material if the initial infective load was high. Recent experiments have also shown that residual infectivity can be present on contaminated surgical devices, even if they were sterilised at higher temperature/pressure/time combinations.
- The distribution of the infectivity in the various tissues of an infected animal or human is not fully known. It is accepted that most of the BSE infective load in a bovine animal showing clinical BSE signs (i.e. at the end of the incubation period) is mainly, but not exclusively, located in the central nervous system (e.g., brain and spinal cord)[5]. It is not fully understood how this infectivity builds up and is distributed in the various body tissues during incubation. The total infective load in young animals is much lower than in

[5] The infectivity distribution and level of infectivity in tissues vary according to the animal species.

animals reaching the end of the incubation period. However, because of their limits of sensitivity, presently available tests and laboratory analyses are unable to detect infectivity below a certain level. It is thus also uncertain whether tissues in which "no detectable infectivity" exists (with present methods of detection) can also be considered as infectivity-free and/or with an infectivity level below the minimal infective doses.

- Sheep have been fed bovine-derived meat-and-bone meal in several European countries where the BSE incidence is high (UK), or where meat and bone meal (MBM) has been imported from the UK. As sheep can experimentally be infected with BSE, the possibility that BSE is present in sheep flocks cannot be excluded. However, this has never been shown so far[6] outside experimental conditions.
- The transmission of a TSE adapted to a given species to another species (e.g., from bovines to humans) has to cross the species-barrier. The magnitude of any species barrier for BSE between bovines and humans is unknown. Current estimates[7] vary from no species barrier to a factor of 100,000, meaning that 100,000 times more BSE contaminated bovine material would be needed to infect a human, compared with that needed for a bovine.

Given the above uncertainties, the human infection risk can not be estimated in quantitative terms. Quantitative risk assessment as a basis for protective measures is thus, at least for the present, impossible.

Thus there remain many scientific unknowns to be solved regarding TSEs. Removal of SRMs[8] would be an important step to significantly minimise the human exposure risk in all countries that cannot reasonably guarantee absence of BSE infected animals from their human food chain. This is explicitly or implicitly stated in several SSC opinions. The SSC, whilst recognising that there remain many scientific unknowns to be solved regarding TSEs, regularly calls for a continuous monitoring of the evolving scientific understanding of TSEs, monitors the appropriateness of the list of SRMs and assesses the evolution of the BSE epidemic in the UK. The SSC considers, however, that a safe product can be offered to consumers if what is already scientifically known about BSE is correctly exploited in a logical order and provided that the resulting risk management measures are properly enforced and controlled. The SSC opinions follow the following sequence of criteria when judging the safety of a product:

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6 Clinically, it is difficult to distinguish BSE in sheep from scrapie, a natural TSE occurring in sheep which is harmless to humans. Differential diagnostic tests are not yet available.

7 [Note: The issue of species barrier is, amongst others, being dealt with in detail in the draft report of the SSC Working Group "Human Exposure Limit Line". The draft will be discussed by the SSC at one of its first meetings of 2000. The present section does not yet take into account the publication by Scott *et al* (1999) which became only available on 21 December 1999.]

8 7 Member States of the European Union are removing SRMs (BE, FR, IRE, LUX, NL, PT and UK). AT, DE; DK, HE; SF, and SW do not have an SRM-ban in place, Italy and Spain request removal of SRM from animals from Countries with BSE.

- the source of an animal; whether there is an (epidemiological) link to the same source of possible infection as confirmed TSE cases (e.g., feed, mother/calf) (for examples, see Opinions N°s 2, 3, 4, 5, 6, 11, 16, 19, 22, 25, 26, 28 and 29 listed in annex 2);
- whether the raw material comes from an animal certified by a veterinarian to be fit for human consumption; (for examples, see Opinions N°s 2, 4, 6, 7, 8, 9, 12, 13, 16, 17, 18, 20, 21, 25 and 28 listed in annex 2);
- removal or not of the SRM; (for examples, see Opinions N°s 1, 2, 4, 6, 7, 8, 9, 11, 12, 13, 14, 17, 18, 21 and 25 listed in annex 2);
- the age of the animal; this is particularly important because the infective load in young infected animals is much lower than in older animals, particularly in terms of the main infective burden of the BSE agent in the central nervous system. It is noteworthy that 98% of the BSE cases in UK were animals over 36 months and BSE infectivity has only been found in the CNS a few months before the clinical onset of the disease. (for examples, see Opinions N°s 1, 2, 4, 16, 22, 25 and 29 listed in annex 2);
- whether the dam has survived without BSE for at least six months after calving (for examples, see Opinions N°s 2, 4 and 29 listed in annex 2);
- appropriate processing of the raw material and its intended end-use (technical uses, human consumption, animal feed, pharmaceuticals, medicinal products, cosmetics etc.); (for examples, see Opinions N°s 7, 8, 9, 12, 13, 14, 15, 17, 18, 20, 21, 25 and 28 listed in annex 2);
- avoidance of cross-contamination; (for examples, see Opinions N°s 1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 15, 16, 17, 18, 21, 25 and 29 listed in annex 2).

Certain animals are more at risk than other ones. According to the opinion of 25 June 1999 of the Scientific Steering Committee on "Fallen stock" and to field observations in Switzerland, the incidence of BSE is higher in fallen stock (15 positive for 6,000 examined[9] in Switzerland) and in cows offered for emergency slaughter (5 positive for 2,900 examined in Switzerland) than in healthy looking animals presented at routine slaughter (3 positive for 6,000 examined in Switzerland).

[9] The mass testing was based on the PRIONICS test. Positives where verified by histopathology and/or immunohistochemistry.

3. ASSESSING HUMAN EXPOSURE RISK

3.1. Definition

Ideally, Human Exposure Risk (HER) would be expressed as the expected number of people that could be exposed to BSE infectivity from one infected bovine entering the human food chain and processed as an animal declared fit for human consumption.

However, the infectious dose to humans is currently not known. Therefore the Cattle Oral Infectious Dose (CoID), as defined by the SSC in its opinion of 26 March 98, will be used as an indicator of infectivity. The HER will then be defined in terms of the number of consumers exposed to the BSE agent. The extent of exposure will be expressed in $CoID_{50}$.

3.2. General Approach to Assessing the Human Exposure Risk

The Human Exposure Risk (HER) in any country, and at any point in time, will depend on four main factors:

⇒ the likelihood that an animal infected with BSE enters the human food chain;

⇒ the amount and distribution of infectivity in that animal;

⇒ the ways in which the various tissues that could contain infectivity are used in the food chain; and

⇒ the marketing of infected foods produced in other countries.

The first of these, the likelihood that an animal infected with BSE enters the human food chain, is the Processing Risk, and will not be considered further here.

The approach taken in this opinion is to consider the exposure in the human population if that one infected animal is slaughtered and processed “normally” for human consumption.

The second factor, the amount of infectivity in that animal to humans will depend on many things, including the length of time after the animal was infected and the overall infectivity of BSE infected tissue to humans. There is much uncertainty and variability in these factors, but, in general, they will be common to all countries. They are discussed below, but do not play a major part in differentiating the HER of different countries.

It is the third of these main factors, the ways in which the various tissues that could contain infectivity are used (hereafter called “routes”), that may differ between different countries, and so could cause variations in the HER, even if the Processing Risk is the same. Any method to assess the HER must therefore concentrate on this factor.

3.3. Steps in Assessing the Human Exposure Risk

3.3.1. Hazard identification

The hazard being considered in this report is the BSE agent. The SSC assumes that consumption of the BSE agent in food can result in variant CJD.

3.3.2. Exposure

Exposure of humans to the BSE-agent depends on the source and the route by which it reaches the consumer.

As the dose response relationship for humans is not known, it is proposed to present the level of exposure in terms of consumption of defined amounts of the BSE agent, measured in Cattle Oral Infective Doses (CoID). However, the SSC wishes to emphasise that the $CoID_{50}$ is used in this opinion only as an indicator and should not be confused with the Human Oral Infective Dose ($HoID_{50}$), which is not known.

3.4. Exposure Assessment

3.4.1. Sources of Infectivity

Different species, as shown by experimental and natural infection, are able to carry the BSE agent. However, this opinion is confined to bovines as the source of the agent. The terms of reference are related to "normal consumption pattern". Therefore the committee did not examine the case of special at-risk groups in the population, for example those exposed to SRMs through the alleged consumption of pet foods. Moreover, because of the lack of data, it was not possible to examine the case of particularly sensitive groups of the population such as children.

The distribution of infectivity in a typical bovine BSE case was considered by the SSC in their opinion on SRM of 9 December 1997 and on the BSE-risk of 19 February 1998. The latter showed that the total infectivity in one animal with clinical BSE is about 8,000 $CoID_{50}$, and that the majority of this infectivity (about 95%) was from the brain, the spinal cord, and the trigeminal and dorsal root ganglia (TRG & DRG). The distal ileum also carries a measurable infectivity and for spleen and eyes a low level of infectivity is assumed based on scrapie experiments. Together these tissues carry about 99% of the infectivity in a clinical BSE case (see table 1).

In making this estimate of the distribution of infectivity, it was assumed that 0.1g of infected brain tissue or spinal cord would make up one cattle oral ID50 (CoID50). This assumption is based on the interim results of the pathogenesis experiment being carried out by the UK MAFF. The infectivity in TRG & DRG is assumed to be the same, while the relative infectivity of other tissues (Ileum, spleen and eyes) is estimated to be lower. This information is based on limited data from mouse bioassay results, for both BSE and scrapie.

With regard to infectivity in other tissues the SSC refers to its opinion of 29 October 1999. There it was noted that "muscle tissue has never been found infective, even from BSE cattle in the later stages of infection, in spite of the fact that peripheral nerves, lymphatic tissue and blood are associated with muscle." It was further shown that currently available experimental data are "strongly suggestive of no infectivity associated with the lymph nodes and spleen in orally infected cattle."

It is known that infectivity builds up in an infected animal over time, so that the infective load in any particular animal will depend on the length of time since that animal was infected with BSE, and what proportion of the incubation period that represents. However, little is known about the dynamics of this. Also, there is no way of knowing when any particular animal would have been infected and age is therefore only an approximation, assuming as a conservative assumption that the animal was infected shortly after birth. The initial dose consumed and the route of transmission will also influence the infective load.

Tissue	**Infectivity density ($CoID_{50}/g$)**	**Weight (kg) per 537 kg Animal**	**ID_{50} per BSE Case**	**% of total infective load per animal**	**Cumulative load**
Brain	10	0.5	5,000	64.1%	64.1%
Spinal cord	10	0.2	2,000	25.6%	89.7%
Trigeminal ganglia	10	0.02	200	2.6%	92.3%
Dorsal root ganglia	10	0.03	300	3.8%	96.1%
Ileum	3.20E-01	0.8	260	3.3%	99.4%
Spleen*	3.20E-02	0.8	26	0.3%	99.7%
Eyes	3.20E-02	0.1	3	0.04%	99.74%

Table 1: Total Infectivity in a BSE Case (*Some data suggests that the extrapolation from scrapie to BSE is not valid and then that spleen is unlikely to be infective.)

In addition to the total infective load, the distribution of the BSE-infectivity in the animal's body also changes over time. The MAFF pathogenesis experiment (Wells *et al*, 1998) has shown that at early stages of the incubation, the intestines are infective while at later stages of the incubation, the CNS carries significantly higher infective loads. Little is known about the way by which the infectivity moves through the body. No infectivity was found in the other tissues that were tested for BSE; i.e., the level of infectivity was below the detection level for the mouse bioassay.

On the basis of the available knowledge, it is possible to define three categories of cattle which have different potential levels of infectivity, mainly as a function of their age at slaughter. Depending on the category, the infectivity which could enter the food chain will differ, both in quantity and with regard to the specified risk tissues:

⇒ Veal Calves (less than 1 year). The level of infectivity in the CNS tissues of these animals can be considered to be negligible. However, there may be infectivity in the intestines, in particular the Ileum.

⇒ Prime Beef (older than 1 year, but less than 30 months). These animals could, if infected at birth, show some level of infectivity, though it would be very unlikely to be the same as in a fully developed case of BSE. The CNS is not necessarily highly infective, even if the animal was infected at birth.

⇒ Mature Cattle (older than 30 months). If infected early in their live, these animals may show infectivity levels close to those of clinical BSE-cases, even if no clinical symptoms are apparent. It is clearly evident from the Swiss surveillance of fallen stock and the UK surveillance of cattle over 30 months i.e. those excluded from the food chain under the Over Thirty Months Scheme (OTMS), that apparently healthy but nonetheless infected animals do enter the human food chain in countries where BSE is prevalent in the cattle population. In this category of bovines, the level of infectivity will be high and the CNS is certain to be highly infective.

3.5. Routes of Exposure

It is recognised that there are a number of possible routes by which humans could be exposed to the BSE-agent. This is illustrated in Figure 1. This report refers only to exposure via direct consumption of SRM or of meat products containing them.

As mentioned above, the large majority of the infectivity in a (clinical) BSE-case will be in the Specified Risk Materials (SRM). In order to assess the routes by which the BSE-agent could reach the consumer, it is therefore necessary to consider all possible ways that SRM could be consumed.

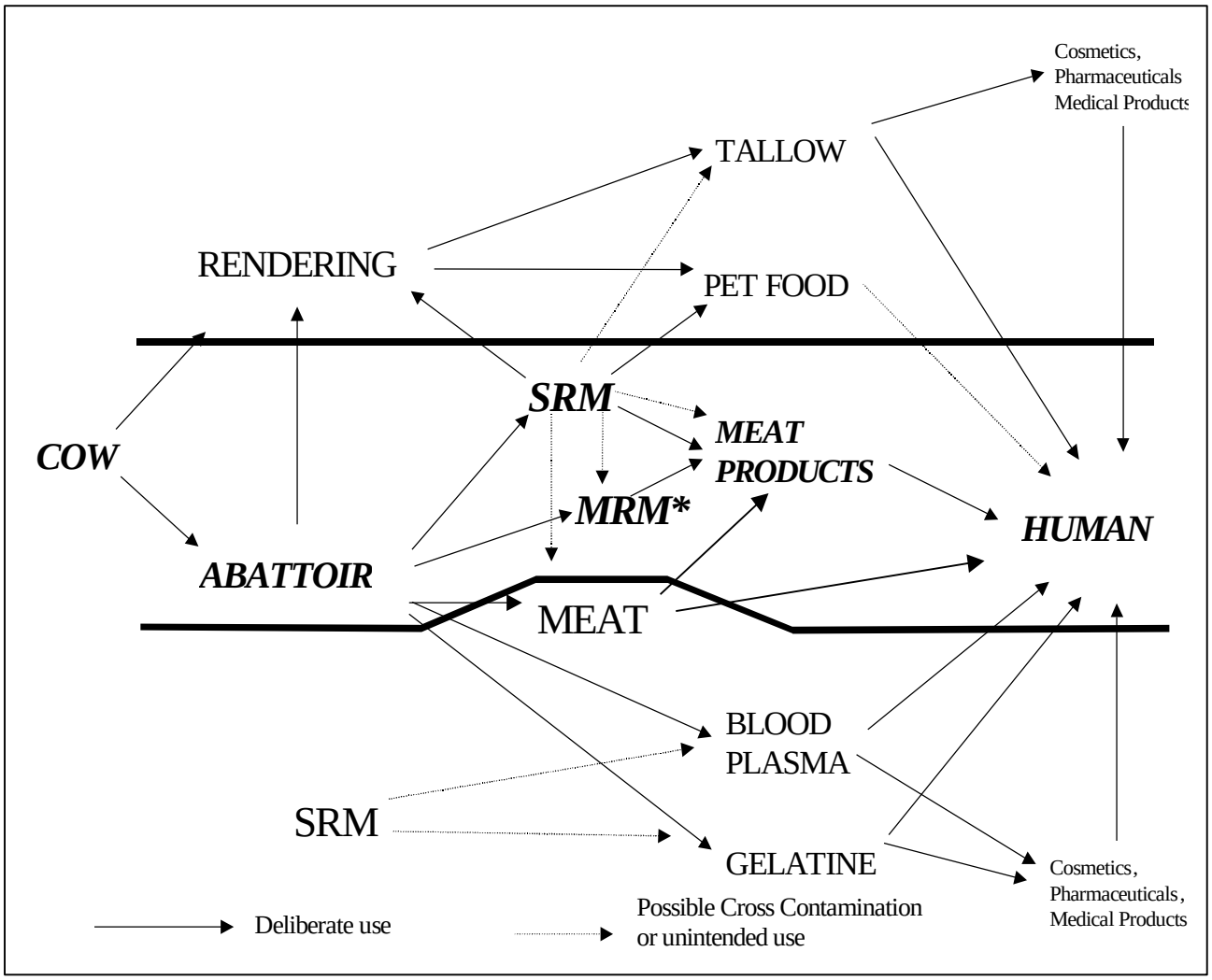
For the purpose of this report, three main routes by which SRM could reach the consumer are distinguished.

3.5.1. Direct consumption

SRMs are consumed as such by the consumer. It is known that brain and spinal cord (amourette in French) are consumed in this way, as well as ileum and all the small intestine (andouillette in French) from young veal (<6months). Even spleen and eyes might occasionally be eaten. Trigeminal ganglia and dorsal root ganglia are not consumed as such, although there will be some direct consumption of DRG (and possibly spinal cord) from cuts of meats served on the bone and including part of the vertebral column (e.g. T-bone steak, rib of beef).

Figure 1. Potential Routes of Exposure to Infective Cattle Tissues

(This opinion deals only with the routes between the two Lines and the factors printed in ***bold italics***; * MRM = Mechanically Recovered Meat, see opinion of the SCVPH, 2/1998)



3.5.2. Indirect consumption.

SRM is transformed and integrated into food products in such a way that it is not detectable by the consumer. The inclusion of SRM into food products may happen voluntarily or by contamination.

3.5.2.1. Voluntary inclusion of SRM.

The use of brain or spinal cord in "paté" or sausages is an example of the voluntary use of SRM. Other SRM may also be included into food products as direct ingredients. Data are available from a recent study in Germany, where there is no ban on the use of SRM in human food, and (bovine) brain tissue was included in sausages. Lücker *et al* (1999_a-1999_d), detected CNS in 14.5% of the 69 samples of a specific sausage (Kochmettwürste) which were analysed using immuno-assays specific to bovine CNS.

3.5.2.2. Contamination of edible products with SRM.

Contamination is always possible if the inclusion of SRM is technically possible and does not create quality problems. Also MRM could be contaminated, particularly if it is produced, inter alia, from vertebral column that could include both DRG and spinal cord. It should be noted that, from a technical point of view, MRM could be included in many "meat" products. Tallow and gelatin would normally not contain any SRM but certain contamination of the raw material with brain or spinal cord could occur.

3.5.3. Estimation of the Exposure Level and of the number of persons exposed.

In order to estimate the expected number of people that would be exposed to an infected dose, several critical factors have to be considered. Some of them are related to the Sources, others to the Routes.

3.5.4 Critical factors determining the HER

3.5.4.1 Critical factors as regards to Sources

⇒ Processing risk. The probability that an infective bovine is slaughtered for food is the most relevant parameter for the Human exposure risk. Its assessment is not the subject of this report.

⇒ Age of the infected animal that is slaughtered and "normally" processed. It influences the infective load and its distribution between the tissues of the animal as indicated by the categories given in Section 3.4.1.

⇒ Infected animals per batch. As long as the BSE-cases remain geographically scattered, the number of exposed consumers would be proportional to the number of processed BSE-infected animals and the average exposure dose would remain rather constant.

If the BSE-density is so high that more than one infective animal could enter a single batch of production, the number of consumers exposed would remain stable while the dose per exposed individual would increase proportional to the number of infected animals entering the batch.

3.5.4.2. Critical factors as regards to Routes

⇒ Processing conditions. In principle, processing conditions could influence the level of infectivity in the product. It is known, for example, that certain production processes for gelatine and tallow reduces the infective load at least a 1,000-fold. (See SSC opinions on these products). However, normal cooking and industrial food processing of the products addressed in this opinion are unlikely to affect the level of infectivity.

⇒ Batch size. The batch size of food products into which SRM is integrated directly (meat products, paté, sausages) or indirectly (via MRM) will significantly influence the number of persons exposed. Larger batches may expose a higher number of people to a smaller dose, and vice-versa.

⇒ Serving size. Together with the batch size, the serving size influences the dose of exposure and the number of persons exposed.

⇒ Contamination. The potential for contamination with SRM (e.g. of MRM) will increase the likelihood of exposure to infectivity. The dose of exposure due to contamination is likely to be low, although the number of persons exposed could be high depending on batch and serving size as above.

⇒ Use of SRM. Deliberate use of SRM will increase the infectious load and hence the exposure dose.

Note: The route into which a given SRM will be channelled, largely depends on two factors:

⇒ Price. The relative price for brain, spinal cord and other SRM for direct consumption (direct eating), integration into higher value added products (paté or sausages), MRM (for low value added food products or pet-feed) or rendering will determine the use made of these tissues. Generally there will be a tendency to choose the most profitable option. For example, the price of the brain or spinal cord for human consumption is between 3,000 and 5,000 FF/ton (460 to 760 €/tonne). The value for the same tissues included in MRM for pet food can be 5 times lower (1,000 to 1,700 FF/ton or 150 to 250 €/tonne).

⇒ Outlet. The size of the different market outlet for the different tissues will also influence the use of the SRM. This size depends, inter alia, on traditions and eating habits but it will also be influenced by legislation.

3.6 Quantitative exposure assessment

The SSC attempted to estimate human exposure risk from all food-borne exposures, including via gelatine and tallow. However, the issue is far more complex than for geographic BSE risk and there is very limited quantitative data available for most of the critically important variables.

The SSC requested detailed information on the use made of different bovine tissues from the Member States. Only three responded but in rather global and qualitative terms only. That information has been taken into account in establishing the scenarios described below.

In the longer term, it should be possible to construct stochastic models to estimate human exposure to not only the BSE agent but other food borne hazards such as dioxin or ochratoxin. Therefore for the purpose of the present opinion, the SSC has focussed on what is possible, i.e. scenarios, with no data on the probability of their occurrence.

4. EXPOSURE SCENARIOS

The following scenarios are intended to illustrate realistic values for the human exposure risk resulting from one infected bovine entering the human food chain and processed as an animal declared fit for human consumption.

4.1. Scenario 1 - Maximal distribution, only indirect consumption

Note: This scenario is based on data generated from a household survey in 1993, food composition databases and interviews with food industry and govern,ent departments. While the assumptions are felt to be realistic for this historic situation, it is not assuming that they describe a currently existing situation. However, it is the opinion of the SSC that the scenario illustrates a realistic upper end of the number of people that could be exposed to the BSE-infectivity. For details of calculation see Annex 1.

4.1.1. Assumptions

The entire infective material of a BSE-case is included in mechanically recovered meat (MRM). It is important to understand that a smaller amount of infectivity entering the MRM would contaminate the same amount of product – only the average infective load would be lower.

MRM is produced in batches of 5 to 7 tonnes. This information was obtained from industry and refers to current production of MRM for pet-food. It is confirmed by quality control prescriptions of the industry, which require destruction of at least 5 tonnes of MRM (=one batch) if a quality problem is recognised (bacterial contamination etc.).

About 7kg of MRM is obtained from one animal. Thus one batch contains material from up to 1,000 animals. If one of these animals is infective, the entire batch is contaminated, and it is assumed that any infectivity would be distributed evenly throughout the batch.

The average MRM content of food products varies between 100% ("meat" filling of cheap stuffed pasta could technically have been made from MRM only) and 5 to 10% (minced meat preparations, for example, could contain that fraction of MRM without technological problems).

Minced meat is normally sold in packages of 600g to households with 2.7 persons on average.

Cheap meat stuffed pasta contains about 13% of filling and is sold in 1,000g packs per household averaging 2.7 persons.

4.1.2. Conclusions

Given the large batch size and the small proportion of MRM in meat-products, one animal could contaminate 5 tonnes (pasta filling) to 116 tonnes (minced meat) of food products.

A large number of servings could thus be contaminated, albeit with a low average dose per serving.

Calculations based on the assumptions made, indicate that one 5-tonne-batch of MRM could expose about 200,000 (via "pasta") to 400,000 persons (via minced meat preparations) to the BSE infectivity (see annex 1).

The same calculation showed that the average infective load would be between 0.023 and 0.043 CoID50 per consumer if the entire infective load of the animal ends up in MRM. Excluding CNS-SRM (Brain, spinal-cord, trigeminal and dorsal route ganglia[10]) from the production of MRM would reduce the dose of exposure by about 95%.

4.2. Scenario 2 - Mean distribution, only indirect consumption

The following scenario is based on assumptions only. It serves as an illustration of a medium level of dispersion of the BSE infectivity.

4.2.1. Assumptions

The entire brain and spinal cord (700g) are mixed into paté or sausages up to a fraction of 5%.

The average serving of "paté" or sausage is 50g to 100g and could hence contain 2.5g – 5g brain or spinal cord.

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[10] Because of the risk of contamination with CNS, the vertebral column and head-bones should not be used for MRM production.

Each serving is eaten by a different person.

The remaining 12 % of the infectivity are rendered or directly fed to animals.

4.2.2. Conclusions

If “paté” or sausages are prepared in batches of 14kg, i.e. where the 700g of brain and spinal cord are just 5%, 280 servings of “paté” or 140 servings of sausages could be contaminated by one single infectious animal.

The average infective load would be between 25 and 50 $CoID_{50}$ per consumer.

If the batches are larger and the fraction of brain and spinal cord included is lower, the number of contaminated servings would increase and the infective load per consumer would decrease accordingly.

4.3. Scenario 3 – Concentration, only direct consumption

This scenario is based on realistic historical data. The assumption, that the entire infectivity outside the brain is not entering the food chain is, however, rather optimistic.

4.3.1. Assumptions

No MRM produced from bovine material.

Brain directly eaten at average servings of 100g.

The remaining infective tissue is rendered or directly fed to animals.

4.3.2. Conclusions

5 persons would eat the brain of the assumed infected animal. They would be exposed to 1,000 $CoID_{50}$, each.

The estimated exposures from these and similar scenarios are plotted in Figure 2, as number of exposed consumers against exposure dose, measured in $CoID_{50}$. No attempt has been made to consider the relative likelihood of these outcomes.

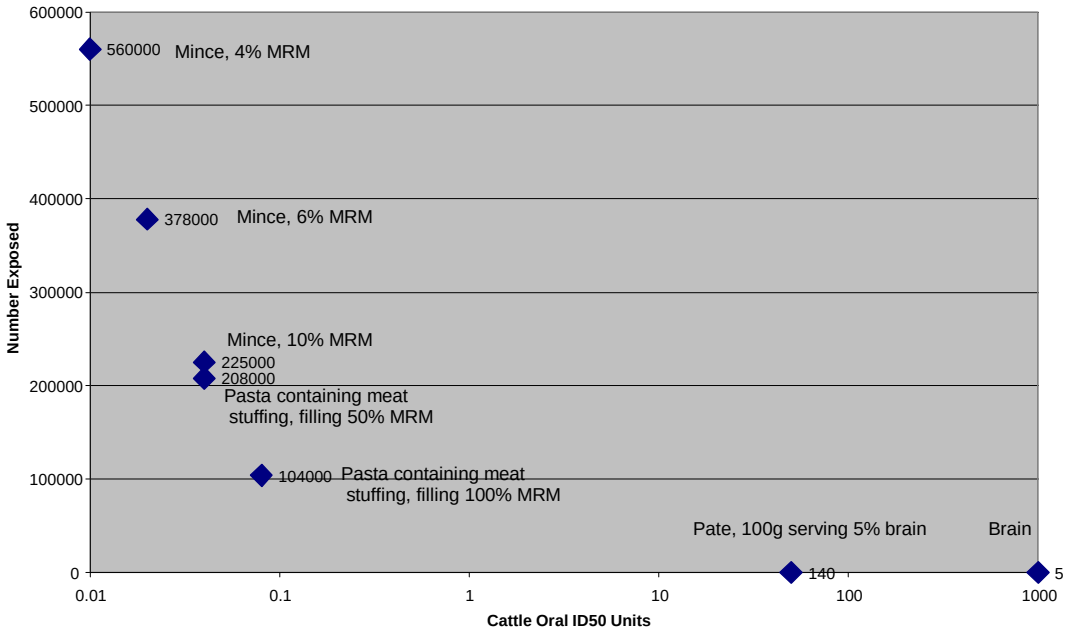

Figure 2: Summary of Exposure Estimates from Scenarios

- Mince, 4%, 6% MRM = Minced meat, containing 4%, 6% MRM, servings of 100g
- Meat stuffed pasta, filling 50%, 100% MRM = Meat stuffed pasta, filling consists of 50%, 100% MRM, serving = 370g containing 13% filling
- "Paté", 100g serving, 5% brain = "Paté" prepared with 5% brain and served at 100g portions.
- Brain = Brain, directly consumed in servings of 100g

5. IMPLICATIONS

1. Previously the SSC emphasised that brain, spinal cord, neuronal ganglia and the ileum of an infected bovine contain the highest concentration of BSE-infectivity. These tissues, therefore, are of particular concern in terms of their potential to induce human vCJD although the dose needed to induce human infection is not known.

2. Intestines used from young infected animals are of particular concern since they become infectious in an early stage of the BSE-incubation.

3. The SSC is aware of the direct human consumption of both intestines and brain material by many population groups within the EU and now has evidence of brain and spinal material being used in common meat products such as pâtés and sausages.

~~4.~~ Wherever the direct consumption of intestine or central nervous tissue is still legally possible, there is a greater likelihood of inducing human infection because of the potentially high infective load of these tissues and hence the high dose involved in consuming them.

5. The pessimistic realistic analyses presented in the three scenarios are recognised to be based on uncertain assumptions. These relate to the rate of transfer of all SRM, in particular the brain and spinal cord, of an infected animal into a batch of food, its distribution within that batch, the estimate of the batch size of a meat ingredient and its incorporation into common food stuffs.

6. The SSC sought to avoid some of these uncertainties in its enquiry of Member States, but it was not possible to refine them because of a lack of reliable data and alternative analyses of risk.

7. The SSC would welcome different views based on new evidence or different analytical approaches, which would allow more reassurance to be given to policy makers and the public.

8. However, with the assumed widest distribution of SRM in food products, up to 0.4 million people could be exposed to infected material when only one infected animal with pre-clinical disease, close to the end of the incubation period but passed as fit for human consumption, enters the food chain.

9. Recent evidence suggests that in countries with a reported low incidence, the actual rate of BSE infected animals entering the food chain is not nil. It should be acknowledged that under such circumstances presently available methods to prevent that an infected animal entering the food chain are far from being satisfactory. The capability of the recently evaluated post-mortem BSE-tests to

identify pre-clinical BSE-cases has still to be determined before they should be considered for mass screening of pre-clinical animals.

10. The SSC therefore reaffirms its original analysis that the removal from the food chain of specified risk materials would significantly decrease the risk of vCJD.

11. Since there is inter-Member State transfer of animals, cross-border trading in animal organs and marketing of offals, ingredients and processed foods into and out of most EU Member States, it is reasonable to conclude that the risk of human exposure to BSE infectivity within any one country is not necessarily linked to the geographical burden of infectivity in the cattle within that Member State.

12. The ideal level of protection of consumers from exposure to BSE-infectivity is the absence of infected animals from the human food chain. In the event that this cannot be reasonably guaranteed, the second level of protection of consumers from exposure to BSE infectivity is the removal of SRMs, particularly CNS-based SRMs which account for 95% of the infective load in a BSE-case approaching the end of the incubation. Failure to do so is likely to expose a large number of consumers to an unnecessary risk.

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ANNEX I : DETAILS OF SCENARIO CALCULATIONS

GENERAL ASSUMPTIONS

- Total infectivity in one fully infected animal: 8.000 $CoID_{50}$ (Cattle oral ID_{50} units)
- Number of persons per household: 2.7

SCENARIO 1

Burger Meat

- MRM is produced in batches of 5 to 7 tonnes. Assume batch size is 5 tonnes, packaged in 20kg packs (250 x 20kg).
- Assume all infectivity (8000 $CoID_{50}$) from one infected animal gets into a batch of MRM. (this would be very unlikely)
- Burger meat is produced in batches of 1 tonne, and may contain 5 - 10% of MRM.
- Burger meat/mince is normally sold in packages of 600g for one household (2.7 persons on average).

Calculations

- If 3 x 20kg packs of MRM are included in one 1000kg batch of MRM (6%), then 5 tonnes (250 packs) of contaminated MRM could contaminate 84 batches of burger meat.
- 84 tonnes of burger meat represent 114,000 (84,000 / 0.6), 600g packs that could expose 378,000 (114,000 x 2.7) persons.
- Average exposure would be 8,000 / 378,000 = 0.02 $CoID_{50}$ per person.
- Note: If MRM content is reduced, more people are exposed to a smaller dose, e.g.:

No. 20kg packs MRM per ton batch of mince	Percent MRM	Tons of mince contaminated	People exposed	Average exposure per person [$CoID_{50}$]
5	10%	50	225,000	0.04
4	8%	63	280,000	0.03
3	6%	84	378,000	0.02
2	4%	125	560,000	0.01
1	2%	250	1,125,000	0.007

MEAT STUFFED PASTA

- Cheap meat stuffed pasta contains about 13% of filling, which could be up to 100% MRM.
- Meat stuffed pasta is sold in 1 kg packs to an average household of 2.7 people.

Calculations:

- If 100% MRM is used in filling, one batch of MRM could contaminate 38,500 1kg packs of meat-stuffed pasta, exposing 104,000 people to an average dose of 0.08 $CoID_{50}$.
- If 50% MRM used in filling, one batch of MRM could contaminate 77,000 1kg packs of Meat stuffed pasta, exposing 208,000 people to an average dose of 0.04 $CoID_{50}$.

Annex 2: Opinions adopted by the SSC since November 1997 on questions related to Transmissible Spongiform Encephalopathies (status : 8.12.1999)

N°	Date of adoption	Title of the opinion
1.	9 December 1997	Listing of Specified Risk Materials: a scheme for assessing relative risks to man
2.		Report on the UK Date Based Export Scheme and the UK proposal on Compulsory Slaughter of the Offspring of BSE Cases
3.	22-23 January 1998	Opinion of the Scientific Steering Committee on defining the BSE risk for specified geographical areas
4.	19-20 February 1998	Opinion on the revised version of the UK Date Based Export Scheme and the UK proposal on compulsory slaughter of the offspring of BSE-cases, submitted on 27.01.98 by the UK Government to the European Commission
5.		Final Opinion on the contents of a "Complete dossier of the epidemiological status with respect to TSEs".
6.	26-27 March 1998	Opinion on BSE risk
7.		Opinion on the Safety of Tallow
8.		Opinion on the Safety of Meat and Bone Meal
9.	25-26 June 1998	The safety of dicalcium phosphate precipitated from ruminant bones and used as an animal feed.
10.		Possible links between BSE and organophosphates used as pesticides against ecto- and endoparaistes in cattle.
11.	24-25 September 1998	Opinion on the risk of infection of sheep and goats with Bovine Spongiform Encephalopathy agent.
12.		Report and Opinion on mammalian derived meat and bone meal forming a cross-contaminant of animal feedstuffs.
13.		Scientific Opinion on the safety of organic fertilisers derived from mammalian animals.
14.		Updated Scientific Report on the safety of meat and bone meal derived from mammalian animals fed to non-ruminant food-producing farm animals, presented to the Scientific Steering Committee on 24-25 September 1998.
15.	22-23 October 1998	Report and Scientific Opinion on the safety of hydrolysed proteins produced from bovine hides.
16.		Opinion on the safety of bones produced as by-product of the Date Based Export Scheme.
17.	10-11 December 1998	Updated Report and Scientific Opinion on the safety of tallow derived from ruminant tissues
18.		Updated Report and Scientific Opinion on the safety of gelatine
19.		Preliminary opinion on a method to assess the geographical BSE-risk of countries or regions

20.	21-22 January 1999	Report and Scientific Opinion on the evaluation of the "*133°/20'/3 bars heat/pressure conditions*" for the production of gelatine regarding its equivalency with commonly used industrial gelatine production processes in terms of its capacity of inactivating/eliminating possible TSE infectivity in the raw material.
21.	18-19 February 1999	Report and Scientific Opinion on the Safety of Gelatine (updated version of opinion adopted on 21-22 January 1999)
22.		Opinion on a method to assess the geographical BSE-risk of countries or regions, including the Manual for the assessment of the geographical BSE-risk.
23.	27-28 May 1999	Opinion on Monitoring some Important aspects of the evolution of the Epidemic of BSE in Great Britain (Status, April 1999)
24.		Opinion on: Actions to be taken on the basis of (1) the September 1998 SSC Opinion on the risk of infection of sheep and goats with the BSE agent and (2) the April 1999 SEAC Subgroup report on Research and Surveillance for TSEs in sheep.
25.	24-25 June 1999	Opinion on risks of non conventional transmissible agents, conventional infectious agents or other hazards such as toxic substances entering the human food or animal feed chains via raw material from fallen stock and dead animals (including also: ruminants, pigs, poultry, fish, wild/exotic/zoo animals, fur animals, cats, laboratory animals and fish) or via condemned materials.
26.	22-23 July 1999	Opinion on the conditions related to "BSE Negligible Risk (Closed) Bovine Herds".
27.		Opinion on the policy of breeding and genotyping of sheep, i.e. the issue whether sheep should be bred to be resistant to scrapie.
28.	16-17 September 1999	The risk born by recycling animal by-products as feed with regard to propagating TSE in non-ruminant farmed animals.
29.	28-29 October 1999	Opinion on the Scientific Grounds of the Advice of 30 September 1999 of the French Food Safety Agency (the *Agence Française de Sécurité Sanitaire des Aliments*, AFSSA), to the French Government on the Draft Decree amending the Decree of 28 October 1998 establishing specific measures applicable to certain products of bovine origin exported from the United Kingdom.
30.		Summary Report based on the meetings of 14 and 25 October 1999 of the TSE/BSE *ad-hoc* group of the Scientific Steering Committee on the Scientific Grounds of the Advice of 30 September 1999 of the French Food Safety Agency (the *Agence Française de Sécurité Sanitaire des Aliments*, AFSSA), to the French Government on the Draft Decree amending the Decree of 28 October 1998 establishing specific measures applicable to certain products of bovine origin exported from the United Kingdom.