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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

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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].

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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).

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