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Dear Professor,

Could you accept my apologies for the letter that I sent to you (c/o Royal Society) in advance of (today) receiving your reply to my article concerning the risks of BSE infecting man. I presume that the original must have disappeared during my leaving York District Hospital.

I found your answers to the problems put forward in the article really quite depressing. I had tried to use the data of MAFF/MLC and other government-associated bodies in calculating the risks and explained why the data that I used fitted in well with the findings of Fraser & Foster and Middleton & Barlow. I also gave you a copy of the article in June 1993, which gave 3 months in which you could have asked me for further explanation. I also offered to attend the meeting of your committee to answer questions directly as I knew that the article would not fit in the MAFF ideals.

The problem with trying to work out the risks from BSE is that we simply do not have enough data with which to calculate this accurately.

Decisions are, unfortunately, having to be made now in order to prevent the disease infecting humans. All we seem able to do at this point is to work out the risks that are being taken if we assume that BSE is similar to other TSEs for which more data is available. The aim of the article was to assess the information that we currently have. One of the problems with the current information is that various authors around the world have differing opinions as to how it is interpreted. e.g. Dr. Kimberlin and Dr. Will seem to have differing views from various American authors. An attempt was made in the
article to either put forward the varying views or to take one of the paths that seemed most reasonable from what is known.

Assumptions that are made in the article:

1. That data from MLC and MAFF are correct concerning the age distribution of cattle in the UK.

2. That all the clinical cases of BSE in cattle (and scrapie, since January 1993) are reported to the Veterinary Officer.

3. That all of the BSE cases are accepted and slaughtered.

4. That the method of diagnosis used by the MAFF is 100% sensitive and specific.

5. That no cattle born after the ban on the use of bovine tissues in bovine food were infected.

6. That the ban on certain bovine tissues in human food was complete; that none of these tissues bypassed it.

7. That none of these banned tissues was present in human food before the ban and that the human diet only contained liver, kidney and meat (i.e. muscle and the tissues that it contains) between 1984 and 1998.

8. That the level of infectivity of BSE to other cattle is similar to that for other animals' TSEs to their own species.

9. That the BSE is scientifically similar to other TSEs (e.g. that the infective agent will be similar and that it will act in a similar way)

10. That the level of BSE infectivity (number of BSE infective units) present in different tissues would between the highest and the lowest reported for other animals.

11. That the minimum oral dose of BSE infectivity needed to infect a human is $10^{4.5}$ IU should humans have a 2 year lifespan and $10^3$ IU as they have a 70 year lifespan. (but that the actual infective dose may be up to $10^9$ IU and we have no way of knowing at which of these levels is correct).

12. That the infectivity of BSE is cumulative. This is discussed in the article.

13. That the age distribution of death due to BSE would have been the same for cattle slaughtered when young as for cattle that lived to die of BSE. (this can be justified; data not included).
14. That the results of tissue infectivity tests carried out in mice were correct and that these represent a species barrier level of $10^3$ (as appears to be a guestimate in sheep). (I personally doubt this and expect that it is closer to $10^4$). This being the case, I would expect the nerve, kidney and liver tissues to be infective to mice only if at the highest levels found in other animals but not at the medium or low levels. If the species barrier was $10^4$ I would expect none of these tissues to be infective to mice even at the highest level of infectivity.

15. That the relative intake of meat, liver and kidneys by different members of the population stayed similar throughout the period of 1985-1998.

16. When working out the relative amounts of infectivity present in the human diet in the UK derived from scrapie and from BSE it was assumed that the levels of infectivity in bovine and ovine tissues were similar at similar points in the incubation period.

17. When assessing the number of humans that would die of BSE after having eaten an infective dose, the only assumption made is that this would be a similar proportion as had taken place in other species when fed TSE infected tissue from a different species.

Clearly most of these assumptions would lead to underestimates of the risks from BSE. The reason that I took these assumptions is so that it would be difficult for MAFF advisers to be able to say that I was crying wolf. As it happens I think that I should be crying much louder as the more realistic risks are much greater than these figures would suggest. For instance, I would not be at all surprised if it was found that many of the population had eaten some infected brain before the ban or that many farmers had not reported their cases, or that there were false-negative reports when using foramen magnum necropsy samples. The figures for the number of people who had eaten different levels of BSE IU should be thought of as minimum levels and I would expect that if infectivity in the tissues was at minimum levels there would be some people that had eaten $10^7$, $10^8$ or $10^9$ IU.

The only assumption that is open to argument is that the infectivity is cumulative. This is assumed by many researchers but is as yet unproved. The assumption is taken on the moral grounds that, as this is a fatal disease with no treatment, we should assume the worst and prove that we are wrong rather than visa versa. Experiments on this topic could easily have been carried out since 1990.

At the moment we have no way of knowing the real level of infectivity in any of the tissues (even though these
experiments could have been done long ago). Looking at the PrP staining procedures in BSE brain (Dr. Kimberlin does not associated PrP levels with infectivity but many other researchers do) it is clear that PrP levels are much lower than in mice or hamsters. These procedures suggest, however, (due to the sensitivity of the method) that the BSE level may only possibly be 10-100 fold less than the mouse scrapie one. As we are talking of a level of $10^8$-$10^{10}$ IU/g in mice then a level of $10^6$-$10^9$ IU/g in cattle may be possible. As Ray Bradley said that the apparent titre of BSE in brain when measured in mice was $10^4$ in that series of experiments then it would estimate the species barrier level to be between $10^2$ and $10^5$. This is, I agree, an inaccurate method of estimation but it shows that the assumptions used in the article are reasonable.

**Absolute vs. relative risks**

You say in your letter that a relative risk calculation would be more reasonable.

No relative risks could be calculated as the absolute risk to humans from no other species TSE was known. The attempt was made therefore to look at the absolute risk. Unfortunately the relative likelihood of the different minimum oral infective doses was also not known and so it had to be assumed that they were all equally likely. If you have any evidence against this I would be very interested to see it.

The article is, indeed, difficult to come to grips with. The findings in it should already have been calculated by MAFF researchers, and you should have been already warned of the risks that were being taken. For instance, before any findings by Fraser and Foster, the titres of infectivity in bovine tissue should have been assumed to have been the same as in other animals with TSE. I can understand how, by not understanding the mathematics, MAFF can convince itself that their findings now show no infectivity in edible tissues. I cannot understand, however, how these results, could have been presumed before 1993 and how the MAFF could have been happy to take such an enormous risk with the human population without evidence that it was right.

When criticising the assumptions made in my article could I ask you to look back at the assumptions made by MAFF and the Southwood Committee when assessing the risks to humans of BSE. They seem to have assumed the best ('that the cow will be a dead end', that 'bovine tissues will not be infective', that 'BSE is just scrapie and, as scrapie does not infect humans, neither will BSE' etc.) and these assumptions were scientifically and morally unacceptable.
I hope that MAFF activity turns out to be correct and there is no rise in CJD. (If there is, then I would expect it to be appearing in about 1996 and in younger people than was the finding in the 1980s). Unfortunately, my research shows that, even taking MAFF data, the scientific literature, and a lot of conservative assumptions into account the risks still appear unacceptably high.

If you are still unhappy with any of the findings I will be glad to explain them to you in person.

Yours sincerely,

[Signature]

Dr. Stephen Dealler
Microbiologist