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COMMUNICATION FROM THE COMMISSION

**A European initiative on transmissible spongiform
encephalopathies (TSE)**



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COMMUNICATION FROM THE COMMISSION

A European initiative on transmissible spongiform encephalopathies (TSE)

I Introduction

1. Since the announcement by the UK authorities on 20 March 1996 that the appearance of 9 cases of a new variant of CREUTZFELDT-JAKOB disease (nvCJD) - a rare human disease - could be linked to exposure to bovine spongiform encephalopathy (BSE), European citizens have become concerned over the consequences of this likelihood for human health.

Known cases of nvCJD currently stand at 15 (14 in the UK, 1 in France). The infectious agent and transmission mechanisms for these diseases, which are always fatal, are very poorly understood. In addition, there is no treatment at present.

2. In this context, a sizeable research initiative within the EU would appear to be essential. This is why in April 1996 the Commission gave a group chaired by Prof. WEISSMANN the task of drawing up an inventory of the state of knowledge and proposing research priorities on BSE.

Since 20 June 1996, the Commission has made public its intention of proposing an action plan for research on BSE and CJD. It set out this intention at the Research Council of 7 October 1996, indicating that supplementary funding would be needed.

The research council of 7 October invited the Commission to reinforce its research activities on BSE and related diseases and to present a communication to the next Research Council on 5 December. This communication is in response to that invitation and includes an action plan in annex.

II The requirements

1. The report of the group chaired by Prof. WEISSMANN was made public on 16 October. It constitutes a full analysis of research needs on BSE and related diseases. There are numerous questions - 16 altogether - for which answers are required, both on practical aspects and basic research. Each question covers several research topics on average.
2. On the basis of the WEISSMANN report, research which needs to be carried out on BSE and related diseases can be divided into five areas (see table 1 of the action plan):
 - clinical and epidemiological research on human spongiform encephalopathies (SE);
 - the infectious agent and its transmission mechanisms;
 - diagnosis of SE;
 - evaluation of the risk of SE;
 - treatment and prevention of SE.

Within these areas, 24 research topics have been identified. Given the complexity of the subject, several research projects per topic are often required.

3. From a careful analysis of the figures, the Commission has evaluated funding requirements at 45.7 MECU (table 1 of the action plan), to which 5 MECU should be added for coordination (table 2 of the action plan), i.e. 50.7 MECU overall.

These are minimum requirements both in terms of quantity of high priority research and overall cost.

This analysis is not surprising when one considers that a serious research project in these areas costs at least 1 MECU and sometimes more. For example, the development and perfection of essential diagnostic tests and the study of means of transmission are extremely costly (7.6 and 4.5 MECU respectively).

Reinforcement of coordination of research activities on TSE between Member States is also needed. The cost of 5 MECU for this may seem relatively high compared with the

lightweight coordination which is usually practised in research matters. Here, though, it is a matter of very serious coordination with a view to harmonising the collection of data and diagnostic criteria for the detection and identification of the disease(s) concerned. To this end, the creation of databases and training programmes are both essential and, inevitably, costly.

III **Funding**

1. The funding of research projects on TSE can only be carried out through the 3 "Life Sciences" specific programmes, BIOMED, BIOTECH and FAIR. The Council decisions on these specific programmes set out indicative breakdowns between areas within the overall funding for each of them (the Amount Deemed Necessary). Only certain areas could incorporate research projects on TSE in any significant way:

- BIOMED 2: Area 3: "Brain Research"
 Area 4.2: "Research on Aids, Tuberculosis and other infectious diseases"
- BIOTECH 2: Area 4: "Cell Communication in Neurosciences"
- FAIR¹: Sub-area "Animal Health", one of the 22 sub-areas of Area 4 "Agriculture, Forestry and Rural Development"

At the Research Council of 7 October, several delegations ruled out the possibility of BSE affecting the breakdown of the current financial envelope of the Framework Programme between specific programmes or even the breakdown between areas within the "Life Sciences" specific programmes.

This is why it is not politically possible to carry out a redeployment in favour of research on TSE:

¹ Sub area 3.4 "Generic Science of Food" could be slightly concerned.
Sub area 4.2 "Quality Policy" could also be concerned.

- either between specific programmes, which would result in the overall funding (Amount Deemed Necessary) for the "Life Sciences" programmes being overshoot by underusing other specific programmes;
- or between areas within the "Life Sciences" specific programmes.

The only redeployment which is foreseeable is thus within the areas of the "Life Sciences" programmes which are relevant for research on TSE.

2. In order to finance the 50.7 MECU required for the action plan, there are three complementary possibilities (see table 1 of the action plan):

- 2.1 Research projects on TSE currently being or about to be financed.

These amount to 5.9 MECU, of which 1.5 MECU have already been allocated in the first BIOMED call for proposals, and 2.4 MECU and 2 MECU are about to be allocated in the BIOMED and FAIR calls for proposals which closed on 17 June and 20 September 1996, respectively.

- 2.2 Redeployment within the areas of the BIOMED, BIOTECH and FAIR programmes relevant for TSE.

The total sum which it is possible to redeploy amounts to 9.8 MECU (8.8 MECU for FAIR, 1 MECU for BIOTECH).

The situation within each of the areas relevant for TSE is as follows:

• **BIOMED 2**

The second call for proposals which closed on 17 June used up the last appropriations for areas 3 (18.5 MECU) and 4.2 (12.4 MECU). Several proposals on TSE were received under area 3. Some of them could be retained for a funding of around 2.4 MECU (see point 2.1).

The third and last call for proposals was launched on

15 September and does not cover any of the relevant areas as all the appropriations have been used up (see above).

•**BIOTECH 2**

The third call for proposals closed on 18 October and does not cover area 4.

The fourth and last call for proposals will be launched on 15 June 1997. It will use up the appropriations for area 4 (4.9 MECU). Of this sum, one could envisage 1 MECU being used for TSE, around 20% of the funding for this area.

•**FAIR**

Animal health, a relevant sub-area for TSE is only one of 22 sub-areas of area 4. This means that there is only around 12 MECU left for 1997 for all animal health areas, to be shared with other important diseases (salmonellosis, rabies, foot and mouth disease, swine fever), of which some are transmissible to man. In this context, it would be difficult to provide for more than 8.8 MECU of redeployment in favour of BSE, i.e. 15% of area 4² and around 75% of research on animal health.

A call for proposals for FAIR, as foreseen in the work programme, is planned for launch on 15 December. At the same time, the Commission intends to launch a specific FAIR call for proposals for BSE using 8.8 MECU. However, it is clear from the outset that any possible redeployment within the FAIR programme would be very insufficient with respect to the financial needs and the subjects of projects limited to animal health which could be financed.

2.3 Supplementary funding

35 MECU of supplementary funding with respect to the current overall funding for the Framework Programme are thus essential for the three Life

² Sub area 3.4 "Generic Science on Food" could also be slightly concerned.

Sciences specific programmes in order to respond to the minimum requirements of 50 MECU identified by the WEISSMANN report.

These 35 MECU would be attributed according to the subjects of the research themes (cf table 1 of action plan) and will be divided up as follows:

- 16 MECU for BIOMED
- 7.5 MECU for BIOTECH
- 11.5 MECU for FAIR

IV Conclusion

1. In parallel with this communication, the Commission has adopted a communication on orientations with a view to a revised proposal for a financial supplement to the fourth Framework Programme for research and technological development. These orientations propose setting aside 35 MECU for research on BSE. The adoption in due course by the Council and Parliament of a common political position on the financial supplement containing a substantial extra amount for research on TSE is a condition for the Commission being able to launch a specific joint call for proposals for the three Life Sciences programmes, on the basis of its own powers.

Thus, the EU would be in a position to respond rapidly to the expectations of European citizens by putting into practice the recommendations of the WEISSMANN report with an ambitious action plan.

2. In conclusion, the Commission hereby informs the Council, and the European Parliament of its intention to launch the action plan on TSE research annexed to this communication, for a total sum of 50.7 MECU, 35 MECU of which is new funding.

This will come from the financial supplement to the fourth Framework Programme for research and development, for which the Commission is preparing a second revised proposal to be submitted to the Council and European Parliament for opinion.

**European Initiative into Bovine Spongiform Encephalopathy
and Subacute Spongiform Encephalopathies**

SUMMARY

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Annex 1

European Initiative on Research into Bovine Spongiform Encephalopathy and Subacute Spongiform Encephalopathies

1. Introduction

Spongiform encephalopathies (SEs) are a group of fatal transmissible neurodegenerative diseases of humans (e.g. kuru, Creutzfeldt-Jakob Disease (CJD), Gerstmann-Straussler-Scheinker Disease (GSSD)) and animals (e.g. scrapie, bovine spongiform encephalopathy (BSE)).

These diseases have become an increasingly important research area both because of their unique biology and also the recent situation concerning the epidemic animal prion disease, which led to legitimate public anxieties over a risk to human health from eating infected tissues.

The recent identification by the National CJD Surveillance Unit (Edinburgh, UK), the coordinator of the European network on epidemiological surveillance supported by the European Community Biomedical and Health Research Programme (BIOMED), of an apparently new clinicopathological variant of CJD in fifteen teenagers and young adults has raised new concerns about the transmission of the BSE agent to man via the food chain.

2. The needs

Despite existing basic and clinical research in this field it has not been possible to identify the nature of the agent, and many factors in the epidemiology of SEs are yet to be explained. It is therefore essential to focus and stimulate research efforts at Community level and to mobilise new research teams in order to attain a critical mass.

The need to intensify research activity in order to address many of the questions still outstanding in relation to BSE was highlighted by the Agriculture Council of 1-3 April 1996. Similarly, at its meeting of May 1996, the Health Council concluded that the issue of BSE constitutes a problem in the field of public health and therefore all appropriate measures should be taken to eliminate the risk of possible transmission of the disease. Finally, the Ministers of Research at the Research Council of October 1996 emphasized the need to improve cooperation and coordination of research efforts and called upon the Commission to reinforce its research activities on topics in this field covering both basic and applied biology and human and animal health aspects, as well as diagnostic aspects.

These efforts, to be implemented by the Commission, and which may be termed an "action plan", will essentially be performed through the coordination of activities between all Member States and a specific Call for Proposals.

The action plan should identify the real needs in terms of research priorities and budgetary position based on the most recent experiences, taking into account the recommendations from the Weissmann Report and the Multidisciplinary Scientific Committee. It will also take into account ongoing Community research activities, including proposals received within the last calls of the BIOMED and FAIR programmes and work under way and planned in Member States:

3. Current research activities in the field of SEs at Community and national level

Research on SEs has been sponsored at EU level since 1990. During that year, and in order to give a prompt response to the needs in this field, an emergency procedure was launched and 1 MECU was allocated to three specific projects identified by the Scientific Veterinary Committee as covering the most important areas for research investment in this field.

The projects were implemented within the RTD programme in the field of Competitiveness of Agriculture and Management of Agricultural Resources (1989-1993, CAMAR, a specific programme of the 2nd Framework Programme), and were concerned with the isolation and identification of the infective agent; the monitoring of the presence of BSE in cattle by examining cattle brains after a negative diagnosis for rabies; and the assessment of European rendering systems in order to determine their effectiveness against the scrapie and BSE agents.

In 1991 an additional project was sponsored, aimed at assessing modifications in the prion protein as a pathogenetic mechanism for BSE and related disorders.

The Commission has also been involved in the organisation and financing of the following initiatives and workshops:

- In 1990, a European Community seminar on "Subacute spongiform encephalopathies" was organised. The meeting was attended by scientists from 18 countries, representatives of the World Health Organisation (WHO) and the Organisation Internationale des Epizooties (OIE). The proceedings of this seminar, the first authoritative book on BSE, were published for the Commission by Kluwer Academic Publishers.
- Similarly, a seminar on the issue of "Prion diseases in humans and animals" was held in London in 1991. Over 100 participants from Member States and third countries attended.
- In addition, two diagnostic workshops were jointly organised by the European Commission and the Central Veterinary Laboratory of the United Kingdom in 1990 (16-20 July, "EEC workshop on BSE diagnosis") and 1991 (8-11 April, "Spongiform encephalopathy diagnosis workshop").

This was further strengthened with the adoption of the 3rd Framework Programme (1990-1994) for research and technological development which provided the basis to tackle the issue of research on transmissible spongiform encephalopathies at European level. Indeed, research on this issue was addressed as a priority within several European Community research programmes, namely:

- * The Agriculture and Agro-industry, including Fisheries, programme (1990-1994, AIR), which supported one project aimed at characterizing the nature of the BSE agent;
- * The Biomedicine and Health Research programme (1990-1994, BIOMED 1), which supported the establishment of a network for epidemiological surveillance of Creutzfeldt-Jakob Disease (originally funded by Directorate General VI in 1990, building on the existing EURODEM project), and the development of harmonized criteria for the neuropathological diagnosis of CJD and related human spongiform encephalopathies;

- * The Biotechnology programme (1990-1994, BIOTECH 1), which supported one project on the molecular mechanisms involved in the pathogenesis of BSE and related neurodegenerative disorders, and also aimed at developing suitable experimental animal models.

The network of epidemiological surveillance of CJD is, at present, the only existing structure able to provide a systematic evaluation of the incidence and the geographic distribution of this disease in the five countries involved. Indeed, the Health Council at its last meeting (20 May 1996) proposed that this structure should be taken as a model to implement the surveillance of CJD in all Member States.

In September 1993, the Commission organised a consultation on BSE with the European Community Scientific Veterinary Committee and the scientists engaged on research in this field to assess the scientific information available. A book of proceedings entitled "Transmissible spongiform encephalopathies" was published by the European Commission.

In 1994, a report depicting protocols for the laboratory diagnosis and confirmation of BSE and scrapie was issued by the Scientific Veterinary Committee. This report was produced in consultation with all Community research laboratories leaders in the field together with several laboratories from third countries.

With the adoption of the 4th Framework Programme for RTD (1994-1998), reinforcement of prion diseases has continued within the European Community research programmes (BIOMED, BIOTECH, FAIR), allowing this issue to be addressed with different methodologies and perspectives. This has resulted in the funding of three additional projects in the first call of the BIOMED 2 programme. The most important one is using animal models to address the issue of interspecies transmission and to assess the efficacy of the species barrier in limiting the transmission of BSE to humans.

Although the available resources are limited, the second call for proposals of the BIOMED 2 programme, which had a deadline of 17 June 1996, will give the possibility to support a few proposals in this field.

Within Member States and associated countries, research in the field of SEs has been addressed at two levels:

- Clinical research and surveillance of human SEs.
- Basic biology of human and animal SEs.

An overview of the activities undertaken at national level in this field is presented in Annex 1. This text, which is not exhaustive, has been compiled on the basis of information provided during the meeting of Directors-General for Research from Member States (held in Brussels, June 1996) aimed at exchanging information on activities undertaken in the field of SEs and establishing mechanisms reinforcing cooperation and coordination, and reports presented at the last meeting of the Office International des Epizooties (OIE), held in Paris on 8-10 October 1996.

Community activities have initiated the possibility of reinforcing the surveillance system for CJD and related diseases in the countries involved and have allowed the establishment of inter-country comparisons and the development of harmonized procedures for the identification and characterization of the disease(s).

Such a system could be used as a base for the development of standard procedures for disease identification and surveillance in all Member States.

4. Weissmann Group advice in the context of ongoing research activities

The Weissmann Report presents a thorough analysis of the needs in the field of BSE research and addresses two types of questions, namely questions related to practical aspects of BSE and questions related to basic research on prion diseases.

4.1. Questions related to practical aspects. These include:

4.1.1 Has BSE been transmitted to man perorally?

The appearance since 1996 of an apparently new clinicopathological variant of Creutzfeldt-Jakob disease in fifteen teenagers and young adults (14 in UK, 1 in France) has raised concerns about the possible transmission of the BSE agent to man via the food chain.

Evidence in favour of such a possibility is based on the fact that the BSE agent can be experimentally transmitted perorally to mice, mink, cattle, goats and sheep, and it could be that the strain-specific properties of the BSE agent are retained after passaging through a variety of animals such as sheep, pigs, goats or mice and differ from those of the passaged scrapie agent.

However, given the present state of the art, no definite conclusions on such a possibility can be reached.

Several experimental approaches are proposed in order to throw more light on this question:

- "Comparison of agent strains recovered from patients affected by vCJD with BSE and normal CJD, GSSS and FFI strains" (Table 1, item 1.1).
Such experiments are partly under way in the United Kingdom and will be underpinned by Community research activities but should be reinforced;
- "Extension of a surveillance programme for CJD" (Table 1, item 1.2).
A European surveillance programme on CJD has been running since 1990, contributing to the identification of the new variant of the disease. Such an initiative should be reinforced in order to include all Member States and to ensure identification at European level of all CJD cases which may correspond to the new variant of the disease, reinforcement of epidemiological analysis of the data and identification of all epidemiological tools which may be necessary for broadening the assessment of risk transmission;
- "Experimental peroral transmission of BSE to primates". Such an approach has not yet been pursued but it is considered to be the best way to answer the above-mentioned question" (Table 1, item 4.1).

4.1.2 Assessment of risk associated with consumption of cattle-derived products

"The assessment of risk for the transmission of BSE to man as a function of BSE incidence in the cattle population and of consumption of cattle-derived products is one of the most important issues to be solved. In order to be able to perform a proper risk assessment, the following actions should be implemented":

- "Extension of the surveillance programme of BSE to all Member States, establishing wide and reliable standardized criteria for BSE detection and characterization".
Such an initiative will allow to obtain exact figures on the incidence of the disease in the different Member States (Table 1, item 4.2);
- "Determination of the incidence of covert disease in cattle", allowing to obtain figures on the number of animals that, although symptomless at present, show the infectious agent in the nervous system (Table 1, item 4.3);
- "Determination of infectivity titers of brain, spinal cord and other tissues of BSE-infected cattle before and after outbreak of clinical disease" (Table 1, item 4.4);

- "Determination of the level of meat contamination with brain/spinal cord after standard butchering procedures" (Table 1, item 4.6);
- "Determination of oral feeding and intracerebral dose responses to BSE agent in primates and whether multiple dosing is cumulative" (Table 1, item 4.7);
- "Determination of the utilization of offal in different human products prior to the ban and the consumption of such products by individual age groups and by socio-economic criteria" (Table 1, item 4.5).

Research on risk assessment in relation to consumption of cattle-derived products and transmission modalities has so far not been supported by any Community research programme. This important area of research could be addressed mainly in the FAIR programme, but also in the BIOMED programme.

4.1.3 Determination of possible infectivity in BSE infected cattle-derived products other than SBO (Table 1, item 4.4)

At present, infectivity has been found in the brain, eye and spinal cord of diseased cattle and in the intestinal wall of calves experimentally infected with brain from BSE-infected cattle.

However, the available assays for detecting infectivity are not very sensitive. It is therefore essential to:

- "implement detection assays in order to examine all products entering the human food chain (muscle, milk, cheese, blood) and used in pharmaceutical products (gelatin, collagen, etc.)"

4.1.4 Evaluation of maternal risk factors for BSE in cattle (Table 1, item 4.8).

- "Determine infectivity in placenta, blood, colostrum, milk and excrements of BSE cattle using sensitive assays"

Transmission studies on a wide range of tissues from confirmed cases of BSE have already been carried out in the UK using mice as the model for bioassay. These studies have had all negative results to date. The objective now is to repeat these studies using a more sensitive bioassay.

4.1.5 Did BSE originate in cattle and has it been transmitted to sheep in recent years? (Table 1, item 4.1)

To address this issue it would be necessary to develop the following initiatives:

- "To extend the surveillance of scrapie in UK sheep"
- "To examine the infectious agent derived from recent cases of sheep scrapie in regard to its strain properties"
- "To feed scrapie-infected brain from sheep to cattle and then monitor for appearance of BSE-like disease"

4.1.6 Can BSE be transmitted orally to pigs and chickens? (Table 1, item 4.1)

Intracerebral inoculation of pigs with the BSE agent leads to infection. Peroral transmissibility of BSE from BSE cattle brain to pigs is actually being tested in the UK. Inoculation of chickens with BSE intracerebrally has not so far resulted in signs of disease.

It would be of interest to determine whether pig-to-pig transmission occurs, in particular orally. Therefore, it is proposed to:

- "feed and inject brain extract of experimentally BSE infected pigs to pigs"

4.1.7 Diagnostic research (Table 1, item 3.2)

"There is still no rapid, specific and sensitive method to detect human and animal SEs. than by analysis of central nervous system (CNS) tissue, by infectivity assays". It is therefore proposed to:

- "develop a sensitive assay in transgenic mice carrying cattle transgenes or cattle/mouse chimeric PrP genes"
- "explore surrogate markers"
- "explore the presence of PrP^{sc} in tonsils and spleen of man"
- "sponsor a large-scale facility for assaying BSE infectivity in calves"

On this issue, infectivity assays in calves (currently the most sensitive assay for the BSE agent) are being performed on a large-scale basis by the Ministry of Agriculture, Fisheries and Food in the United Kingdom. Also bioassays in mice are sensitive but may not be able to detect low levels of the agent.

Development of diagnostics must be underpinned by basic research on the infectious agent.

4.1.8 Inactivation of the BSE agent under different conditions (Table 1, item 5.1).

- "Determine inactivation kinetics of BSE infectivity under conditions used currently in industry and explore additional procedures"
This will allow to determine the efficiency of BSE agent inactivation by procedures used in food and the pharmaceutical industry.

Industry studies have been carried out on inactivation (i.e. gelatin) but these should be further validated under the FAIR programme. Provisional results of a study on the inactivation of BSE and scrapie in rendering processes (supported by the CAMAR programme) have been received during 1996.

4.1.9 Therapeutic research (Table 1, item 5.2),

No therapy is at present available. Possible approaches for further research in this field could include:

- "specific inhibition of PrP synthesis"
- prevention of the conversion of PrP^c into the pathological form PrP^{sc}

Not addressed so far by any Community research programme. Should be based on fundamental research which will establish and identify the nature of the agent.

4.1.10 Can BSE-resistant cattle and sheep be generated and would these be of practical use? (Table 1, item 5.3)

It has been shown that inactivation of the prion protein (PrP) gene has no major detrimental effect on the mouse and it confers absolute protection against the disease. Further research should be pursued on the means to:

- "determine whether sheep devoid of the prion protein are viable and resistant to scrapie",
- develop methods for generating cattle devoid of PrP.

Transgenic cattle devoid of the prion protein may be of practical use in the pharmaceutical industry.

4.2 Questions related to basic research on prion diseases

The following issues deserving further investigation are as follows:

4.2.1 The nature of the infectious agent

The exact nature of the infectious agent is still not understood. Reinforcement of research in this area should be pursued with the aim of :

- * "Purification of the infected agent from BSE-infected cattle brain and analysis" (Table 1, item 2.1)
- * "Identification of the three-dimensional structure of both PrP^c and PrP^{sc}" (Table 1, item 2.4)

Several Community research programmes are at present addressing this issue.

4.2.2. Multiplication of the agent

In order to assess the issue of multiplication, the following approaches should be pursued:

- * "Determine whether PrP^c can be converted into the infectious agent in vitro" (Table 1, item 2.4)
- * "Determine which other components (receptors?, etc) are required for propagation of the infectious agent" (Table 1, item 2.2).

4.2.3. Pathogenesis (Table 1, item 2.2)

The pathogenesis of the disease is not yet understood. Further research should be pursued in order to acquire knowledge of the precise mechanism of pathogenesis, the cell types and tissues which can replicate the infectious agent, and the biochemical requirements for such a process.

On the issue of pathogenesis of SEs, one research project is actually being supported at Community level. The project intends to assess the role of the prion protein in the activation of glial cells as the first mechanism in the sequence of events leading to final neurodegeneration, and is being supported within the BIOMED 2 programme.

4.2.4. Transport of the infectious agent (Table 1, item 2.2)

Further research should be pursued on the issue of transport of the agent within the organism, in order to:

- ° "determine where and how the agent enters the organism after ingestion"
- ° "determine how the agent passes from the periphery to the central nervous system and vice-versa".

4.2.5. Research on different agent strains (Table 1, item 2.3)

Further research should be pursued in order to:

- ° "explain what is the molecular feature of the infectious agent that determines strain specificity"

The mechanisms of prion propagation and the characteristics of strain specificity are being partly assessed in an ongoing Community research project supported within the BIOMED 2 programme.

4.2.6. Susceptibility of the host to the infectious agent (Table 1, item 2.6)

Research in this area should be pursued in order to :

- ° "identify the genetic factors which contribute to susceptibility and determine incubation time"
- ° "determine which factors other than the sequence of PrP determines the species barrier"

The identification of genetic factors which could contribute to confer susceptibility to the disease are currently being partly assessed in an ongoing Community research project supported within the BIOMED 2 programme.

4.2.7. Natural function of PrP (Table 1, item 2.4)

At present its function is unknown. Research should be pursued in order to obtain further knowledge of the normal function of this protein and to characterize what happens in its absence.

5. Action plan for future activities

The action plan has been established taking into account the recommendations put forward in the Weissmann Report and the Multidisciplinary Scientific Committee as well as analysis of ongoing Community and national research activities. It will comprise two levels:

- the coordination of activities between Member States;
- a specific Call for Proposals, in order to create a critical mass by pooling the best research centres in Europe.

5.1. The coordination of activities between all Member States (see Table 2)

Harmonisation of data collection and diagnostic criteria for the detection and identification of the disease(s) within Member States is essential for a proper comparability.

Coordination of activities between Member States should therefore essentially ensure:

- a) standardization of case definitions for collection of data, of data analysis and of dissemination of information in order to ensure a proper surveillance,
- b) harmonised procedures for early detection and diagnosis of the disease(s),
- c) continuous updating and dissemination of scientific knowledge in this field,
- d) fluent and rapid dissemination of these data,
- e) activation of an early warning system in case of crucial developments,
- f) exchange and mobility activities including training of research staff,
- g) a continuous inventory of the progress of national research programmes,
- h) the establishment of harmonized procedures and quality control of diagnostic methods for human and animal SEs.

To this aim coordination of national specialized reference centres on SEs should be fostered, notably by the setting up of a research network of these centres aimed at:

- the establishment and use of harmonized criteria for collection and evaluation of data, case definition and classification of the disease(s)
- the development of an efficient and on line communication system (through informatisation),
- the exchange of staff.

The participants should be able to harmonise and share scientific and technical resources and services provided by each agreed centre. The network should have an user-oriented approach providing European researchers with regular distribution of and access to relevant information and training activities.

This coordination with Member States will need active input from the relevant Programme Committees.

5.2. Specific Call for Proposals

The following areas of research have been identified (see Table 1, point 7.1 of the Financial Statement):

5.2.1. Clinical, epidemiological and social research on human SEs (see Table 1, item 1)

The continued analysis of incidence, clinical features and risk factors for diseases of the CJD type in European countries is likely to be crucial in an assessment of any change of the incidence of the disease(s).

Reinforcement and further development of the epidemiological surveillance of CJD and related diseases should therefore be pursued with the aim of assessing:

- 1.1 a comparison of agent strains recovered from variant CJD patients with BSE and "normal" CJD, GSSS and FFI strains
- 1.2 the incidence (including reevaluation of previously diagnosed CJD cases), geographical distribution and role of specific risk factors (genotype, diet, exposure, environment);
- 1.3 the process of identification of suspected cases and the sensitivity of the surveillance system;

5.2.2. The infectious agent and its mechanisms of transmission (see Table 1, item 2)

The precise structure of the agent is unknown, as are the mechanisms of transmission.

Research reinforcing the characterization of the agent and the mechanisms involved in the pathological process should be pursued with the aim of assessing:

- 2.1 the characterization of the agent;
- 2.2 the mechanisms of propagation, transport and pathogenesis including elucidation of possible common links with other neurodegenerative diseases;
- 2.3 the characterization of the different strains, including comparison of scrapie strains with BSE;
- 2.4 the structure of both PrP^c and PrP^{sc}, the normal function of PrP^c and the mechanisms of conversion of PrP^c into PrP^{sc};
- 2.5 the basis of species barriers limiting inter- and intra-species transmission;
- 2.6 the susceptibility factors for the development of animal and human prion diseases.

5.2.3. Diagnosis of SEs (see Table 1, item 3)

Despite the urgent need, no early diagnostic tools are available at present. Reinforcement of research allowing for the production of diagnostic tools should therefore be pursued with the aim of allowing:

- 3.1 further development of cell cultures and banks for tissues and cells;
- 3.2 development of rapid and sensitive early diagnostic tests including surrogate markers, especially in living animals and humans;

- 3.3 development of sensitive assay in transgenic mice carrying cattle transgenes or cattle/mouse chimeric PrP genes

5.2.4. Risk assessment of SEs (see Table 1, item 4)

Epidemiological evidence has raised concerns that the so called variant CJD is linked to the consumption of products derived from BSE-infected cattle. Moreover, the BSE agent is orally transmissible to a number of species including: mice, mink, cats, cattle, sheep, goats and various other ruminants. In order to perform an estimation of the risk of transmission of the disease, the following areas should therefore be pursued:

- 4.1 an evaluation of SEs transmission modalities (including oral transmission) from cattle to man and other food animals, environmental vectors e.g. mites.
- 4.2 an extended surveillance programme of BSE and related diseases
- 4.3 the identification of covert disease in cattle
- 4.4 the determination of the infectivity titers in cattle tissues and cattle derived products entering the human food chain or used in pharmaceutical and cosmetic products
- 4.5 the potential exposure of the human population
- 4.6 determination of the level of meat contamination by brain/spinal cord after standard butchering procedures
- 4.7 determination of oral feeding and intracerebral dose response to BSE agent and whether multiple dosing is cumulative
- 4.8 investigation of possible biological mechanisms of maternal transmission of BSE

5.2.5. Treatment and prevention of SEs (see Table 1, item 5)

At present no therapies are available. Reinforcement of research in this field should be pursued with the aim of allowing:

- 5.1 Assessment and development of inactivation procedures currently used in industry (food, pharmaceutical, cosmetics)
- 5.2 the development of therapeutic approaches;
- 5.3 the development of methods for generating cattle and sheep devoid of PrP and practical use of these animals.

6. Priority setting and financial arrangements

The European Union has been involved in research on SEs since 1990. This initiative has resulted in the support of 11 research projects within several Community research programmes (CAMAR, BIOMED 1 and 2, BIOTECH 1 and AIR) with an overall budget contribution of 3.545 MECU (2.120 MECU during the 2nd and 3rd Framework Programmes and 1.425 MECU for the 4th Framework Programme).

Table 1 depicts the total estimated costs and additional resources needed to address the research priorities in the field of BSE and prion-associated diseases for the period 1997-1998.

The specific Call for Proposals outlined in item 5 identifies five priority areas in the field of SEs deserving further investment.

The breakdown provided for each area is based on the assumption that at least one research project and, in several cases, more than one, should be supported in order to fully implement the research priorities outlined.

The setting of a usual research Community project involves up to five research laboratories with an average contribution per laboratory, per year, of 100,000 ECU. This amount has demonstrated to cover the salary of one scientist (66,000 ECU/year), half the salary of a technician (20,000 ECU/year) and the necessary consumable and equipment material to perform the research tasks to be carried out by the laboratory.

For the implementation of a concerted action, where the main objective is the sharing of information and the gathering of different expertises and methodologies, the average contribution deemed necessary to implement the work is estimated to be 10,000 ECU per laboratory, per year. This will cover the costs for travel meetings, short-term exchange of staff and exchange of material for each laboratory.

For the implementation of a centralized facility, defined as a unique general service tool for other projects supported by the specific action plan in order to enable standardization, joint experiments, data collection and analysis with access to particular products, experimental materials, specialised services (e.g primate research expertise), the Community funding may cover 100% of the costs of the costs of services rendered by the Centralized Facility to the research center, universities, undertakings and enterprises participating in shared cost and concerted actions.

6.1 Total estimated costs and additional resources needed to address the specific Call for Proposals

Table 1 point 7.1 of the Financial Statement provides an overview of the total financial resources needed to implement each of the areas depicted in the specific call for proposals. These include:

6.1.1 Clinical and epidemiological research on human SEs

The BIOMED 2 programme, key specific programme in terms of research on human SEs, will be in charge of the implementation of this area.

At present the BIOMED 2 programme is practically completed with all Calls for Proposals having already been launched. Strategies for the redeployment of financial resources could therefore not be envisaged. However, it is expected that, as a result of the last Call for Proposals in BIOMED 2, one project could be supported.

Therefore, and in order to fully implement this research area, additional resources are necessary.

6.1.2 The infectious agent and its mechanisms of transmission

The implementation of this research area could be done within the three specific programmes (BIOMED 2, BIOTECH 2 and FAIR), depending on the specific issues to be tackled.

At present, ongoing research activities in this area within the BIOMED 2 programme partially address issues such as the pathogenic mechanisms of prion diseases, the structure of the normal and abnormal prion protein, the basis of species barriers and the susceptibility factors for the development of human prion diseases, with an overall Community contribution of 1.425 MECU. In addition, and as a result of the 2nd Call for Proposals of the BIOMED 2 programme (deadline 17 June 1996), a further budgetary commitment is expected.

Within the BIOTECH. 2 and FAIR programmes, a limited budget could be reshifted in order to address specific issues such as the mechanisms of propagation, transport and pathogenesis of the prion agent.

Additional resources are therefore needed in order to fully implement research in this field.

6.1.3 Diagnosis of SEs

This area of research will be implemented by the three programmes. At present, no ongoing Community research activities are implementing the outlined priorities.

Ongoing calls in the BIOMED 2 and FAIR programmes could be able to mobilise funds aiming at addressing the issue of the development of rapid and sensitive early diagnostic tests. Similarly, an estimated budget could be reshifted towards this area of research from the BIOTECH 2 and the FAIR programmes.

Therefore, and in order to allow a proper implementation, supplementary funds are necessary.

6.1.4 Risk assessment of SEs

The research areas included are covered by the BIOMED 2, BIOTECH and FAIR programmes.

At present, no ongoing research activity within the Community research programmes is addressing this issue.

The possibility of reshifting financial resources within the FAIR programme towards this domain could be envisaged. This initiative will allow to initiate the financial support of projects addressing areas such as the evaluation of BSE transmission modalities, the determination of the infectivity titers in cattle tissues or the evaluation of the risk of maternal transmission for BSE.

Therefore, and in order to fully implement the important aspect of the transmission modalities of BSE (including oral transmission) where studies on primates may be necessary (BIOMED 2), additional resources are necessary.

6.1.5 Treatment and prevention of SEs

The area covers research approaches aimed at developing inactivation procedures, therapeutic compounds and prevention strategies and could be developed within the three specific programmes (BIOMED 2, BIOTECH and FAIR), depending on the specific issue to be tackled.

At present, no ongoing Community research activities are dealing with these issues.

The possibilities of reshifting resources towards the FAIR programme are envisaged and will allow to initiate supporting research in this area.

Additional resources are needed to allow a full implementation of the tasks.

6.2 Total estimated costs and additional resources needed for the coordination of activities between Member States

The total estimated costs necessary for the full implementation of this activity, based on the assumption of the participation of one laboratory per Member State, are depicted in Table 2, point 7.1 of the Financial Statement.

TOTAL ESTIMATED COSTS AND ADDITIONAL RESOURCES NEEDED TO ADDRESS THE RESEARCH PRIORITIES IN THE FIELD OF BSE AND SUBACUTE SPONGIFORM ENCEPHALOPATHIES (1997-1998)

TABLE 1

Research area	Priority	Total Estimated cost in ** MECU's	Existing EU contribution *** MECU's	Prospects for EU funding MECU's	Possible EU funding with redeployment MECU's	Additional resources needed ** MECU's
1. Clinical, epidemiological and social research on human SE's						
1.1 compare agent strains recovered from vCJD patients with BSE and "normal" CJD, GSSS and FFI strains; □ *	A	1.5				1.5 Biomed
1.2 the incidence (including reevaluation of previously diagnosed CJD cases), geographical distribution and role of specific risk factors (genotype, diet exposure, environment); □ *	A	2.0		0.5 Biomed		1.5 Biomed
1.3 the process of identification of suspected cases and the sensitivity of the surveillance system	A	0.5				0.5 Biomed
1.4 the research on risk perception of the population in relation to prion diseases; □	A	0.5				0.5 Biomed
		Total: 4.5		Total: 0.5		Total: 4.0
2. The infectious agent and its mechanisms of transmission						
2.1 the characterization of the agent; □ *	A	2.5				2.5 Biotech/Fair
2.2 the mechanisms of propagation, transport and pathogenesis (special attention will be given to the possibility of oral transmission) including elucidation of possible common links with other neurodegenerative diseases; □ *	A	4.8	0.4 Biomed	0.4 Biomed	0.5 Biotech	3.5 Biotech Biomed/Fair
2.3 characterization of the different strains, compare scrapie strains with BSE; □ *	A	0.8			0.3 Fair	0.5 Biomed/Biotech
2.4 the structure of both PrP ^c and PrP ^{sc} , the normal function of PrP ^c and the mechanisms of conversion of PrP ^c into PrP ^{sc} in vitro; □ *	A	1.5	0.5 Biomed	0.5 Biomed		0.5 Biomed / Biotech
2.5 the basis of species barrier limiting inter- and intra-species transmission; □ *	A	1.4	0.5 Biomed	0.4 Biomed		0.5 Biomed/Biotech
2.6 the susceptibility factors for the development of animal and human prion diseases □ *	A	1.1	0.1 Biomed		0.5 Fair	0.5 Biomed
		Total: 12.1	Total: 1.5	Total: 1.3	Total: 1.3	Total: 8.0
3. Diagnosis OF SE's						
3.1 further development of cell cultures, and banks for tissues and cells; □ *	A	1.0			0.5 Biotech	0.5 Biotech
3.2 development of rapid and sensitive early diagnostic tests including surrogate markers, specially in living animals and humans; □ *	A	7.6		2.0 Fair 0.6 Biomed	1.5 Fair	3.5 Fair/Biom/Biotech
3.3 development of sensitive assay in transgenic mice □ *	A	1.3			0.5 Fair	0.8 Biotech/Fair
		Total: 9.9		Total: 2.6	Total: 2.5	Total: 4.8

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**TOTAL ESTIMATED COSTS AND ADDITIONAL RESOURCES NEEDED TO ADDRESS THE COORDINATION OF ACTIVITIES
BETWEEN MEMBER STATES IN
THE FIELD OF BSE AND SUBACUTE SPONGIFORM ENCEPHALOPATHIES (1997-1998)**

TABLE 2

Research area	Priority	Total Estimated cost in ** MECU's	Existing EU contribution MECU's	Prospects for EU funding MECU's	Possible EU funding with redeployment MECU's	Additional resources needed** MECU's
A. Standardization of case definitions for collection of data, of data analysis and of dissemination of information in order to ensure a proper surveillance	A	1.00				1.00
B. Harmonised procedures for early detection and diagnosis of the disease(s) <input type="checkbox"/>	A	0.50				0.50
C. Continuous updating and dissemination of scientific knowledge in this field <input type="checkbox"/>	A	0.35				0.35
D. Fluent and rapid dissemination of these data <input type="checkbox"/>	A	0.35				0.35
E. Activation of an early warning system in case of crucial developments <input type="checkbox"/>	A	0.35				0.35
F. Exchange and mobility activities including training of research staff <input type="checkbox"/>	A	0.60				0.60
G. A continuous inventory of the progress of national research programmes <input type="checkbox"/>	A	0.35				0.35
H. Harmonisation and control of diagnostic methods for human and animal SE's <input type="checkbox"/>	A	1.50				1.50
TOTAL		5.0				5.0

Background for the proposal of an European Initiative at the Research Council of October 7, 1996

** For area A and H the following assumption is made: +/- 75,000 ECU per laboratory in each Member State and associated countries for 2 years (including 1/2 scientist, consumables, travel and equipment) and additional 10,000 ECU to the laboratory responsible for the overall coordination.

For areas B, C, D, F, E the following assumption is made: +/- 20,000 ECU per laboratory in each Member State and associated countries for 2 years (including 1/4 scientist, technician, equipment, consumables and travel costs)

For area F, the following assumption is made: +/- 35,000 ECU per laboratory in each Member State and associated countries for 2 years.

**OVERVIEW ON NATIONAL RESEARCH ACTIVITIES
IN THE FIELD OF BSE/CJD**

ANNEX 1

MEMBER STATES

1. Austria

Research on spongiform encephalopathies (SEs) in Austria is centred at the Department of Neuropathology and Neurochemistry, Institute of Neurology of the University of Vienna.

The main areas of research in this centre includes the epidemiology (the department has performed an epidemiological study of the incidence of CJD in Austria) and neuropathology of human SEs (CJD and gerstmann-Straussler-Scheiker disease (GSS)).

In addition, the above mentioned department coordinates a Community research programme gathering 100 European neuropathological and basic research laboratories dealing with neuropathologic diagnosis of, and tissue based research in, human SEs. The network has defined criteria for neuropathological diagnosis of, and tissue handling in human SEs.

2. Belgium

This country is involved in research in the field of SEs in the following areas:

* Epidemiological surveillance of BSE/scrapie, funded by the Agricultural ministry.
No specific programme on SEs is set up at present.

3. Denmark

No specific programme on SEs exists at present. A new national register for CJD has been set up and a programme on mutation screening for PrP is going to be developed.

4. Finland

Research in this field is focused on the following areas:

* Neuropathology of human SEs
* Surveillance of human SEs (familial form of CJD)
* Molecular pathology of SEs

The work is being carried out at the University of Helsinki. At present, no special programmes on the subject have been set up.

5. France

A national reference centre for animal SEs was set up in 1990 (CNEVA, Lyon). A National Advisory Expert Committee for SEs has been established in 1996.

Sixteen laboratories are working in the field of prion diseases. The main areas of research include:

* Characterization of the french BSE strains (CNEVA, Lyon)
* Characterization of the PrP gene polymorphism linked to scrapie resistance (INRA, Toulouse)

- * Characterization of the number of infected cattle in a herd where a single case has been identified (CNEVA, Lyon)
- * Research for new diagnostic tools
- * Research for criteria of inactivation of MBM in various rendering systems (CNEVA, INRA, CEMAGREF, to be implemented)
- * Transmission studies (using transgenic animals) and studies on the structure of the agent and on the function of PrP. These include:
 - Study of the role of the immune system in the development of the prion agent at early stages of infection
 - Role of PrP in the development of the disease
 - In vitro studies, using a cellular model, of normal and pathological PrP
 - Conformational studies on PrP structure
 - Cellular localisation of normal and pathologic PrP and structure of amyloid plaques
 - Research on possibilities, using two experimental models, to block accumulation of PrP at different stages of the disease
 - Analysis of transmission mechanisms of the disease
- * Epidemiological research including research on risk factors for the development of SEs (genetic, diet, environmental):
 - surveillance of CJD and related diseases
 - research on genetic factors favouring the development of SEs and comparison with Alzheimer and related diseases
 - Genetic and clinic follow-up of a cohort of 1000 individuals receiving growth hormone apparently contaminated with the infectious agent (1984-1985) among which 35 cases of CJD have been diagnosed.

The above mentioned work is being carried out at the CNRS, Units 9026 (Bordeaux), 2420 and 2431 (Gif sur Yvette) and 9045 (Villejuif), INSERM, Units 415 (Lille), 153 and 360 (Paris), 180 and 431 (Montpellier), INRA (Jouy-en-Josas, Tours, Toulouse), CEA-DSV (Fontenay-aux-Roses).

6. Germany

TSE research in Germany is supported by the ministries of Research, Health and Agriculture. Major areas of research involve both animal and human SEs in the following areas:

- * Structure and function of PrP including the structure and structural transformation of the infectious prion protein and the structural mapping
- * Pathogenesis, function and therapy including investigations on pathogenic mechanisms of SEs in cell cultures of PrP^{Sc} mice, the use of PrP^{Sc} mice as an experimental system for the investigation of infectivity and cell biology of the prion proteins, the characterization of the prion protein domains responsible for the disease, the chemoprophylaxis and chemotherapy of prion infections
- * Diagnostics and transmission including the establishment of cell culture titration methods for the detection of the scrapie agent, the oral infection of hamster with the scrapie agent and the production of antibodies against prion proteins of humans and animals

This work is being carried out at the Deutsches Primatenzentrum and Institute of Neuropathology (Göttingen), DKFZ (Heidelberg), Robert Koch Institut (Berlin), Institute for

Molecular Biology (München), Federal Research Institut for Viral Diseases of Animals (Tubingen), Institut for Physiological Chemistry (Mainz), Institut for Physical Biology (Dusseldorf) and GBF, Structural Research (Braunschweig).

7. Greece

Research in the field of SEs is developed within the following areas:

- * Comparative study of carbohydrates in BSE and normal cow brains
- * Improvement of scrapie diagnosis and study of scrapie infectious agent
- * Characterization of the BSE infectious agent. On this subject the University of Thessaloniki (Department of Pharmacology) is coordinator of a Community research. In addition, this laboratory is participating to three other Community research projects.

Sponsoring bodies are the Greek National Research Foundation, the Greek Ministry of Development and the National Office of Programming in Cyprus.

At present, no special programmes on SEs have been set up.

8. Ireland

Research in this field is mainly developed at the Veterinary Research Laboratory Abbotstown (Dublin) and the Zoology Department University College of Dublin.

The main area of research include the development of rabbit polyclonal antisera to a number of synthetic PrP peptides which have been assessed immunohistochemically for their ability to differentiate BSE and scrapie affected tissues from negative tissues.

Recently, a Scientific Committee has been set up to establish priorities in this field.

9. Italy

Italy is performing research in this field within two main areas:

° Surveillance

- epidemiology of CJD and other prion related encephalopathies in humans and animals;
- identification of patients with mutations and/or polymorphisms in the PrPN gene
- collection of CJD patients information in selected institutions and studies of familial clusters with identification of genotypes and possible point mutations.

° Neuropathology and basic research

- identification of new phenotypes for these diseases;
- study of synthetic PrP peptides: biological effects, physico-chemical properties relevant to biology, interaction with plasma membranes;
- study of cells with mutated PrPN fragments;
- interaction drug-amyloid in vitro and in vivo.

The National Research Council (CNP) has recently launched a strategic research project on BSE covering the areas of:

- ° physiopathology of SEs
- ° research about transmission mechanisms between italian breeds.

The Ministry of Health, through the Institute of Zooprofilaxis and Veterinary Diseases, is sponsoring a programme on "Integrative measures for the permanent surveillance of BSE".

The Istituto Superiore di Sanità is supporting the National Registry for Surveillance of CJD (coordinator: Prof. M. Pocchiari).

The two main institutions in Italy developing research in this field are the Istituto Superiore di Sanità (Rome) and the Istituto Neurologico Carlo Besta (Milan).

10. Netherlands

The main areas of research in the field of SEs include:

- Development of tools for diagnostic methods on scrapie and BSE
- Antigenic studies of bovine prion protein
- Immunohistochemical detection of PrP in brain for scrapie diagnosis
- Immunohistochemical detection of prion protein on lymphoid tissues of diseased and infected sheep
- Genetic resistance to scrapie

The above mentioned work is being carried out at the Institute for Animal Science and Health (ID-DLO) Lelystad. In addition, this Institute is coordinator of a Community research programme aimed at assessing the role of PrP^{Sc} in glial activation.

This country has also been deeply involved, through the work carried out at the Department of Epidemiology and Biostatistics (Erasmus University Medical School), in the epidemiological surveillance of CJD, as part of the Community research project on surveillance for this disease.

The Dutch Health Council is at present preparing a strategy for research on SEs which will be available soon.

11. Portugal

A national programme on surveillance of scrapie has been recently set up. They are also setting up the basis to develop a national registry for CJD.

12. Spain

No specific programme on SEs research exists at present. This country has been taking part, as an observer, to the European surveillance network on CJD and is setting up a national register for the disease.

13. Sweden

No specific programme set up for SEs. No BSE, few cases of scrapie

14. United Kingdom

Priorities for government research on animal SEs are currently based on specific needs as they are identified and advice from the Spongiform Encephalopathy Advisory Committee (SEAC).

The Ministry for Agriculture, Fisheries and Food (MAFF) programme is complemented by the research programmes of the Biotechnological and Biological Science Research Council (BBSRC); the Medical Research Council (MRC); the Department of Health (DH) and the Wellcome Trust.

Coordination between these group is achieved by liaison at several levels most recently through the Transmissible Spongiform Encephalopathy Research and Development Funders Coordination Group, chaired by the Department of Health.

Five main areas are addressed (as defined in the SEAC report, 1995) covering both human and animal prion diseases:

a) Nature of the agent

Research on this issue is being sponsored by the MAFF, the BSEP, the Biotechnological and Biological Science Research Council (BBSRC), the MRC, the BBSRC/MRC Core and the Wellcome Trust. Institutions involved include the Universities of Edinburgh, Reading, the Imperial College of Science, Technology and Medicine of London, the Animal Health Trust and the Institute for Animal Health.

b) Pathological changes

Research in this field is being carried out by the Universities of Edinburgh, Birmingham, Nottingham, the Imperial College of London, the Institute of Zoology and the Central Veterinary Laboratory (CVL). Sponsoring bodies include the MAFF, BBSRC/MRC, the MRC, the BSEP and the Wellcome Trust.

c) Transmission studies including transgenic animals

Substantial research in this field is being performed at the Neuropathogenesis Unit of the Institute for Animal Health (NPU, Edinburgh), University of Cambridge and Imperial College of London, the CVL, the Scottish Agricultural College and the Agricultural Development Advisory Board. Sponsoring bodies include the MAFF, BSEP, the BBSRC/MRC Core and Wellcome Trust.

d) Control of BSE epidemic

Research on this issue is being sponsored mainly by the MAFF, at the NPU, the CVL, the Agricultural Development Advisory Board and the University of Edinburgh.

e) Applied questions including CJD surveillance

CJD has been monitored nationally since 1990. This issue is being carried out at the National CJD Surveillance Unit (Edinburgh), the NPU, the CVL and the Imperial College of London, St. Mary's Hospital, and is mainly supported by the MAFF, DH, Scottish Home and Health Department (SHHD), EC and MRC.

A specific Coordination Programme on Health Aspects of Transmissible Spongiform Encephalopathies (SEs) has been recently set up in this country, with major fundings from the Agricultural Ministry, the Medical Research Council and the Wellcome Trust.

The MRC, jointly with the Department of Health, has proposed a 10 year initiative to be developed in two 5-year phases. This initiative intends to strengthen research capacity (skills and infrastructure), increase collaboration between existing centres of expertise and to improve understanding by public and health professionals of prion diseases and associated risks.

A call for proposals has recently been launched in identified areas. The programme has a strong human health orientation with broad biological approach.

The main priority scientific themes are:

- * Molecular, cellular, genetic and functional approaches to elucidating mechanisms of TSEs transmission, PrP replication, pathogenesis and clinical progression
- * Integrated molecular, epidemiological and clinical approaches to understanding the cause(s) of sporadic CJD
- * Biological and epidemiological relationship between BSE and CJD and atypical dementias
- * Early disease progression and diagnosis in life
- * Analysis, perception and communication of risk in relation to CJD
- * The biological function of normal PrP
- * The molecular structure of prion proteins
- * Rational approaches to developing therapy

ASSOCIATED COUNTRIES AND THIRD COUNTRIES

1. Norway

A research programme in the field of animal and human SEs has been recently proposed. The programme includes:

- ° Norwegian College of Veterinary Medicine
 - Prevalence studies of scrapie changes in scrapie affected herds
 - Genetic disposition of scrapie in Norwegian herds
 - Comparative studies of absorption and persistence of scrapie-agent in intestine and lymphatic tissues in sheep and CDJ in humans
 - Comparative studies of post mortem changes in scrapie affected sheep and CJD in humans
 - Survey on genetic disposition in sheep herds for factors involved in the normal function of prion proteins and the development of disease.
- ° Central Veterinary Laboratories
 - Development of sensitive methods for detection of prion proteins in vivo
 - Epidemiological studies of risk factors in outbreaks of scrapie in sheep herds
- ° National Institute of Public Health
 - Epidemiological studies of risk factors involved in development of CJD in humans
 - Improved surveillance of CJD and other human spongiform encephalopathies in Norway by establishing criteria for diagnosis
 - Development of models of cooperation between human and veterinary medicine in the field of prion diseases

The three above mentioned institutions will be in charge of implementing the proposed plan.

2. Iceland

In Iceland there is a specific knowledge on the pathology and epidemiology of scrapie, as scrapie has been endemic in some parts of this country. The work carried out at the Institute of Experimental Pathology at Keldur has been the basis for the eradication programme of scrapie in Iceland.

In addition, two new areas of research are being implemented:

- Research on the effect of prion gene genotypes on scrapie susceptibility in Icelandic sheep
- Study of mutations and DNA polymorphism in three CJD patients in Iceland.

3. Switzerland

- Two reference centres for human and animal SEs
- In situ hybridization and immunochemistry for PrP in BSE (Institute of Animal neuropathology, Bern)
- Case control study / BSE risk assessment in Switzerland (Institut for virology and immunoprophylaxis, Mittelhäuser).

FINANCIAL STATEMENT

1 TITLE OF OPERATION

Communication from the Commission to the Council relating to research on bovine spongiform encephalopathy (BSE) and subacute spongiform encephalopathies.

2 BUDGET HEADING INVOLVED

Fourth FP: - Biotechnology - B6 7141
- Biomedicine - B6 7142
- Agriculture and fisheries - B6 7143

3 LEGAL BASIS

Council Decision No 94/912/EC of 15 December 1994 adopting a specific programme in the field of biotechnology. Council Decision No 94/913/EC of 15 December 1994 adopting a specific programme in the field of biomedicine and health. Council Decision No 94/805/EC of 23 November 1994 adopting a specific programme in the field of agriculture and fisheries.

Decision No 616/96/EC of the Council and the European Parliament of 25 March 1996.

4 DESCRIPTION OF OPERATION

Despite current efforts in fundamental and clinical research on bovine spongiform encephalopathy (BSE) and subacute spongiform encephalopathies, it has to date not been possible to identify the nature of the infective agents of these diseases and numerous epidemiological factors of human spongiform encephalopathies.

However, these factors must be identified for the fight against these diseases to be effective. Consequently, it is essential to mobilize the scientific community and stimulate research efforts at Community level. These efforts will require the mobilization of new research teams so as to attain a critical mass.

In view of the above, the fundamental objective of this communication is to strengthen the activities of research on bovine spongiform encephalopathy (BSE) and subacute spongiform encephalopathies.

This objective involves a two-pronged approach:

- coordination of national activities;

- the work to be undertaken on the basis of a call for additional proposals specifically in the fields of clinical and epidemiological research, infective agents and their modes of transmission, diagnosis, risk assessment, treatment and prevention.

5 CLASSIFICATION OF EXPENDITURE

Non-compulsory expenditure/Differentiated appropriations

6 TYPE OF EXPENDITURE

- Shared-cost actions consisting of RTD projects and demonstration projects benefit from a contribution not exceeding 50%.
- Universities and other research centres taking part in RTD projects and demonstration projects that cannot, in the Commission's opinion, show sufficiently accurate proof of their total costs, determined on the basis of an analytical accounts system, will be financed at the rate of 100% of additional costs.
- For concerted action, the contribution may go up to 100% of additional costs.

7 FINANCIAL IMPACT

7.1 Appropriations required (in MECU)

The appropriations necessary to attain the objectives set out at point 4 above form part of the increase provided for in the Proposal for a decision of the European Parliament and the Council on the second adaptation of Decision 1110/94/EC, as adapted by Decision 616/96/EC, relating to the fourth framework programme for research, technological development and demonstration projects (1994-98), which is subject to the approval, in the co-decision procedure, of Parliament and the Council and to the prior grant of funds by the budget authority.

From a financial point of view, this financial statement concerns only the breakdown of the following sums into commitment and payment appropriations between 1997 and 1999+:

	Coordination of activities	Priority research	Total
Biotechnology		7.5	7.5
Biomedicine and health	3.5	12.5	16
Agriculture and fisheries	1.5	10	11.5

This overall estimate may be detailed, purely indicatively, in accordance with the data shown in Tables 1 and 2 below.

TOTAL ESTIMATED COSTS AND ADDITIONAL RESOURCES NEEDED TO ADDRESS THE RESEARCH PRIORITIES IN THE FIELD OF BSE AND SUBACUTE SPONGIFORM ENCEPHALOPATHIES (1997-1998)

TABLE 1

Research area	Priority	Total Estimated cost in ** MECU's	Existing EU contribution *** MECU's	Prospects for EU funding MECU's	Possible EU funding with redeployment MECU's	Additional resources needed ** MECU's
1. Clinical, epidemiological and social research on human SE's						
1.1 compare agent strains recovered from vCJD patients with BSE and "normal" CJD, GSSS and FFI strains; □ *	A	1.5				1.5 Biomed
1.2 the incidence (including reevaluation of previously diagnosed CJD cases), geographical distribution and role of specific risk factors (genotype, diet exposure, environment); □ *	A	2.0		0.5 Biomed		1.5 Biomed
1.3 the process of identification of suspected cases and the sensitivity of the surveillance system	A	0.5				0.5 Biomed
1.4 the research on risk perception of the population in relation to prion diseases; □	A	0.5				0.5 Biomed
		Total: 4.5		Total: 0.5		Total: 4.0
2. The infectious agent and its mechanisms of transmission						
2.1 the characterization of the agent; □ *	A	2.5				2.5 Biotech/Fair
2.2 the mechanisms of propagation, transport and pathogenesis (special attention will be given to the possibility of oral transmission) including elucidation of possible common links with other neurodegenerative diseases; □ *	A	4.8	0.4 Biomed	0.4 Biomed	0.5 Biotech	3.5 Biotech Biomed/Fair
2.3 characterization of the different strains, compare scrapie strains with BSE; □ *	A	0.8			0.3 Fair	0.5 Biomed/Biotech
2.4 the structure of both PrP ^c and PrP ^{sc} , the normal function of PrP ^c and the mechanisms of conversion of PrP ^c into PrP ^{sc} in vitro; □ *	A	1.5	0.5 Biomed	0.5 Biomed		0.5 Biomed / Biotech
2.5 the basis of species barrier limiting inter- and intra-species transmission; □ *	A	1.4	0.5 Biomed	0.4 Biomed		0.5 Biomed/Biotech
2.6 the susceptibility factors for the development of animal and human prion diseases □ *	A	1.1	0.1 Biomed		0.5 Fair	0.5 Biomed
		Total: 12.1	Total: 1.5	Total: 1.3	Total: 1.3	Total: 8.0
3. Diagnosis OF SE's						
3.1 further development of cell cultures, and banks for tissues and cells; □ *	A	1.0			0.5 Biotech	0.5 Biotech
3.2 development of rapid and sensitive early diagnostic tests including surrogate markers, specially in living animals and humans; □ *	A	7.6		2.0 Fair 0.6 Biomed	1.5 Fair	3.5 Fair/Biom/Biotech
3.3 development of sensitive assay in transgenic mice □ *	A	1.3			0.5 Fair	0.8 Biotech/Fair
		Total: 9.9		Total: 2.6	Total: 2.5	Total: 4.8

4.	<i>Risk assessment of SE's</i>						
4.1	an evaluation of SE's transmission modalities (including oral transmission) from cattle to man and other food animals, environmental vectors□ *	A	4.5			4.5 Biomed/Fair	
4.2	extended surveillance programme on BSE and related diseases□ *	A	2.0			2.0 Fair ****	
4.3	identification of covert disease in cattle *	A	2.0		2.0 Fair		
4.4	determination of the infectivity titres in cattle tissues and cattle derived products entering the human food chain or used in pharmaceutical and cosmetics products□ *	A	3.5		1.5 Fair	2.0 Fair/Biotech	
4.5	the potential exposure of the human population □ *	A	0.5			0.5 Biomed	
4.6	determination of the level of meat contamination by brain/spinal cord after standard butchering procedures *	A	0.5		0.5 Fair		
4.7	determination of oral feeding and intracerebral dose responses to BSE agent and whether multiple doses is cumulative *	A	1.0		0.5 Fair	0.5 Fair	
4.8	investigation of possible biological mechanisms of maternal transmission of BSE *	A	1.0		0.5 Fair	0.5 Fair	
			Total: 15		Total: 5.0	Total: 10	
5.	<i>Treatment and prevention of SE's</i>						
5.1	Assessment and development of inactivation procedures currently used in industry; * (food, pharmaceuticals, cosmetics)	A	1.7		1.0 Fair	0.7 Fair/Biotech	
5.2	development of therapeutic approaches□ *	A	2.0			2.0 Biomed/Biotech	
5.3	generation of cattle and sheep devoid of PrP□ *	C	0.5			0.5 Fair	
			Total: 4.2		Total: 1.0	Total: 3.2	
TOTAL			45.7	1.5	4.4	£.8	30.0

Priorities are: A>B>C

- * Weissmann report
- Background for the proposal of an European Initiative at the Research Council of October 7, 1996
- ** The following assumption is made: 100.000 ECU's per laboratory per year (including 1 scientist for 12 months = 66.000 ECU, 1/2 technician for 12 months = 20.000 ECU, consumables and equipment)
- *** EU-contribution under IV FP
- **** in collaboration with national authorities

**TOTAL ESTIMATED COSTS AND ADDITIONAL RESOURCES NEEDED TO ADDRESS THE COORDINATION OF ACTIVITIES
BETWEEN MEMBER STATES IN
THE FIELD OF BSE AND SUBACUTE SPONGIFORM ENCEPHALOPATHIES (1997-1998)**

TABLE 2

Research area	Priority	Total Estimated cost in ** MECU's	Existing EU contribution MECU's	Prospects for EU funding MECU's	Possible EU funding with redeployment MECU's	Additional resources needed** MECU's
A. Standardization of case definitions for collection of data, of data analysis and of dissemination of information in order to ensure a proper surveillance	A	1.00				1.00
B. Harmonised procedures for early detection and diagnosis of the disease(s) □	A	0.50				0.50
C. Continuous updating and dissemination of scientific knowledge in this field □	A	0.35				0.35
D. Fluent and rapid dissemination of these data □	A	0.35				0.35
E. Activation of an early warning system in case of crucial developments □	A	0.35				0.35
F. Exchange and mobility activities including training of research staff □	A	0.60				0.60
G. A continuous inventory of the progress of national research programmes □	A	0.35				0.35
H. Harmonisation and control of diagnostic methods for human and animal SE's □	A	1.50				1.50
TOTAL		5.0				5.0

□ Background for the proposal of an European Initiative at the Research Council of October 7, 1996

** For area A and H the following assumption is made: +/- 75,000 ECU per laboratory in each Member State and associated countries for 2 years (including 1/2 scientific consumables, travel and equipment) and additional 10,000 ECU to the laboratory responsible for the overall coordination.

For areas B, C, D, F, E the following assumption is made: +/- 20,000 ECU per laboratory in each Member State and associated countries for 2 years (including 1/4 scientific technician, equipment, consumables and travel costs)

For area F, the following assumption is made: +/- 35,000 ECU per laboratory in each Member State and associated countries for 2 years.

7.2 Indicative schedule of appropriations¹

For the specific "Biotechnology" programme - Budget heading: B6 - 7141

(In MECU)	1995	1996	1997	1998	1999+	TOTAL
Commitment appropriations ¹	70.037	230.000	132.000	155.963	PM	588.000
Additional commitment appropriations			2.250	5.250		7.500
Payment appropriations ¹	19.789	115.666	124.200	163.000	165.345	588.000
Additional payment appropriations				4.500	3.000	7.500

For the specific "Biomedicine" programme - Budget heading: B6 - 7142

(In MECU)	1995	1996	1997	1998	1999+	TOTAL
Commitment appropriations ¹	37.833	126.000	90.000	104.167	PM	358.000
Additional commitment appropriations			4.800	11.200		16.000
Payment appropriations ¹	10.831	49.000	85.800	95.000	117.369	358.000
Additional payment appropriations				9.600	6.400	16.000

For the specific "Agriculture and fisheries" programme - Budget heading: B6 - 7143

(In MECU)	1995	1996	1997	1998	1999+	TOTAL
Commitment appropriations ¹	120.737	181.000	162.000	182.763	PM	646.500
Additional commitment appropriations			3.450	8.050		11.500
Payment appropriations ¹	19.768	70.000	114.700	230.000	212.032	646.500

¹ Appropriations of the 4th FP, as included in PDB 1997.

Additional payment appropriations				6.900	4.600	11.500
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The final annual sums will be determined by the Budget Authority.

7.3 Administrative and personnel expenditure

With regard to administrative expenditure, the programmes must ensure that the total sum of the financial supplement allocated is by priority used to finance research projects (as provided for in the proposal referred to in point 4 above).

8 ANTI-FRAUD MEASURES

There is a whole range of administrative and financial checks at all stages of the procedure for awarding and executing research contracts, including the following:

Prior to conclusion of the contract

- Initial selection of proposals on the basis of the scientific value of the project and of an assessment as to whether the research costs quoted are realistic in relation to the nature of the research, its duration and its potential impact.
- Analysis of the financial data transmitted by the proposers on their application form.

After the contract has been signed

- Scrutiny of statements of expenditure prior to payment, carried out at several levels (financial manager, scientific officer).
- Internal audit by the financial controller.
- On-the-spot checks enabling the detection of errors or other irregularities through an examination of the supporting documents. In order to make these checks more effective, the Commission's departments have set up an audit unit which brings together the results of all the checks performed. These checks are either carried out by members of the audit unit or entrusted to auditing companies with which the Commission has concluded framework contracts, under the supervision of officials from the audit unit.
- On-the-spot inspection by the financial controller and by the Court of Auditors of the European Union.

9 ELEMENTS OF COST-EFFECTIVENESS ANALYSIS

9.1 Specific and quantifiable objectives

The general objective as set out in point 4 encompasses six specific objectives, which may be classified as follows:

- (a) Priorities of research into bovine spongiform encephalopathy (BSE) and subacute spongiform encephalopathies;
 - clinical and epidemiological research on human spongiform encephalopathies;
 - infective agents and their modes of transmission;
 - diagnosis of human spongiform encephalopathies;
 - risk assessment of human spongiform encephalopathies;
 - treatment and prevention of human spongiform encephalopathies.
- (b) Coordination between the Member States of research on bovine spongiform encephalopathy (BSE) and subacute spongiform encephalopathies.

The resources necessary for the attainment of these objectives have been calculated on the basis of the following criteria:

- Each proposal will on average comprise five laboratories.
- The European Community's contribution to each laboratory should range between ECU 10 000 and ECU 100 000 per annum.

These objectives will be attained through shared-cost and concerted actions. These will be enhanced by general facilities made available to researchers and through targeted training for them (workshops, interdisciplinary conferences, studies, etc.).

9.2 Target population

Immediate beneficiaries: Researchers in industry and in the academic world and also hospital clinicians and engineers.

Ultimate beneficiaries: The citizens of Europe who have access to research results, consumers, food sectors, farmers.

9.3 Grounds for the operation

The spongiform encephalopathies (SE) are a group of human lethal neurodegenerative transmissible diseases (Kuru, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSSD)) and animal lethal neurodegenerative transmissible diseases (scrapie, bovine spongiform encephalopathy (BSE)).

An increasing amount of research is being carried out on these diseases, on the one hand because of their particular biology and on the other hand because of concern about the possible transmission of the infective agents to man. It is therefore essential that this group of diseases be given scientific priority. This calls for an impetus being given to research efforts at Community level and the establishment of new scientific equilibria with a view to attaining a critical mass.

9.4 Monitoring and evaluation of the operation

The operation will be monitored by the departments of the DGs responsible for its execution, with the support of the Programme Committees.

In order to contribute to the overall evaluation of the Community activities provided for in Article 4(2) of the Decision establishing the fourth framework programme of the European Community for research, technological development and demonstration projects, the Commission will in due course instruct independent experts to evaluate the activities pursued in the field directly covered by these programmes and their management in the five years prior to such evaluation. This operation will also be evaluated as part of the overall evaluation of Community activities within the fourth framework programme. The Commission will in due course instruct independent experts to carry out an evaluation of the activities and their management during the five years prior to such evaluation.

An interim report and a final report will be drawn up on the contracts that will be signed within the framework of the operation described in points 4 and 9.1 above.

In drafting the fifth framework programme, account will be taken of the following reports:

- Annual report of the Commission on the research and technological development activities of the European Union based on Article 130P of the EC Treaty.

- An annual report on the continuous monitoring of each specific programme and of the framework programme. This report will be compiled by independent experts.
- A five-yearly evaluation report of each specific programme and of the framework programme. This report will likewise be compiled by independent experts and will be published in 1996.