Scientific Steering Committee (SSC)

Minutes of the meeting of 14-15 May 1998

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1. Welcome, apologies, introductory remarks

Prof.G.Pascal, chairman, welcomed the participants and provided apologises of Prof. G.Bories (replaced by Prof. Anadon), V.Silano, P.James, H.Klein (only available on Friday), K.Jones, I.Knudsen (replaced by Prof.A.Knaap). The list of participants is given as annex 1.

In his introductory remarks Prof.Pascal first wished a rapid recovery to Prof.Jones, who could not attend because of illness. He further stated that the problems with the reimbursement of the participant's expenses apparently have been solved and expressed his hope that this uncomfortable situation would not be repeated.

2. Approval of the agenda

The agenda was modified in terms of sequence in order to take account of the availability of Prof.Klein, rapporteur for the EMF-report and Prof.Vanopdenbosch, rapporteur for the reports on Organophosphates and BSE in sheep.

With these changes the agenda was adopted (annex 2).

It was agreed that a draft agenda for the next meeting should be established before the end of the month in order to decide if a two or one day meeting would be required.

3. Approval of the minutes of the meeting of 14-15 April 1998

The minutes where adopted without any changes.

4. Work plan for the SSC

4.1. Progress on multidisciplinary matters, not primarily related to TSE/BSE:

- *resistance to antimicrobials*

  The mandate of the SSC's working group on the subject was discussed and adopted as given in annex 3.

  It was further decided that each SC could nominate one expert to participate in that group and that SCs with more experts interested in the subject, could discuss the issue in own working groups in order to provide their representative with useful input.

  The SC-6 (Cosmetics and non-Food Consumer Products) nominated Prof. Vives Rego. The other Committees shall inform the secretariat as soon as possible.

- *exposure limits to electromagnetic fields*

  Prof.Klein presented the draft report and opinion. It was extensively discussed and shall be revised in the light of the comments received. It is envisaged to adopt the opinion at the next meeting.

- *other ongoing activities*:

No further points were discussed under this item.

4.2. Multidisciplinary matters relating to TSE/BSE

a. Production systems and products

- *Safety of Bi-calcium phosphate*

  The draft opinion was presented by Prof.Vanbelle and extensively discussed. With some amendments and including the process scheme prepared by the rapporteur, it shall be published at the INTERNET as pre-Opinion and remain open for comments by interested parties until 12 June 1998.

  A cover note should be added, underlining that the safety of any bovine-based product is critically dependent on the quality of the implementation and control of the appropriate measures and that it is not the responsibility of the SSC to define these.

- *BSE in Sheep*

  Prof.Vanopdenbosch, chairman of the working group on this issue, was welcomed by the chairman of the SSC and thanked for his co-operation. He presented a draft report of the first meeting of the working group. The SSC appreciated the good progress made so far. In the discussion certain members of the SSC underlined the importance of the subject which is particularly aggravated by the fact that one has to assume that the distribution of the BSE-agent in sheep organs and tissues would be similar to Scrapie, which has been found in peripheral nerves and spleen. The likelihood that BSE is naturally occurring in sheep is therefore a critical parameter of the assessment.

  Ongoing work in projects funded by MAFF and under the FAIR-programme of the EU should be taken account of.

- *Possible links between pesticide Organo-Phosphates (OP) and BSE*

  The report, presented by E.Vanopdenbosch, also chairing this WG, was welcomed by the SSC as a good starting point. The rapporteur was asked to draft an opinion on this basis, taking due account of the comments made during the discussion. The draft opinion should be presented and adopted by the TSE/BSE ad-hoc group at its next meeting in order to be adopted by the SSC in June.

  As a preliminary statement to be included into the minutes, the SSC agreed that the scientific knowledge of the impact of Organo-Phosphates on humans and animals does not support the hypothesis that OPs could create BSE.

b. Human exposure risk

- *Group composition and work plan*

  The working group "human exposure risk" (WG-HER) consists currently of Prof.Verger (member of the TSE/BSE ad-hoc group and chairman of the WG-HER), Prof. Gibney and James (both members of SSC and TSE/BSE ad-hoc group), M.Löwik (TNO) and P.Comer (DNV, both external experts).

  The first meeting was held on 29/4/98 and a precise mandate defined (see annex 4). The group also decided on their task allocation and agreed that in a first step the consumption of bovine derived food and food-products should be assessed.

- *Specified Risk Materials (state of affairs)*

  No new developments.

- *Blood, blood products, implantables, sutures (state of affairs)*

  The SC-Medical Products and Medical Devices has started its work on the subject. A first discussion was held and no further progress made so far.

c. Geographical risk

- *Sourcing & Modelling (report from the working group)*

  The WG-"Sourcing" and "Modelling" held a joint meeting with the TSE/BSE ad-hoc group on 7/5/98. The Modelling group presented its work and received helpful comments from the TSE/BSE ad-hoc group. The progress made so far was appreciated and the modellers where asked to continue along their lines. It was recommended to contact experts, who have carried out extensive statistical analysis of UK data for a similar purpose. It was felt that their experience could proof very complementary.

  The Sourcing group was asked to intensify its work on a procedure to exploit information on the epidemiological situation of a country or geographical region, starting from the assumption that this information would be provided in accordance with the requirements for a complete dossier on the subject as established by the SSC in its opinion of 20/2/98.

d. Monitoring

- *TSE in bovines: diagnosis test (progress report)*

  The commission informed the SSC that a call for expressions of interest was in the process of being published, inviting all natural and legal personalities who have a suitable test for the diagnosis of TSE in bovines, to expose this to an evaluation organised by the Commission.

  It was agreed that all SSC members would provide the secretariat with names for top level experts on BSE, BSE-diagnosis, validation of diagnostic tests, etc. before the 25/5/98.

  The Commission had decided to establish an expert committee consisting of top level experts on BSE, BSE diagnosis, validation of diagnostic tests, etc. This group will be actively involved in the evaluation procedure. This process will be followed by the TSE/BSE *ad hoc* Group of the SSC. To facilitate this, Professor Osterhaus, a member of the TSE/BSE *ad hoc* Group and of the

SSC, will function as a focal point. In this capacity he will closely monitor the work of the expert committee and present the results and documentation of the expert committee's achievements to the TSE/BSE *ad hoc* Group.

- *Validation by JRC of tests for mammalian protein in feed and correct heat treatment of MBM*

  An interim report of the JRC was distributed for information. The SSC Secretariat informed the Committee of the intention of the JRC to present the current state of the work at the next TSE/BSE ad-hoc group meeting of 19 June 1998. In-depth discussions could then take place and will be reported to the SSC at its next meeting.

6. Organisational matters:

6.1. Additional members for the TSE/BSE ad hoc group.

The list of the present membership of the TSE/BSE ad-hoc group, including the additional members identified as a follow up of the SSC meeting of 16 and 17 April 1998, is given in annex 5.

6.2 Declaration of independence and confidentiality (SSC secretariat)

The appropriate forms were distributed and members requested to complete them and to send them to the secretariat.

6.3. Exchange of CVs

Members were asked to provide short CVs to the secretariat for their mutual information.

6.4. Planning of the SSC meetings until December 1999

A schedule for SSC-plenary meetings was presented and adopted, covering the period June 1998 to December 1999 (incl.). The dates are given as annex 6.

6.5. Progress on payments

The secretariat informed the SSC of the successful treatment of all payments, which has allowed reaching a situation where no undue delays are to be expected. The secretariat appreciated the strong efforts of Mr.G.Morrison, DG XXIV-B1, which where particularly instrumental for this success.

7. Co-ordination

7.1. Report of the Chairmen of the 8 Scientific Committees on issues treated or on the forthcoming agenda, including information on pesticides in baby food.

- *The Scientific Committee on Food*

  The commission informed the SSC on the issue of pesticides in baby food and explained that the current opinion of the SCF raised additional questions that will be posed to the SCF and the Scientific Committee for Plants, respectively. As far as appropriate the two committees should co-operate on the issue. The chairpersons of both committees accepted the task and underlined the good experienced made with their co-operation. The SSC asked the Commission to ensure that the questions are of a scientific nature, linked to risk assessment, and not purely risk management issues.

  Prof.A.Knaap, vice-chairperson of the Committee, informed the SSC on the numerous working groups of the SCF and on some of the issues these are

addressing. Examples given included: the WG Contaminants (presently addressing, amongst others, the issue of ochratoxin), WG Additives (addressing, for example, questions related to energy drinks), WG Materials in contact with food, WG Nutrition (addressing, inter alia, the issue of additional vitamins and minerals in food), WG Intake.

- *The Scientific Committee Animal Nutrition*

  No reporting on the activities of the SCAN was done.

- *The Scientific Committee Animal Health and Animal Welfare*

  Prof.Garrido, chairman, reported on the activities of his Committee. Both Subcommittees on Animal Health and on Animal Welfare had been quite active. Reports and opinions were being prepared on, amongst others: stunning methods for poultry, ventilation standards for transport of animals, forced feeding of ducks and gees, emergency vaccination for Foot and Mouth Disease, possible links between Crohn's Disease and Johne's Disease, diagnosis methods for Tuberculosis and Brucellosis.

  Prof.Garrido also confirmed that the Committee would nominate representatives in the SSC working groups on harmonised methods for risk assessment and on antimicrobial resistance.

  A schedule of meetings is attached as annex 7.

- *The Scientific Committee Veterinary Measures related to Public Health*

  Prof.A.Osterhaus, chairman of the committee, provided a summary report on the activities of the Committee. During its plenary session of 27 April 1998, the Committee adopted an opinion on "Allergic reactions to ingested *Anisakis Simplex* antigens and evaluation of the possible risk to human health".

- *The Scientific Committee on Plants*

  Prof.Silva Fernandes, chairman, reported that no plenary session had been held since last SSC meeting. Several more requests for an opinion on GMOs had been received, and reports and opinions are in the pipeline. Further, more detailed reporting on this matter will be done during the next SSC meeting of 25-26 June 1998.

- *The Scientific Committee on Cosmetics and non-Food Products*

  Prof.F.Kemper, chairman, reported. No plenary meeting was held since last SSC meeting of 16-17 April. The next plenary was planned for 20 May 1998. The following specialised working groups held several meetings: *Alternatives & Dossier* (including activities on the Notes of Guidance, phototoxicity, percutaneous absorption, human testing, microbial quality management, skin irritation), *Preservatives Colorants & Fragrances* (including activities on musks, nitro & polycyclic, Alpha Hydroxy Acids, Benzylheminformal 3-Iodo-2-propynyl butyl carbamate, Benzlkonium Chloride, Bromide and Saccharinate, Acrylamide, Allergic reaction to fragrances, Boric Acid, borates and tetraborates, hypo-allergic skin), *UV-Filters*, *Hair Dyes* (including A18, A21, A75, B31, B49, B52, B58, B66, B67, B81) and *Inventory*.

  A large number of opinions had recently been adopted and published in the INTERNET:

  - "Angelopharm" acc. European Court of Justice of 25.1.94 (European Court Reports 1994, page I-0171)

- 11-α-Hydroxypregn-4-ene,3,20-dione (11-α-OHP)
- Acetyl ethyl tetramethyl tetralin (AETT)
- Aristolochic acid and salts
- Acetronitrile
- 2,3,7,8 Tetrachlorodibenzo-p-dioxin (TTCD)
- Tribromosalicylanilide
- CI 42 640
- Anti-Androgens with steroid structure
- Minoxidil and salts
- Tyrothricine
- Tetrahydrozoline and salts
- Phytolacca spp. and preparations
- Zirconium and Compounds
- **UV Filters**:
  - UVASORB HEB
  - 2-Ethylhexyl salicylate
  - 3-(4'-Methyl-benzylidene)-d-1-camphor
  - 3-Benzylidene-bornan-2-one

- *The Scientific Committee on Medicinal Products and Medical Devices.*

  The SCMPMD held a plenary meeting on 22 April 1998. The following points where discussed and progress was made. Results are reported where appropriate:

  - Guidelines for the use of specified risk materials for the manufacture of implantable medical devices.
  - Equivalency of alternative products for surgical sutures.
  - GMP for starting materials: list of excipients to be considered.
  - Guidance on the notions "same medicinal product" and "clinical superiority" for the purpose of marketing exclusivity of Orphan Medicinal Products.
  - Colouring substances in medicinal products.
  - Transmission of CJD by blood and its derivatives and by transplantation of human organs.
  - Resistance to antimicrobials.

    A Working Group was created that will meet in London on 2 June 1998 to establish a list of items concerning the mandate of the SCMPMD on this subject as an input to the Working Group created by the SSC on this issue..
  - Request from a company concerning the evaluation of homeophatic veterinary products by EMEA.

    The Committee agreed that, as this is a subject already dealt with by EMEA, the SCMPMD should not re-evaluate a specific product. The mandate to evaluate products is given to the EMEA. (The SSC agreed to this position but left it open if a general discussion on risk assessment in the context of ultra low doses of toxic substances should be taken up).

  - Non conventional medicines.
    The SCMPMD agreed in principle to reflect on the complicated subject of "non conventional medicines". However, the SSC decided already in April to attend a reformulation of the request received from DG V.

- *The Scientific Committee on Toxicology, Ecotoxicology and Environment*

  Prof.Bridges, chairman of the Committee reported on the latest activities of the Committee. Opinions have been given on 1) phthalates in toys and 2) the drinking water directive.

  Phthalates in toys:

  Six phthalates have been assessed. For each a risk assessment has been conducted, based on the individual estimated "worst case" extractability data and no observable effect levels. Where appropriate SCTEE adopted the NOEL values identified by the Scientific Committee on Food.

  Using these data the SCTEE confirmed that no adverse effects were likely to arise from children chewing toys containing current levels of 4 phthalates DBP, BBP, DOP, DDP.

  For DEHP (Diethyl hexyl Phthalate a calculated safety margin of less than 100 (67) was calculated however the SCTEE considered that there was sufficient toxicology data to show that the use of DEHP at current levels was not of significant concern.

  For DINP (Di-isononylphthalate) the calculated safety margin was much lower (8.8). This was considered inadequate by the SCTEE consequently the Committee proposed that current levels of DINP, which is widely used in children toys, constituted a significant risk to the health of very young children.

  In making its recommendations the SCTEE expressed concern on the following matters; none of which are likely to be confined to phthalates:

  a) the lack of a scientifically base standardised procedure for evaluating the extractability of material from plastic through chewing/extraction by saliva
  b) the need for a rational basis for varying the safety factor / safety margin from 100
  c) what level of information on mechanism of toxicity is required before an effect observed in animals (in this case peroxisme proliferation) can be discounted as relevant to man?

  The Drinking Water Directive:

  This is a complex directive covering surface waters and groundwater. It incorporates a number of previously separate directives (e.g. fish water directive, shell fish water directive). A central element of the new directive is the use of ecological quality to distinguish various classes of water from high to fair. SCTEE proposed many detailed amendments. A common aspect of many of the amendments was the imprecision in the definitions and the need for an identification of the methodology to be used to assign water bodies to the different quality classes. In some instances SGTEE identified that inappropriate, or an inadequate range of organisms were being proposed to validate water quality.

  Progress on other matters

  The SCTEE discussed progress on the opinions for the following:

- Tin, Cadmiun and Arsenic as wood preservatives (opinion scheduled for the June meeting)
- Pentachloropherol (opinion scheduled for the June meeting)
- Chrysotile asbestos (opinion scheduled for the September meeting)
- Endocrine disruptors

7.2. Harmonisation of working procedures, in particular in relation to risk assessment methodologies.

No discussion but the chairpersons from the SCs where asked to provide their input to Prof.Bridges (see minutes of the SSC meeting of 26-27 March 1998), who then will draft a discussion document.

7.3. The role of the Scientific Committees and the SSC in relation to risk assessment and risk management. Definition of "acceptable" or "negligible" risk levels.

Prof.Kroes announced a discussion paper for the next SSC-meeting.

7.4. Discussion on the draft Guidelines "The format and structure for the opinions Scientific Committees"

The guidelines (annex 8) where presented by the Commission and endorsed by the SSC. All scientific Committees are invited to apply these guidelines as far as possible.

8. Information by the Commission services on matters related to consumer health.

B.Hansen, Director for Life Sciences in **DG XII**, presented the current situation as regards the 5th Framework Programme for RTD&D of the Community. He was congratulated by the SSC for the clearness of his presentation and the timeliness of his information.

He underlined that the SSC would be welcome to indicate research needs which then could be taken into account in calls for proposals or any up-dating of the work programs of the different activities under the FP5.

Mr.Hansen further agreed to provide the Scientific Steering Committee regularly with a written summary update on the state of affairs of preparation and, later, the implementation of the 5th Framework Programme.

The Commission also informed the SSC on the recent communication of the Commission to the European Parliament, the ECOSOC, the Committee of the Regions and the Council on a future consumer health policy of the European Union.

Regarding **DG III,** Mr.O.Rohte (DGIII/E/1) illustrated the actual status of the application of Council Directive 93/5/EEC on assistance to the Commission and co-operation by the Member States in the scientific examination of questions relating to food. Article 3 of the Directive provides for an updating at least every six months of the inventory and distribution of tasks.

At the time being there are nine working groups dealing with nine topics. The results of six earlier topics have already been printed. A further two topics have also been completed and will be printed shortly. Finally, two other topics will be

presented to the Working Group on Scientific Co-operation meeting on 8 June 1998 for approval.

Due to a shortage in time, there was no room for a more detailed discussion.

9. Any other business.

No other busienss were discussed.

The meeting ended on Friday 15 May 1998, 13h30.

ANNEX 1

List of Participants in the plenary meeting of the SSC 14/15 May 1998

List of presence

Members of the SSC:

– Prof. Georges Bories (not present)
– Prof. W.Bridges
– Prof. F.Garrido-Abellán
– Prof. Michael J. Gibney
– Prof. Philip James (not present)
– Prof. Keith H.Jones (not present)
– Prof. Fritz H.Kemper
– Prof. Werner Klein (only 15 May 1998)
– Prof. Ib Knudsen (not present)
– Prof. Robert Kroes (only 15 May 1998)
– Prof. Albert Osterhaus
– Prof. Gérard Pascal
– Prof. Antonio Silva Fernandes
– Prof. Marcel Vanbelle
– Prof. Martin Wierup
– Prof. Arturo Anadón (replaced Prof. Bories on 14/05/98)
– Dr. Ada Knaap (replaced Prof. Knudsen on 15/05/98)
– Dr. Emmanuel Vanopdenbosch (expert, present on 15/05/98)

Participants from the Commission:

DGIII: L. Bansil, O.Rohte

DG V C. Schatzl (15 May)

DGXII: M.L.Vidal (15 May), A. Fabre (15 May), B. Hansen (15 May)

DGXXIV: B. Carsin, T. Daskaleros, C.Deckart, W.De Klerck, C.Diez Ubierna, J.Kreysa, M. Lauridsen, G.Morrison, J.Moynagh, A. Sanabria, A.Van Elst, R. Vanhoorde, P.Vossen, P. Wagstaffe, M. Zampaglione.
L. Benali

Annex 2:

Scientific Steering Committee (SSC) Meeting of 14/15 May 1998
Final agenda

1. Welcome, apologies, introductory remarks
2. Approval of the agenda
3. Approval of the minutes of the meeting of 14-15 April 1998
4. Work plan for the SSC
   - 4.1. Progress on multidisciplinary matters, not primarily related to TSE/BSE:
     - resistance to antimicrobials
     - exposure limits to electromagnetic fields (progress report and possible opinion)
   - 4.2. Multidisciplinary matters relating to TSE/BSE
     - a. Production systems and products
       - Safety of Bi-calcium phosphate (progress report and opinion)
       - BSE in Sheep (report from working group)
       - WG-Organo-phosphates (progress report and possible opinion)
     - b. Human exposure risk
       - Group composition and work plan
       - Specified Risk Materials (state of affairs)
       - Blood, blood products, implantables, sutures (state of affairs)
     - c. Geographical risk
       - Sourcing & Modelling (report from the working group)
     - d. Monitoring
       - TSE in bovines diagnosis test (progress report)
       - Monitoring of validation by JRC of test for mammalian protein in feed and correct heat treatment of MBM
6. Organisational matters:
   - 6.1. Additional members for the TSE/BSE ad hoc group.
   - 6.2 Declaration of independence and confidentiality (SSC secretariat)
   - 6.3. Exchange of CVs
   - 6.4. Planning of the SSC meetings until December 1999 (SSC secretariat)
   - 6.5. Progress on payments (SSC secretariat)
7. Co-ordination
   - 7.1. Report of the Chairmen of the 8 Scientific Committees on issues treated or on the forthcoming agenda, including information on Pesticides in baby food.
   - 7.2. Harmonisation of working procedures, in particular in relation to risk assessment methodologies.
   - 7.3. The role of the Scientific Committees and the SSC in relation to risk assessment and risk management. Definition of “acceptable” or “negligible” risk levels.
   - 7.4. Discussion on the draft Guidelines “The format and structure for the opinions Scientific Committees”.
8. Information by the Commission services on matters related to consumer health, including information on the 5th Framework Programme for Research.
9. Any other business.

ANNEX 3

BACKGROUND INFORMATION, MANDATE AND TENTATIVE PLANNING FOR THE WORKING GROUP ON THE USE OF ANTIMICROBIALS

1. INTRODUCTION

In the Communication on Consumer Health and Food Safety of 30 April 1997, the Commission indicated that recommendations for action could originate either from the results of scientific advice, risk analysis or control missions. It also specified that the Evaluation of Health Risks Unit was to fulfil a forward looking role for identifying potential or emerging hazards relating to consumer health and that any Scientific Committee and the Scientific Steering Committee could draw the attention of the Commission to potential and emerging hazards in relation to consumer health.

The question of antimicrobial resistance falls under both criteria. The Evaluation of Health Risks Unit has become aware of a growing number of converging reports on increased antimicrobial resistance, in particular against some food-borne pathogens. Additionally, two scientific committees as well as the Scientific Steering Committee have discussed the matter recently:

- At its meeting of 18-19 September 1997, the Scientific Committee for Food drew the attention of the Commission "to the urgent need to give detailed consideration to the general question of antimicrobial resistance. Although the question had arisen in the context of risks of microbial resistance arising through food consumption, the problem was of relevance in other fields such as pharmaceuticals, animal nutrition and medicine." The Committee concluded that increasing antimicrobial resistance gave rise to potential risks to public health. It recognised the multi-disciplinary nature of the problem and suggested that it may be considered by the Scientific Steering Committee
- At its meeting of 22 December 1997, the Scientific Committee on Veterinary Measures relating to Public Health (SCVPH) recognised that the Scientific Committee for Animal Nutrition (SCAN) addresses the issue of feed additives. It was considered that this issue, that was an outstanding question to the former Scientific Veterinary committee (Public Health Section), needs both input from veterinary and from human medicine and that a series of scientific reports from international bodies were in the pipeline. Therefore, the SCVPH concluded not to address the question of antimicrobial resistance immediately, but asked its Chairman to highlight the multi-disciplinary aspect of the problem to the SSC and to include an expert of the SCVPH in the SCAN working groups when discussing this question.
- At its meeting on 26-27 March 1998, the Scientific Steering Committee agreed on the establishment of a multi-disciplinary Working Group to examine all aspects related to the use of antimicrobials and the development of resistance. The Working Group shall comprise i.a. experts from the Scientific Committees with special competence in this field, as well as external experts in order to ensure coverage of the full range of areas concerned.

Summary information on the use and on the authorisation procedures of antimicrobials in humans, in veterinary medicine and as feed additives is provided in attachment 1.

2. BACKGROUND

The introduction of penicillin into clinical practice in the 1940s made a significant contribution to the treatment of a wide range of infectious diseases in humans and animals. The potential for micro-organisms to become resistant to antibiotics however was recognised early by the development of antibiotic resistant staphylococci - particularly those resistant to methicillin (the methicillin resistant staphylococcus aureus - MRSA).

Until recently the problem had been partially addressed by the development of a succession of new effective antimicrobial chemotherapeutic agents. In recent years however there has been a significant slowing down in the rate of development of such agents, and at the same time, there has been rapid and extensive development of antimicrobial resistance.

Although there have been several important advances in the availability of antiviral and anti fungal agents, there have been no truly novel antimicrobial medicinal products developed in more than 10 years. Increasing problems have therefore arisen in finding effective anti microbial chemotherapy for a number of major pathogens including methicillin resistant Staphylococcus aureus, vancomycin resistant enteroccoci, and multidrug resistant Mycobacterium tuberculosis. This has led to increasing difficulties in the management of a range of human and animal infections.

An important concern must be the cause for this rapid and widespread development of resistance. Although resistance to antimicrobials might be expected to develop through a process of natural selection, it is considered (though not yet conclusively proven) that inappropriate use - both in human medicine and in animal husbandry - has been a major contributory factor. The precise mechanism for the development and transfer of resistance remains unidentified in most cases and considerable effort needs to be directed towards resolving the scientific basis of this problem. The concern amongst scientists however is sufficiently great for it to have been proposed that every administration of an antimicrobial must be considered as an opportunity for the further development of antimicrobial resistance and this attitude needs to be registered with those who use antimicrobials if the problems in clinical medicine are to be satisfactorily contained.

The problem of antimicrobial resistance needs to be addressed urgently to ensure that best use is made of the antimicrobials that currently remain effective in human and in veterinary medecine. Failure to do so could have serious implications for the provision of healthcare in the future, by, for example, potentially limiting medical and surgical advances, lengthening and increasing the difficulty of post operative care and requiring the major provision of isolation facilities. The problem of antimicrobial resistance may also have adverse effects on animal health allowing diseases to spread in animal populations, decreasing animal productivity and animal welfare and with possible adverse effects on public health. Any strategy directed at human and veterinary medicine needs to be comprehensive to ensure the preservation of current product efficacy, to encompass education of practitioners, patients and animal owners, and also to consider how encouragement might be given to the development of disease prevention methods and effective treatment alternatives.

Although antimicrobial resistance has wide spread implications for current practice in clinical prescribing in humans and for the treatment of disease in animals, a comprehensive assessment of the implications needs also to take account of the importance and impact of use of antimicrobials in the treatment of animals destined to enter the human food chain, their use as growth promoters in veterinary practice and agriculture and the possible impact on human health of use of GMOs which carry antibiotic resistance genes (as food

both for humans and for animals destined for the human food chain). The working group is asked to take full account of all of these issues in fulfilling its remit.

The problem of antimicrobial resistance does not recognise national - nor indeed Community - boundaries and the international dimension of the problem needs to be recognised taking account of initiatives underway in WHO and in third countries. Within the European Community itself there is a major body of scientific expertise, to which the working group will need access.

Because of the seriousness of it potential consequence, this issue of antimicrobial resistance has been considered and debated widely by numerous academic, professional, industry and Government groups world-wide. Several countries have shown concern and the WHO have studied the matter in depth and issued major reports. Several bodies have recently reported, some are about to report findings and recommendations, and a substantial body of information already exists across many scientific disciplines. This literature has not been comprehensively reviewed for this consideration.

3. MANDATE / TERMS OF REFERENCE FOR THE WORKING GROUP ON THE USE OF ANTIMICROBIALS

The mandate of the working group needs to be wide ranging, addressing all facets of the subject, including the extent of the problem, its aetiology in terms of scientific mechanisms and the relation of these to the practices of human and veterinary medicine, animal husbandry and food production. It should also address the effects and implications of the continuing development of antimicrobial resistance, means of influencing its further progress and scientifically sound practical advice on how to solve or ameliorate these problems.

The working group is asked to: ***"Scientifically evaluate the current position regarding the prevalence and development of anti microbial resistance, examine its implications for human and animal health, particularly with regard to the development and management of infections. The group should evaluate factors contributing to the aetiology of the present situation, examine means of influencing or controlling the development of antimicrobial resistance and make recommendations based on scientific evidence. It should also advise on the means of monitoring the outcome of measures which it might recommend and consider the implications of its advice. In particular the following elements should be considered:***

- ***surveillance and monitoring of the use of antimicrobials,***
- ***use/misuse in human and veterinary medicine (prophylactic and therapeutic), including over-prescription;***
- ***poor compliance of patients with the prescribed treatment (e.g. using lower dosage or interrupting therapy as soon as symptoms disappear);***
- ***poor compliance of the dosage regimen by animal owners;***
- ***nosocomial infections;***
- ***use/misuse as feed additives;***
- ***use/misuse for plant protection purposes;***
- ***use/misuse of antibiotic resistance genes in GMOs;***
- ***prevention of zoonoses - food safety;***
- ***resistant/multi-resistant microbials;***
- ***microbial ecology (changes in normal microbial flora in particular environments e.g. in hospitals due to frequent use of disinfectants);***
- ***identification of the factors involved in the increase in antimicrobial resistance;***

- ***alternative preventive methods in human and veterinary medecine (level of implementation, promotion).***

4. TENTATIVE PLANNING OF THE INITIAL ACTIVITIES OF THE WORKING GROUP ON ANTIMICROBIAL RESISTANCE.

The time table hereafter is only indicative and might be amended in the light of the outcome of the discussions at the meeting in July.

17.04.98: Creation of an ad hoc steering group which will be chaired by Dr. K. Jones and which will include:

- an expert designed by each Scientific Committee having a direct interest in the subject of antimicrobial resistance;
- additional external expertise covering aspects which are currently not or insufficiently covered by the mandate of any of the 8 Scientific Committees.

This ad hoc steering group will be in charge of the co-ordination.

30.04.98: A draft background document including a proposal for the mandate is available (copy attached). This document results from the 2 draft documents which were prepared respectively by Dr. Jones and by DG XXIV and which were discussed at the plenary of 16 April 1998.

14-15.05.98 Progress report to the SSC.

01.06.98: The chairpersons of the Scientific Committees having a direct interest in the subject are asked:

- to communicate as soon as possible and at the latest by 01 June 1998 to Dr Jones (fax + 44/1372.37.67.47) and to Mr. Vanhoorde of DG XXIV/B-3 (fax +32/2.299.63.01), the name of the expert designed by their Committee to participate in the ad hoc steering group.
- to collect and to communicate, to the persons mentioned above, data and reports issued by national and international scientific bodies (e.g. WHO, …) on antimicrobial resistance. The Scientific Committees are invited to evaluate these reports and to communicate their comments, suggestions and recommendations on the issue.

25-26.06.98 Progress report to the SSC.

01.07.98: First meeting of the ad hoc steering group. The following draft agenda is proposed:

- discussion and adoption of the background document;
- identification of the key questions, problems and aspects which need to be addressed;
- attribution of the various questions to the members of the ad hoc steering group (hence to the Scientific Committees they represent);
- identification of areas not covered by the already available expertise within the steering group and Scientific Committees, identification of additional members of the steering group;
- discussion and planning of further tasks and activities.

16-17.07.98: Progress report to the SSC.

Further activities (requiring input from the individual members of the Working Group)

- depending on the outcome of the discussions in the ad hoc steering group and the feedback from the SSC the organisation of a restricted workshop could be considered;
- analysis and evaluation of scientific data and reports issued by national or international bodies (e.g. WHO, …) and preparation of a scientific report covering each specific aspect of antimicrobial resistance;
- discussion on the individual contributions;
- preparation of a draft scientific opinion covering the various aspects of antimicrobial resistance;
- submission of the draft opinion to the SSC for discussion and adoption (deadline: 12. 1998).

Attachment 1 to annex 3: The use of antimicrobials and procedures of authorisation

1. USE OF ANTIMICROBIALS

Antimicrobials are used for :

- prophylactic/therapeutic use in humans
- prophylactic/therapeutic use in animals
- improvement of feed efficiency in animals (growth promoters)
- plant protection purposes (e.g. in case of fire blight).

2. PROCEDURES OF AUTHORISATION

2.1. Medicinal products for human use

A medicinal product for human use must be authorised for use within the EU either centrally by the Commission (biotechnology and high technology medicinal products) or nationally by each Member State where it is to be placed on the market with a procedure for mutual recognition of national authorisations (Regulation Nr (EEC) 2309/93 and Directives 65/65/EEC and 75/319/EEC as amended). The authorisation specifies amongst others the therapeutic indications and the dosage. For centralised procedures, evaluations are carried out by the Committee for Proprietary Medicinal Products (CPMP) at the European Agency for the Evaluation of Medicines (EMEA) and Community authorisations are delivered in accordance with a comitology procedure. Authorisations are valid for 5 years and are renewed upon request and submission of any new information gained during real use of the medicinal product.

2.2. Veterinary medicinal products

Veterinary medicinal products are also subject to marketing authorisation. In addition to biotechnology and high technology products, any new medicinal products which are intended primarily for use as a performance enhancer in order to promote growth of treated animals or to increase yields from treated animals are subject to the centralised authorisation procedure (Regulation Nr (EEC) 2309/93 and Directive 81/851/EEC as amended). Other veterinary medicinal products are authorised nationally with a mutual recognition procedure. Each authorisation specifies the animal species in which it may be used, the therapeutic indications, the dosage and the withdrawal period in food producing animals (time which must elapse between the last dose and slaughter). Maximum residue limits (MRLs) must be established for veterinary medicinal products for food-producing animals in accordance with Regulation (EEC) Nr 2377/90. The evaluation of applications for authorisation in the centralised procedure and MRL files is carried out by the Committee for Veterinary Medicinal Products (CVMP) at the EMEA. The Community authorisations and MRLs are adopted in accordance with a comitology procedure. Authorisations are valid for 5 years and are renewed upon request and submission of any new information gained during real use of the veterinary medicinal product.

2.3 Feed additives

2.3.1. The placing on the market of feed additives is regulated by Directive 70/524/EEC as amended. Antibiotics, coccidiostats and growth promoters authorised as feed additives before 1 January 1988 must be re-authorised following a full re-evaluation no later than 1 October 2003. Authorisations will be linked to named producers and shall be valid for 10 years.

For antibiotics, coccidiostats and growth promoters authorised after 31 December 1987 no scientific re-evaluation is foreseen. The new authorisations shall be granted no later than 1 October 1999 for a period of 10 years. The purpose of this new authorisation is to relate each substance to named producers.

2.3.2. Directive 70/524/EEC specifies that an additive shall be authorised at EU level only if:

- It has a favourable effect on the characteristics of those feedingstuffs or on livestock production when incorporated in such feedingstuffs;
- At the level permitted in feedingstuffs, it does not adversely affect human or animal health or the environment, nor harm the consumer by altering the characteristics of livestock products;
- Its presence in feedingstuffs can be controlled;
- At the level permitted in feedingstuffs, treatment or prevention of animal disease is excluded; this condition applies to all feed additives (including those listed in the annex to the Directive under the heading 'antibiotics') but does not apply to those listed as 'coccidiostats and other medicinal products';
- For serious reasons concerning human or animal health its use must not be restricted to medical or veterinary purposes (*quote from the Directive*).
- Antimicrobials in feed additives are used at lower dosages than in therapy.

<u>Attachment 2 to Annex 3</u>: Antimicrobial resistance – scope of the mandate of the Working Group: complementary Orientations document distributed to the SSC at its meeting of 14-15 May 1998,

1. Following the concerns expressed by the Risk Evaluation Unit, the Scientific Steering Committee and several Scientific Committees concerning the development of resistance of micro-organisms to antimicrobials agents, the question was referred to the Scientific Steering Committee. At its meeting on 16-17 April 1998, it was agreed to establish an ad hoc Working Party. The mandate of this group was discussed, in particular with regard to the scope of products to be covered.

2. This note aims to provide various elements for the definition of this scope.

3. For the Commission Services, the exercise on antimicrobial resistance has to respond to two objectives :

   - on the one hand, to the public health concerns expressed by scientists on an individual basis or by international organisations such as WHO;
   - on the other hand, to the end of the 4-year transition period laid down in the Accession Treaty for new Member States, period for which these Member States could maintain their ban of the use of antimicrobials as feed additives. The justification of this ban is the risk of development of resistance to antimicrobials that may arise from the use of these substances as feed additives. It was foreseen that following the submission by the Member States, the Commission would use the transition period to evaluate the scientific arguments on basis of which the new Member States had taken the ban and would act accordingly (either by lifting the exemption or by adopting measures in accordance with the exemptions) at Community level.

4. Definitions :

   - Antibiotic : substance produced by a micro-organism which inhibits or kills other micro-organisms (= antimicrobial activity).
   - Chemotherapeutic antimicrobial : substance obtained by chemical synthesis which kills (for example bactericides such as quinolones) or inhibits micro-organisms (for example bacteriostatic products such as sulfonamides).

   These two terms relate therefore to the method of production of the substances (production by a micro-organism or by chemical synthesis) and not the scope of activity of the substance, e.g. the organisms against which they act.

   There are four categories of micro-organisms: bacteria, protozoa, fungi and viruses. Active substances against each one of these categories are available. The antimicrobials comprise therefore antibiotic, antiprotozoal, antifungal and antiviral agents, which can be either antibiotics or chemotherapeutics.

5. Scope of the mandate of the Working Party of the Scientific Steering Committee :

   The development of resistance to antimicrobials has been observed in all four categories of micro-organisms. Until now, it is primarily the resistance in bacteria which is the most widespread and attention therefore been focused mostly on bacterial resistance. However, strains which are resistant to antimicrobial treatments have already appeared in each of the three other categories.

It also must be recalled that some antibacterial and some antiprotozoal agents are used as feed additives (see the Swedish report). Limiting the discussion to antibiotics would lead to the exclusion of antibacterials such as sulfonamides and quinolones (chemotherapeutic agents). In particular, quinolones have showed their efficacy in the treatment of infections with organisms such as salmonella, E.coli and campylobacter and development of resistance to these antimicrobials must be avoided.

For these reasons of a scientific nature, the mandate of the Working Party should cover antimicrobials, whether they are antibiotics or chemotherapeutics.

6. Moreover, in order to allow the Commission to fulfil its commitments with respect to the new Member States and to allow it to take well-founded decisions on the action to be taken on the exemptions mentioned above, the Commission needs a scientific evaluation regarding the development of resistance covering **at least** the same categories of products as those covered by the exemptions. **This involves antibacterial and antiprotozoal agents, whether they belong to the category of antibiotics or chemotherapeutics.**

   While recognising that resistance to antiviral and to antifungal agents is also developing, these two categories of products should be excluded from the mandate of the current Working Party. Moreover, products commonly designated under the name of desinfectants (for example, organic acids, chlorinated derivatives, etc) should also be excluded from the current exercise.

7. **In conclusion, for the moment, the mandate of the group should cover the antimicrobials (antibacterials and antiprotozoals) belonging either to the category of antibiotics or chemotherapeutics.**

ANNEX 4

Mandate of the WG - HER :

The WG-HER will develop a method for assessing the probability that under "normal" consumption patterns a consumer would be exposed to defined amounts of the BSE agent (Human Exposure Risk = HER).

The method should produce an output that would allow assessing the risk that nvCJD-infections occur, as soon as the minimal infective dose and the incubation time are known for humans.

The task could be broken down into (a) hazard identification and (b) risk assessment.

Hazard identification

The Hazard is defined as the event that a human being would consume (be exposed to) an amount of the BSE agent which would potentially be sufficient to create nvCJD. As long as no information on an eventual threshold dose is known a zero-threshold level has to be assumed.

Risk definition

The Risk is defined as the probability/likelihood that this hazard occurs.

ANNEX 5

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ANNEX 6

Planned dates of SSC meetings in the period June 1998 to December 1999

as adopted by the SSC on 15/5/1998

1998

25/26 June 1998

16/17 July 1998

24/25 September 1998

22/23 October 1998

12/13 November 1998

10/11 December 1998

1999

21/22 January 1999

18/19 February 1999

18/19 March 1999

22/23 April 1999

27/28 May 1999

24/25 June 1999

22/23 July 1999

16/17 September 1999

14/15 October 1999

11/12 November 1999

9/10 December 1999

Annex 7

Scientific Committee for Animal Health and Animal Welfare

Meeting schedule as presented on 15/5/98

20 April

Meeting Working Group of Animal Welfare Subcommittee on Stunning methods for Poultry. Report is in an advanced stage – possible approval by Animal Welfare Sub-Committee on 18 May and then to plenary of Animal Health and Animal Welfare Committee on 23 June.

27 April

Meeting Working Group of Animal Welfare Subcommittee on Ventilation Standards for Animal Transports (forced ventilation)

28 April

Meeting Working Group of Animal Welfare Subcommittee on Forced Feeding of Ducks and Geese – Gavage. This is a difficult issue needing much discussion but progress being made.

7 May

Meeting Working Group of Animal Health subcommittee on Emergency vaccination for Foot and Mouth Disease. Well progressed but at least one more meeting needed.

12 May

Meeting Working Group of Animal Health subcommittee on Possible links between Crohns Disease and Johnes Disease. Well advanced but proving to be a complex issue. .

Meetings in Near Future

18 May: Sub-Committee on Animal Health

19 May: Sub Committee on Animal Welfare

28 May: Working Group of Animal Health subcommittee on Directive 64/432 – Diagnostic Methods for Tuberculosis, Brucellosis and Enzootic Bovine leucosis.

Annex 8

Guidelines for the format and structure for the opinions Scientific Committees

Foreword:

There are now 9 Scientific Committees charged with delivery of independent advice to the Commission in the field of consumer health. The experience of the Committees varies. Some have established procedures and styles over many years, some are just developing their style.

It is evident that it is not possible to establish a unique model or format which could cover the vast diversity of questions. However, it is essential that similar questions are evaluated in each Committee in a comparable way and that the conclusions and the underlying reasoning are presented in a uniform manner. This will contribute to the transparency of the work of the Committees.

There is, hence, a need to harmonise the structure and presentation of the opinions of the Committees as far as possible. As a first step, the following general structure is proposed for the presentation of opinions. It is assumed that their application would also contribute to the evolution of harmonised risk assessment methods.

Terminology:

These guidelines employ the "Terms and Definitions used in Risk Analysis" as recommended for interim use by CODEX (CL 1996/21 GEN of June 96)

Guidelines for the format and structure for the opinions Scientific Committees

Title of Opinion:…….

- **Opinion of the Scientific Committee for…….**
- **expressed on ……..**

Executive Summary

(where appropriate for complex opinions)

The Executive summary should be able to be distributed without the full opinion and therefore contain the following elements:

- Question
- Answer
- Main elements of the scientific justification of the answer

Full OPINION

Terms of Reference (i.e. the question)

As given to the Committee by the Commission

Context of the question (prepared with assistance of Secretariat, if necessary, and based on documentation provided by the "Source" of the question)

- Legislative/policy/scientific aspects; references to previous opinions of the Committee or other Commission Scientific Committees/international bodies.
- Definitions of terms were appropriate.

Assessment

(Content and technical approach will vary greatly according the question but some general elements should always be covered:)

- Strategy adopted for the evaluation and risk assessment; assumptions made, for example, in modelling.
- State of the art: Description of present practices, production processes, accepted risk levels, current risk management practices, etc. related to the question;

[Examples for an evaluation

Type a) Classical risks assessments such as for discrete chemicals or substances

(1) Hazard characterisation

- *Scientific/technical state of the art; review and analysis of relevant literature (confidential, open literature, other sources)*
- *Clear identification of studies which form basis of conclusions*
- *Description of the nature of the hazard e.g. toxicological profile*
- *Clear description of no effect levels, safety factors and justification, ADIs, TDIs*

(2) Exposure assessment

- *Evaluation of exposures of individuals in general population/specific risk groups*
- *Indications of relative importance of major sources of exposure/risk*

(3) Risk characterisation

- *Assessment of risk based on risk characterisation and exposure assessment.*
- *Reasons for departing from previous opinions on same or closely related subject*
- *Gaps in the knowledge which will require judgement of the Committee or which can not be overcome without further research*

Type b) Other kinds of well-defined hazards – to be developed according to the nature of the question

Type c) Reports of a general nature]

Opinion[1] (i.e. answer to question)

- Precise response to the question posed.
- *Concise* conclusions of the Committee based on arguments developed above in a form allowing free-standing quotation with minimum risk of misinterpretation;
- The conclusion should be limited to a science-based answer, in case of risk assessment consisting of a description of the risk with an indication of uncertainties in the underlying assumptions.
- It should not include proposals for risk management but may include risk assessments of different risk scenarios if requested in the question.

Other considerations (if any)

Where the Committee feels the need to join additional considerations (for example, scientific recommendations), they should be clearly separated from the opinion itself.

Minority opinions (if any)

Details to be given in annex.

[1] Alternatively, the "Opinion" could be given at the beginning, immediately after the "Terms of Reference"

References

Bibliographic references to literature cited in text or used in any manner for the preparation of the opinion.. Citations should follow the normal conventions used in scientific literature, e.g. the Vancouver system, and allow sources to be identified and accessed where not confidential.

N.B. References to confidential information such as commercially sensitive submissions can only be made available with the consent of the author.

Acknowledgements

To be considered : the possibility of including acknowledgement to individual experts who made an exceptional contribution to the background work