European Science Foundation

Life and Environmental Sciences (LESC) Exploratory Workshop

The Horizontal Gene Pool; the functional role of mobile genetic information - how bacteria perceive, sample and utilise genetic elements in evolution and local adaptation

Zechner, Ellen L. (University of Graz, Austria) and Bailey, Mark J. (CEH-Oxford, UK)

The executive report discusses the workshop aims, structure and logistics as well as summarizes the prospects for future interactions between European laboratories interested in the dynamic nature of bacterial genome structure and adaptation. Additional documents include the scientific summary/reports a financial report, the final programme, a final list of participants and statistical information on participants.

Executive report

The purpose of this exploratory workshop was to identify how recent advances in the application of genomics and microbial ecology can be harnessed to determine the genetic mechanisms that underpin the biological role of the horizontal gene pool. The workshop was held at St. Catherine's College, Oxford, UK from July 25 - 27. Funding for the workshop was provided exclusively by ESF. St. Catherine's College provided the conference facilities, accommodation and meals for the participants at a reasonable rate. Administration was handled expertly by Ms. Angela Morrison, CEH Oxford.

Scientific excellence at the workshop was contributed by senior scientists and young investigators from research institutes located in nine European countries. The participants' expertise included a diversity of disciplines – microbial ecology, bioinformatics, medical microbiology, epidemiology, biochemistry, molecular biology, bacterial genetics and evolution. The diversity of fields represented was unfortunately restricted as conflicting travel plans or ill health prevented several invitees from attending – Dennis Bamford (Finland), Victor de Lorenzo (Spain), Manuel Espinosa (Spain), Erich Lanka (Germany), Didier Mazel (France), Julian Parkhill (UK), David Sherratt (UK), Francois Taddei (France), and JD van Elsas (Netherlands). The programme was organized into five sessions **1. Development of a MGE "MINE-database", 2. Perception and recognition, 3. Dissemination, 4. Establishment and functional Diversity, and 5. Population genetics and evolutionary Biology** that were alternately chaired by the organizers Mark Bailey (UK) and Ellen Zechner (Austria). A special seminar was given by Rainer Haas (Germany). Dr. Blanka Rihová (Czech Republic) presented a summary of ESF functions and policies for collaborative research in Europe. A tribute to honor the important contributions of Brian M. Wilkins (1939 – 2003), University of Leicester, to our current understanding of horizontal gene transfer was prepared by Ellen Zechner with key contributions from Erich Lanka. The workshop was dedicated to the memory of our valued colleague and friend.

Mobile Genes
Perceptions of the microbial gene pool

Whole genome approaches have shown unequivocally that the process of horizontal gene transfer (HGT) in bacteria contributes profoundly to genetic diversity and evolution. Processes belonging to HGT include transformation, transposition, transduction, and conjugation. Vehicles of this genome plasticity, the mobile genetic elements (MGE), include insertion sequences, transposons, integrons, bacteriophages, plasmids, genomic islands, (e.g., pathogenicity islands), and combinations of these elements. MGE are neither genome- nor species-specific, but may be exchanged promiscuously among a broad spectrum of bacteria.

The compilation of genome sequence data is proceeding at a remarkable rate. Five hundred genomes are predicted to become available by the end of 2004. Correct annotation and management of these data requires classification that accounts for the partition of genes between mobile and less mobile elements of the genome. Criteria for recognition of mobile DNA are a subject of continuous reassessment. Simply defined, the horizontal gene pool (HGP) consists of genes that are or can be "actively" transferred between species on mobile elements. In many cases, these genes are not essential under all conditions, but are strongly favoured in certain environments; they act as accessory genes. A point of debate therefore is whether a clear distinction can be made between the horizontal, or accessory, gene pool and the basic genome, and whether there is more than one class of accessory genome. An attractive use of 'omics terminology was suggested by Peter Young to distinguish accessory gene pool and the basic genome; the **"mobilome"** and the **"stayatome"**! Evaluating genomic characteristics of the different gene pools in different organisms coupled with improved understanding of the mechanisms of genetic exchange provides the basis for predicting the mobility of genetic material.

Several important points relevant to the workshop aims and conclusions drawn are summarized below. Continued acquisition of DNA sequence data is essential. Dedicated sequencing of MGE is lagging far behind the level of interest in these elements for basic and applied science. Most notably we agree that the current approaches to curating sequence databases are inadequate to accommodate laterally transferred genes. Crucially it is recognized that development of a biologically cohesive system to curate databases for microbial genomes and the MGE requires consensus of the global scientific community and internationally uniform strategies for taxonomy, management and links to ecologically relevant data. We conclude that a key priority for collaborative effort in Europe should be to strengthen our investment in established databases including expansion of the links at local, regional and international nodes. Importantly, these issues are not restricted to Europe. It was established that US led initiatives are also emerging from the scientific community calling for nomination of an international Horizontal Genomics Advisory Group and encouraging NCBI, the US Department of Energy Joint Genome Initiative, the US Department of Defence, and the National Science Foundation to commit funds to correct the lack of dedicated MGE sequencing projects, to solve existing problems with the databases and maximize efficient utilization of these resources. The ESF is uniquely placed to provide European representation in that effort. Importantly, the value of these databases extends far beyond the curation of simple genetic information. Analysis and utilisation of this information should be maximized to inform our experimental systems and understand biodiversity and the mechanisms of bacterial evolution. Collaborative effort will be crucial to achieve a commitment from scientists to expand databases with the sum of what we know including ecological diversity of bacteriophage, plasmids and other MGE.

There is evidence that HGT can occur between bacteria during infection yet very little is known about the signals that induce genetic exchange in vivo or in the environment. Regulatory relationships between mobile and less mobile genes are largely unknown under any physiologically relevant conditions, and the transition from normal to infection activities among opportunistic pathogens exemplify aspects of gene regulation and flexible genomes that require innovative investigation. Most European laboratories work in isolation but issues of this scale would clearly benefit from collaborative efforts using chip technology, and relevant environmental and in vivo models in coordinated surveys that go beyond the resources of individual labs. A broad instrument base and multidisciplinary approach to cell biology and structural biology including ultrastructural analysis of complex structures such as cell surface filaments are essential components in solving the molecular mechanisms behind gene transfer events.

The HGP has in the past been regarded as a specialised subject area. Plasmid and bacteriophage biologists have long held the view that these mobile elements provide considerable plasticity to the bacterial genome. Genomics, often centered on the chromosome, has confirmed these assumptions and underlines the need for more focused research on mobile elements, as they may provide the key to understanding microbial evolution and the reagents with which to conduct real time studies on adaptation and specialization and reveal the factors that constrain rampant horizontal gene transfer. We argue that the small, tractable genomes of the HGP have immense utility as model systems to investigate bacterial evolution. An effective strategy here may be to coordinate which genomes are sequenced, to focus on more novel MGEs, and finally use comparative genomics to drive functional hypotheses that can be tested experimentally. We aim to continue to gain information on the genetic and ecological diversity of plasmids and bacteriophage. Insight to their genetics and host range will provide the data we need to define the extent of operational bacterial gene pools and the "mobilome". These elements are relatively small in size, often readily accessible and amenable to purification. To sequence large collections would be a relatively trivial event but would provide a wealth of direct information on the rate and reality of gene flux and recombination within and between the bacteria and archaea. The rate of sequencing is no longer a constraint, it is now relatively inexpensive and rates of 30Mb a day are typical of national centres. We can use the "retrospective" insights concerning microbial evolution and genetic exchange to fuel hypotheses of dissemination mechanisms and predictive modelling of gene mobility and bacterial adaptation. Pooling the efforts of individual laboratories into a coordinated network that focuses on hypothesis led studies of a selected group of model genomes and selected processes should be emphasized. The collaboration would be uniquely placed to test defined hypotheses experimentally.

The way forward:

The workshop generated considerable excitement and a commitment from the various representatives that we should extend the initiative and develop a practical platform for information exchange, data base development and basic research into evolution and the mechanisms of HGT. Importantly the issues are not limited to Europe. Clearly we recognize the need to determine common strategies and pursue unified solutions to the management of the global network of microbial genome databases. To this end collaborative efforts with US, Japan and European databases are essential. Dr. Blanka Rihová, the ESF representative offered key information about ESF policies and valuable guidance for future ESF proposals. Dr. Rihova´s enthusiasm for the placement of the Horizon initiative in the framework of an ESF Programme was quite positive. The ultimate outcome of the Horizon exploratory workshop has been the decision to move forward with the initiative. Convenors MJB and ELZ will develop the proposal for ESF Programme funding. By combining the emerging disciplines of bioinformatics, genomics, population genetics and molecular biology we are in an ideal position to undertake precise hypothesis led experimentation. Such informed, rather than intuitive, predictive approaches will allow us to describe the mechanistic nature of horizontal gene transfer and the role of mobile genetic elements in the adaptation and evolution of microorganisms. Importantly, the workshop underlined the fact that MGEs do not result in genetic chaos or a dilution or homogenisation of diversity. Quite the opposite, these events are structured and regulated in defined genetic and ultimately evolutionary terms. The challenge is determining the variety of systems and understanding the controlling or constraining factors.

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Scientific Report

1. Development of Mobile genetic element's MINE-database

The conference was opened by a detailed set of presentations from Dawn Field, Nicholas Thomson and Ariane Toussaint illustrating the tools available for genome analyses. The importance of bioinformatics and associated databases for genomic information was stressed, as was the need for complete and accurate annotation accompanied by the cataloguing of relevant ecological data. Biologists and geneticists working together are unravelling important insights to bacterial adaptation and evolution. These studies are reliant on access to suitable informatics systems that facilitate the mining of information. What is critical is that the data held are accurate and correctly annotated. The variance in the accuracy of data deposited in the past and to a lesser extent recently represents an immediate problem to scientific research. To address these problems a level of collaborative effort needs be established to map out and implement database correction procedures. Data sets of fully sequenced genomes are being deposited at a remarkable rate that is approaching one a week. These data include sequence of chromosomes and accessory genetic elements including plasmids and bacteriophage. Each speaker concentrated on the recent developments in the assembly of specific data bases for plasmids (http://www.genomics.ceh.ac.uk/plasmiddb) bacterial genomes (http://www.cbs.dtu.dk/services/GenomeAtlas) and bacteriophage (http://aclame.ulb.ac.be). The latter contains 119 phage genomes represented by 5069 proteins. These systems underpin future developments in microbial genetics and understanding the importance of the horizontal gene pool in bacterial adaptation and evolution.

Importantly, the value of these databases extends far beyond the curation of simple genetic information. How this information can be analysed is elegantly illustrated on the Genome Atlas site described by Dave Ussery. The inclusion of associated ecological and related meta-data is critical. The availability of tools and links to related bioinformatics sites is essential to logically navigate the complexity of biological information. Ultimately the utility of genomic data is crucially dependent on the involvement of the research community to provide information on all aspects of the biology and genetics of bacteria and their horizontal gene pool. The aim must be a maximally comprehensive resource to fuel predictions of molecular mechanisms and inform experimental approaches. The value of the current data sets in comparative and predictive biology was illustrated throughout the workshop by most if not all the speakers.

2. Gene dissemination and adaptive selection

Modulation of genomic composition determines both bacterial diversity and adaptability, discernible by the expression of phenotypic variation such as virulence and exploitation of specific niches. The broad spectrum of physiological and virulence properties of bacterial pathogens reflects the existence of different subsets of genes facilitating different aspects of the pathogen's lifestyle(s). The HGP is an important reservoir and motor of this variability. Antibiotic resistance genes, certain toxins, a number of virulence determinants and pathways for xenobiotic degradation are specifically located on components of the bacterial HGP,

transposons, plasmids and bacteriophage. Assemblages or collections of genes and functions, coupled to the selective pressures of the environment, were common themes when considering the development of pathogenicity islands or pathways for the degradation of xenobiotics. The diversity of microorganisms and their capacity to sample their available genetic pool should not be underestimated. HGT provides bacteria with an unlimited and rapid capacity to adapt to ever-changing environments. Nonetheless it is clear that acquired genetic information is rarely maintained in recipient cells, unless uptake coincides with specific selection events. Despite the evidence for frequent gene transfer the integrity of speciation and abundance of microbial diversity is retained; this fact of evolution requires that we address a number of fundamental questions pertinent to the HGP: what are the limiting factors of DNA transfer, what drives the uptake of DNA, how is DNA uptake regulated and processed by the cell, do we understand the constraints to recombination, how are hot spots for integration defined and are they specifically retained in the genome? Clearly we have much to learn of the mechanisms and cues for such events. Detailed knowledge of the activity, diversity and regulation of MGEs is key to providing the answers. We expect that greater exploitation of bioinformatics and genomics will provide insights to how bacteria perceive their environment and sample the available gene pool.

3. Motility, adhesion, and perception of the environment

The workshop programme illustrated the diversity of approaches that are needed in elucidating the contribution of cell surface components to genetic exchange through motility, adhesion, location of specific receptors and / or the mechanical conveyors of gene material. While details of intercellular interactions mediating sexual transmission remain essentially unknown, recent discoveries in the mechanism of filament assembly, surface adhesion and retraction in other bacterial secretion systems involving pili, highlighted by Michael Koomey's work with Neisseria type IV pili, are expected to reveal important insights. The application of molecular biology and genetics methods together with in situ microscopic investigation of bacterial life at surface / liquid interfaces are providing an intriguing view of biofilm development. Cell surface composition, motility and the general physiology of bacteria in relation to the surrounding environmental conditions are important features in the development of biofilm communities which, in some instances, provide an ideal venue for enhanced gene transfer. Soeren Molin developed the case for a fascinating interplay between self assembly processes and the activities and overall structure of the community as a determinant of the biofilm developmental cycle. Exciting progress has been made in recent years towards understanding bacterial adhesion and virulence since the emergence of signature tagged mutagenesis technology. The approach was developed by W. Holden and colleagues to identify microbial genes required for infection of host cells. An elegant application of this technique was illustrated at the meeting by Rainer Haas' screen for novel genes involved in *H. pylori* colonization of the gastric mucosa. The power of the STM approach is also quite promising in screens designed to identify genes involved in the dissemination and uptake of selectable markers through HGT.

In some instances, acquisition of DNA may be detrimental or provide no discernible benefit to the transgenic cell. Other acquired genes provide immediate selective benefit and antibiotic resistance is a well known example. Selective pressure through antibiotic therapies on small segments of the human population can lead to substantial selection of resistance. The issue of long term stability and transmission of those selected resistances was addressed by Peter Hawkey. While the prevailing expectation is that the fitness costs of maintaining resistance in the absence of selection is prohibitive, recent work suggests the costs may not be universally high for all hosts, or even vehicles of the resistance genes. The molecular epidemiology of new resistance phenotypes gains significance as the diversity of contributing mechanisms are recognised.

4. Mechanisms governing dissemination, establishment and functional diversity

Insights to the molecular mechanisms of assembly, transmission and establishment of mobile genes were provided in several seminars. These data emphasised that mobile genetic elements play a central role not only as the vectors of accessory genes, but also the genetic hot spots for the assembly of novel pathways and their subtle variation and evolution under selective adaptation through recombination and mutation. Mick Chandler argues that while the number of transposons is quite large, diversity in the enzymology of transposition is limited. Mechanistic details over transposon activities are increasingly better known. Site of insertion is an important determinant for subsequent diversification to transposon sequence. Bianca Hochhut summarized features of integrative and conjugative elements (ICE) found in Gram-positive and Gram-negative pathogens. These elements resemble both bacteriophage and conjugative plasmids. Trafficking of the elements between the chromosome and an excised, transient state is mediated by phage-like recombinases. Knowledge of dissemination of ICE via conjugation-like mechanisms remains limited. Matxalen Llosa's recent findings concerning the macromolecular architecture of a conjugative Type IV secretion system provide new insights to the mechanism of targeting genes for dissemination and raise new questions about the technical feasibility of manipulating the selection of genetic cargo for biotechnology.

Aspects of the functional diversity conferred by catabolic plasmids were presented by Peter Williams. The pathways capable of degrading xenobiotic chemicals are apparently modular in construction. Clusters of genes have undergone a recent, turbulent history of reassortment and dispersion via transposon and plasmid vectors. Extensive comparisons of the annotated genomes of pathogenic and closely related non-pathogenic bacteria enable a correlation between disease and prokaryotic genome structure (Jörg Hacker). *E. coli* 536 carries at least six pathogenicity islands that encode most of the factors responsible for this strain's virulence in urinary tract infection. New data are becoming available over the mobility of pathogenicity islands in *E. coli* and the contribution of gene loss to the optimization of fitness of colonizing bacteria vs acutely infectious counterparts. The importance of recombination to functional diversity was summarized by Chris Thomas with the proposal that bacteria sample the genetic space by creating continuously new combinations of genes. Plasmids provide the accessible pool for recombination and motor exchange by cycling in and out of genomes and in an out of hosts. Pseudomonas plasmids in particular offer a good model system to quantify the impact of plasmids on bacterial diversity and adaptation.

5. HGT and bacterial evolution

The value of bioinformatics to developing the understanding of HGT in bacterial evolution was exquisitely illustrated in the final session on evolutionary biology. Detailed presentations on antibiotic resistance in Streptomycetes (E Wellington), the epidemiology of *Neisseria* sp. and TB (M Maiden), the use of arrays in the study of plasmid evolution (K Smalla), and gene flow in Rhizobia (P Young) demonstrated the wealth of knowledge that we are acquiring and how these data sets are allowing directed experimentation and hypothesis led study. These excellent presentations set the scene for the final talk where the value of the Genome Atlas (D Ussery) was shown. This site provides a suite of tools for genome annotation and extensive data sets that facilitate comparisons of genome structure and architecture and specific searches to assess HGT etc. One particular illustration was provided that revealed the presence of inverted repeats that inferred the location of novel transposable elements. Data from natural, agricultural and clinical environments provided insight to the diversity and distribution of a number of functional traits including antibiotic resistance, pathogenicity determinants as well as basic backbone elements in extrachromosomal elements such as the genes for transfer and replication machinery. In the case of the Streptomycetes it was clear that hot spots for gene acquisition and duplication result in a mosaic of genes located at the ends of the linear

chromosome. This is perhaps logical and facilitates duplication with out disrupting the housekeeping requirements for the genome. In the pathogen discussions the natural competence of Neisseria was clearly a determining factor in virulence as recombination and regulation allowed selection of variants that could elude host immunity. Estimates were provided that recombination rates were 10 times those of mutation and provide an essential adaptive strategy for this pathogen that enjoys a variety of life styles. The apparent complexity and recombination rate generates variance within the genome resulting in many genotypes. This contrasted with TB where this highly specialized bacterium is effectively clonal and undergoes little recombination or HGT.

The broader role of the horizontal gene pool, particularly the role of conjugative plasmids rather than chromosomal gene flux, was discussed. Konny Smalla detailed the study of the broad host range IncP family of plasmids that is commonly found in pseudomonads. Despite the fact that the IncP plasmids were originally isolated from clinical samples there is mounting molecular and ecological evidence that they are typical of environmental bacteria, especially in polluted soils where they play a direct role in host bacterial adaptation to environmental stress. In an exciting development, the use of micro-arrays demonstrated that a variety of sequences common to prototype IncP-like plasmids could be found – these data indicate their mosaic nature and should facilitate the classification of newly isolated plasmids allowing further study of relatedness with known replicons, other accessory elements and functional traits.

This theme was further developed when considering the evolutionary link between plant colonizing Rhizobia that carry the genes required for nodulation (nod) and for nitrogen fixation (nif). These traits are important when the bacteria invade a legume host but not necessary in the free-living phase. Interestingly these genes represent the accessory genome as their phylogeny and lower G+C content is different from that of basic genes in the same genome. These data may indicate historical transfer between species, and that they are components of the HGP and located on plasmids in some (but not all) species. The analysis of complete genome sequences reveal that the nod and nif genes are part of a much larger class of genes that share some or all of these properties. *Mesorhizobium loti*, *Sinorhizobium meliloti*, *Agrobacterium tumefaciens* and *Bradyrhizobium japonicum* share a common core of genes that are chromosomally-encoded, high G+C and have a consistent phylogenetic relationship. By contrast, each genome also has a substantial class of genes that are lower in G+C, located either on plasmids or in potentially mobile genetic islands within the chromosome.

6. Conclusions

Deeper understanding of the mechanisms involved in genome plasticity and in the evolution of bacterial species and variants is crucial for developing the strategies needed to combat pathogens, understand evolution and for exploiting the opportunities for novel product discovery. All these opportunities are presented by the flexibility of the genome in both prokaryotic and eukaryotic systems. However we do need action in the near future to guide research and optimise discovery. Through the combination of scientific disciplines we have already developed considerable insight. A lively discussion at the conclusion of the conference, led by Mark Bailey and Ellen Zechner and incorporating extensive contributions from all participants, drew conclusions of the workshop and planned the way forward (see Executive Report).

ESF Exploratory Workshop
St Catherine's College
Oxford, United Kingdom
25-27 July 2003

FINAL PROGRAMME

Friday 25th July

17.00	Arrival and registration
18.30	Reception (drinks in bar)
19.00	Dinner

Saturday 26th July

8.40 – 8.45	**Mark Bailey** *"Welcome"*
8.45 – 9.00	**Professor Blanka Rihova, ESF representative** *"European Science Foundation and its funding instruments"*

Session 1 - Development of a MGE "MINE-database"

9.00 – 9.30	**Dawn Field** *"Using public collections of genomes to study evolution and ecology"*
9.30 – 10.00	**Nicholas Thomson** *"Insights into bacterial genome evolution from genomics"*
10.00 – 10.30	**Arianne Toussaint** *"A database for the classification of the prokaryotic mobilome"*
10.30 – 11.00	Morning coffee

Session 2 - Perception and recognition

11.00 – 11.30	**Michael Koomey** *"Components and dynamics of Type IV pilus expression linked to organelle structure and function"*
11.30 – 12.00	**Soeren Molin** *"Microbial ecology and physiology perception and response to neighbours"*
12.00 – 12.30	**Peter Hawkey** *"Impact of HGT on antibiotic resistance development in medically significant bacteria-where will the next superbug come from?"*
12.45	Lunch

Session 3 - Dissemination

14.00 – 14.30	**Mick Chandler** *"I do it my way: transposition of the bacterial insertion sequence IS911"*
14.30 – 15.00	**Bianca Hochhut** "*Conjugative and integrative elements in pathogenic bacteria"*
15.00 – 15.30	**Matxalen Llosa** *"Conjugative coupling proteins: Interactions with cognate and heterologous transporters"*
15.30 – 16.00	Afternoon tea

Session 4 - Establishment and functional Diversity

16.00 – 16.30	**Peter Williams** *"Catabolic plasmids, modular pathways and rapid evolution"*
16.30 – 17.00	**Jörg Hacker** *"Genome analysis of pathogenicity islands and other mobile genetic elements in pathogenic bacteria"*
17.00 – 17.30	**Chris Thomas** *"Lessons from Pseudomonas plasmids"*
17. 30 – 18.15	Break/General discussion

Guest Lecture

18.15 – 18.45	**Rainer Haas – Guest Speaker** *"Signature tagging in Helicobacter pylori: an efficient negative selection procedure to identify essential genes"*
18.45	Pre-dinner drinks in the bar
19.00	Dinner

Sunday 27th July 2003

Session 5 - Population genetics and evolutionary Biology

9.00 – 9.30	**Liz Wellington** *"Gene flow and the evolution of antibiotic gene clusters in streptomycetes"*
9.30 – 10.00	**Martin Maiden** *"Implications of horizontal genetic exchange for the evolution of pathogenic bacteria"*
10.00 – 10.30	**Konny Smalla** *"Contribution of IncP1 plasmids to bacterial adaptation under environmental stress"*
10.30 – 11.00	Morning coffee
11.00 – 11.30	**Peter Young** *"How many gene pools are there?"*
11.30 – 12.00	**David Ussery** *"Genome atlas for the study of evolutionary systems"*
12.00 – 12.50	**General discussion and the way forward**
13.00	Lunch and depart

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Statistical Information on Participants

i) Age Structure

invited speakers: 4 x [30-39], 10 x [40-49], 5 x [50+]
other participants: 5 x [20-29], 2 x [30-39], 4 x [40-49], 1 x [50+]

ii) Country of origin:

invited speakers: 1 Belgium, 1 Czech Republic, 1 Denmark,
4 Germany, 1 Spain, 9 United Kingdom, 2 United States of America
other participants: 2 Belgium, 1 Denmark, 7 United Kingdom, 1 United States of America, 1 China

iii) Current country of work:

invited speakers: 1 Belgium, 1 Czech Republic, 2 Denmark, 1 France,
4 Germany, 1 Norway, 1 Spain, 8 United Kingdom,
other participants: 1 Austria, 2 Belgium, 1 Denmark, 8 United Kingdom