Project no. 513943

Project acronym: ECNIS

Project title: “Environmental cancer risk, nutrition and individual susceptibility”

Instrument: Network of Excellence

Thematic Priority: 5 FOOD QUALITY AND SAFETY

Final Activity Report

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Duration: 66 months

Project coordinator name: Prof. Konrad Rydzynski, MD, PhD
Project coordinator organisation name: Nofer Institute of Occupational Medicine

Partners of ECNIS – 25 partners in 13 countries

1. The Nofer Institute of Occupational Medicine, Lodz, Poland
2. German Cancer Research Center, Heidelberg, Germany
3. University of Copenhagen, Denmark
4. Karolinska Institutet, Stockholm, Sweden
5. Institute for Scientific Interchange Foundation, Torino, Italy
6. The National Hellenic Research Foundation, Athens, Greece
7. University of Leicester, United Kingdom
8. National Institute of Environmental Health, Budapest, Hungary
9. Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz, Poland
10. Genetics Research Institute & Ospedale Policlinics, Milano, Italy
11. Johannes Gutenberg University, Mainz, Germany
12. Finnish Institute of Occupational Health, Helsinki, Finland
13. Vrije University of Brussells, Belgium
14. Lund University, Sweden
15. Katholieke Universiteit Leuven, Belgium
16. Institute of Cancer Research, Sutton, United Kingdom
17. Maastricht University, Netherlands
18. Biochemical Institute for Environmental Carcinogens Prof. dr Gernot Grimmer Foundation, Grosshansdorf, Germany
19. Catalan Institute of Oncology, Barcelona, Spain
20. Utrecht University, Institute Of Risk Assessment Science, Netherlands
21. University of Dundee Biomedical Research Centre, United Kingdom
22. International Agency for Research on Cancer, Lyon, France
23. NETIX Skrzypczynski, Krzysztofowicz Sp. J., Warsaw, Poland
24. Leocordia AB, Stockholm, Sweden
25. Imperial College, London, UK

ECNIS Website

www.ecnis.org

ECNIS
Environmental Cancer Risk, Nutrition and Individual Susceptibility
Network of Excellence

ECNIS (Environmental Cancer Risk, Nutrition and Individual Susceptibility), a Network of Excellence within the EU 6th Framework Programme, launched in May 2005, has brought together some of the best European research groups from 25 institutions of 13 countries active in the area of environmental cancer and its modulation by nutrition and genetic makeup, into a durable network of partners to conduct high-class research on cancer causation and prevention. The vision of ECNIS has been creation of a dynamic research network which will work to decrease cancer incidence by:

- identifying chemicals or other factors in the environment and food which cause cancer,
- elucidating the mechanisms by which dietary and lifestyle patterns increase or decrease cancer risk,
- facilitating the development of new foods with cancer-preventive properties,
- discovering genetic (hereditary) factors which make individuals more or less susceptible to cancer,
- formulating improved approaches to the risk assessment of carcinogens.

A major approach employed in ECNIS research has been the use of biomarkers of carcinogenesis.

To reach its objectives, ECNIS activities were organised around three axes:

Integrating Activities, to promote the establishment of a durable network of European research groups committed to co-ordinated research planning, personnel mobility and sharing infrastructures and data, with four workpackages:

WP1 Integration of available resources and setting up quality standards (Resources)
WP2 Integrated organization of knowledge and information flow (Knowledge and information)
WP3 Joint training and mobility program (Training)
WP4 Construction of a knowledge data base on molecular epidemiology and cancer (MEC)

Joint Research Activities, focussed on high quality, multidisciplinary investigations in the area of molecular cancer epidemiology, environmental carcinogenesis and its modulation by nutrition and genetics,

WP5 Science Monitoring and Review (Science Review)
WP6 Development and validation of biomarkers of exposure and of bioindicators of disease for use in epidemiology (Biomarkers of exposure)
WP7 Development and validation of biomarkers of individual Susceptibility (Biomarkers of individual susceptibility)
WP8 Implementation of biomarker technology for cancer prevention (Cancer prevention)
WP9 Mechanisms of modulation of cancer by dietary factors (Modulation by diet)
WP10 Mechanistic research to support cancer hazard and risk assessment (Mechanism of action)
WP11 Integrated risk assessment (Risk assessment)
WP12 Socio-ethical impact of biomarker use (Ethics)

Spreading of Excellence Activities, including researcher training and mobility programmes as well as sharing of new scientific knowledge with different stakeholders (researchers, the general public, regulators, health care specialists, industry, etc.)

WP13 Dissemination of knowledge to the scientific community
WP14 Dissemination of acquired knowledge to different stakeholders
WP15 Management Activities

Management of the Consortium activities was carried out in a WP15- Management Activities

Through works carried out during five years a vivid and mature network of strongly collaborating participants, using harmonized, integrated resources, data bases, procedures and quality standards for common use as a base for performing coordinated joined research activities was established. One of the primary objectives of the network has been to integrate the research efforts and to facilitate exchange of the knowledge and expertise. Indeed, considerable progress has been made by ECNIS in integration reflected in the ECNIS inventory of techniques and expertise and harmonization of protocols. ECNIS network has formed an extraordinary multidisciplinary forum for exchange knowledge and expertise for almost 200 participating researchers. The Network was unique in the range of methodologies involved and the state of the art technology available in the laboratories of the ECNIS partners. None of the existing individual laboratories could provide such a level of multidisciplinary capabilities and research methods.
To accomplish its scientific aims ECNIS has been focusing on the field of biomarkers and their application in population studies as well as on the studies of mechanisms of gene-environment and gene-food interactions in carcinogenesis. ECNIS funds have been supporting scientific events including conferences, symposia and workshops – during five years; altogether as many as 75 workshops were organized with over 3 000 attendees, besides conferences with support or satellite ECNIS events. As many as 236 joint publications acknowledging ECNIS were published.
ECNIS network of excellence major performance indicators are presented in the table below.

Indicators	At the end of 5th year
Number of hits[1] on the ECNIS web site	2 710 000
Number of visits[2] on the ECNIS web site	636 000
Number of conferences/workshops	9/75
Number of videoconferences	75
Number of international conferences supported by the NOE	9
Number of NOE-internal attendees to conferences/workshops supported by the NOE	3180
Number of NOE-external attendees to conferences/workshops supported by the NOE	48
Number of ECNIS courses organized	13
Number of training courses outside ECNIS supported by the NOE	11
Number of NOE-internal attendees to training courses supported by the NOE	152
Number of NOE-external attendees to training courses supported by the NOE	386
Number of PhD students	75
Number of exchange of researchers/students	36
Number of joint projects	24
Number of joint publications	236
Number of citations of ECNIS NOE papers on Scopus	2 408
Citations in the media	88

[1] A hit is counted each time someone views a file (HTML file or graphic file) on the Web site.

[2] A visit happens when someone visits ECNIS website. It consists of one or more page hits.

"Compared to the baseline ECNIS successfully increases the rate of integration. The joint research performed qualifies as excellent. The project is conducted by scientists with a very good standing."

"ECNIS is well known in Europe and is considered by most partners to be a recognized brand in scientific circles concerned. ..."

Citation from Interim Impact Assessment of Networks of Excellence (NoEs) within the Food Quality and Safety Programme (a part of FP6) undertaken in the autumn of 2008/spring of 2009.(Cited further as COWI Report)

ECNIS researchers have performed in-depth evaluations of the state of science relevant to cancer etiology and have formulated corresponding proposals for future research. The conclusions of such deliberations were published in the series "ECNIS Reports" and disseminated in the form of workshops directed at a broad range of stakeholders.

ECNIS State of the Art Reviews

- Biomarkers of carcinogen exposure and early effects
  Edited by Peter B. Farmer, Jean M. Emeny
- Dietary vitamins, polyphenols, selenium and probiotics: biomarkers of exposure and mechanism of anticarcinogenic action
  Edited by Björn Åkesson, Per Mercke
- Epidemiological concepts of validation of biomarkers for the identification/quantification of environmental carcinogenic exposures
  Edited by Paolo Vineis, Valentina Gallo
- State of validation of biomarkers of carcinogen exposure and early effects and their applicability to molecular epidemiology
  Edited by Peter B. Farmer, Soterios A. Kyrtopoulos, Jean M. Emeny
- State of the art of genotype vs. phenotype studies
  Edited by Ari Hirvonen
- Mechanisms of chemical carcinogenesis and their impact on dose-response relationships - the examples of dioxin and benzo[a]pyrene
  Edited by Cornelia Dietrich, Franz Oesch, Barbara Oesch-Bartlomowicz, Carsten Weiss
- Ethics and Data Protection in Human Biomarkers
  Edited by Ludvine Casteleyn, Birgit Dumez, An Jamers and Karel Van Damme

As a result of common effort of the ECNIS researchers a number of initiatives important for European integrative research on cancer, biomarkers, and food have been initiated including so called "ECNIS added values":

1. Molecular Epidemiology and Cancer" (MEC) database,
2. Core facilities

3. European Standards Committee on Urinary DNA Lesion Analysis (ESCULA).
4. European Comet Assay Validation Group (ECVAG)
5. ECNIS Repository
6. ECNIS videoconferencing network
7. Training instruments

Within ECNIS a special effort has been made to facilitate the optimal utilization of already existing knowledge and data, through the construction of the "Molecular Epidemiology and Cancer" (MEC) database, which brings together the data of a number of population studies, thus providing increased statistical power to evaluate the influence of various environmental or other factors on cancer risk. Currently MEC incorporates: information on exposure, including nutrition and cancer chemoprevention, biomarkers of exposure, biomarkers of individual susceptibility, cytogenetic and other genotoxic damage, data sets of molecular epidemiology studies.

ECNIS Core facilities

Significant progress has been made towards the development of certain core facilities within ECNIS, which provide standardized chemicals, antibodies and analytical methodology for ECNIS partners. The core facilities of ECNIS have been set up for 1) antibodies, 2) reference materials and standards, and 3) analytical procedures, all in relation to the development and application of biomarkers of carcinogenesis. The intention during the tenure of the NoE has been to synthesize antigens for several compounds of interest to ECNIS members and to prepare antibodies to them; to synthesize a selected group of chemicals for use by ECNIS members in their biomarker procedures; and to establish a virtual facility of laboratories which have expertise in selected analytical techniques and who are willing to provide a service to others.

ECNIS funds allowed to finance 24 small grants - collaborative research projects. Among them two projects funded by ECNIS have been highly relevant to biomarkers comparison and validation and gave the background for new consortia initiatives:

European Standards Committee on Urinary DNA Lesion Analysis (ESCULA).

European Standards Committee on Urinary DNA Lesion Analysis (ESCULA). International cross-validation exercise of the measurement of urinary 8-oxodG. http://escula.org

ESCULA presently comprises 31 laboratories (including 4 SME), from 16 countries globally. This network focuses on validation of the methods for determination of urinary 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG), a well established biomarker of oxidative stress. Under ESCULA a urine biobank has been set up and works are going on to determine reference ranges for healthy and diseased people. Several studies have been already done (e.g. FASEB - in 16 labs - comparison of 19 different methods) including comparison of immunoassay and chromatographic assays of urinary 8-oxodG[2].

ECVAG- European Comet Assay Validation Group)

ECVAG at the moment comprises 12 laboratories from 9 different EU countries. The main objective of European Comet Assay Validation Group (ECVAG) project is to reach consensus on the likely level of DNA damage in lymphocytes and on procedures and values of the DNA repair incision assay, and additionally development of bona fide internal standard materials to minimise variability in the measures of comet assay endpoints. In a first round of ECVAG inter-laboratory validation trial we have described the variation in DNA damage and repair activity between laboratories and investigated whether or not the calibration of the assay would reduce the inter-laboratory variation.

ECNIS Repository

ECNIS Repository (http://ecnis.openrepository.com) has been developed in the form of electronic platform for storing and providing access to digital documents dealing with the matters of environmental hazards for cancer. It has an Open Access service, and enables reading, copying and printing full texts of the publications. It ensures efficient propagation of the scientific research results. ECNIS repository includes ECNIS Review, which is an annotated biomarkers bibliographic database covering relevant publications since 2006 focusing mainly on experimental or field studies on the development, validation and application of biomarkers of exposure to environmental carcinogens, biomarkers of effect and genetic susceptibility, and modulation by the environment, food or lifestyle of cancer risk or related biomarkers.

ECNIS videoconferencing network

Internet- operating ECNIS videoconferencing network is the greatest network of this kind built in Europe. It consists of 23-partner grids allowing point to point as well as multi points connections. Most of the devices are remotely monitored by the appropriate software.

> ECNIS has done an excellent job in developing its website. Events to interact with the research communities are significant but there is scope for reaching wider.
>
> COWI Report, 2009

Training in ECNIS

Provision of training opportunities within ECNIS was met through organizing and promoting training events: workshops, courses and advanced courses and on site trainings through the fellowship training program. Besides a web-based course titled 'Molecular epidemiology: principles and applications' has been developed. This course is targeted to researchers who take part in human studies, but lack basic education in epidemiology or molecular epidemiology. It consists of a number of well-defined modules designed by those groups within the network who have a well-organized system available for the implementation of e-learning materials.

Contribution to the co-ordination of high quality research

The stimulus for the ECNIS Network of Excellence during its planning in 2004 was that although several multinational efforts had been undertaken, research on the association of environmental cancer risk, nutrition and individual susceptibility was to a large extent highly fragmented within EU due to a lack of coordination of research sponsoring, which in turn negatively or adversely affected the conduct of work. The ECNIS NoE successfully contributed to the realization of an Integrated European Research Area by improving the coherence and coordination across the Community of relevant research activities in the field of biomarkers and molecular cancer epidemiology. The main focus of the NoE was to bring together researchers from relevant areas to identify data gaps and forward suggestions for improvements of existing techniques, to utilize common material as well as human resources in the conduct of new studies, and to lay the theoretical and practical foundations for merging European efforts. ECNIS enabled national systems to take on tasks collectively that they would not have been able to tackle independently, and also resulted in avoiding duplication of research. This goal was partially achieved by providing an integrated platform for the pooling of

resources and joint interdisciplinary activities in such diverse areas as the sharing of research infrastructures, the operation of an extensive exchange and training scheme, the preparation of a large number of high-level reports on the state of science and research strategy, the dissemination of new knowledge to policy makers and other stakeholders and, last but not least, the conduct of collaborative research.

The primary scientific objective of ECNIS was to achieve improved understanding of cancer risks posed by exposure to carcinogens present in the environment in its broadest sense, i.e. food, air, water and other environmental media, or resulting from lifestyle-related activities such as exposure to environmental pollution or tobacco smoke, and of the way that such risks are modulated by nutrition and individual genetic predisposition. In particular the Joint Research Programme of ECNIS focused on the development and validation of biomarkers of exposure and of bioindicators of disease for use in environmental cancer epidemiology, as well as on biomarkers of susceptibility. This led to the use of biomarker data to refine and validate pharmacokinetic and pharmacodynamic models and their potential application in risk assessment protocols. The NoE also systematically addressed the ethical impact of biomarker use. Recognising the importance of mechanistic information for the risk assessment process, the ECNIS network promoted mechanistic research to support these assessments. Finally the mechanism of modulation of cancer by dietary factors was investigated in order to provide a better basis for dietary advice, functional food formulation and chemoprevention trials.

A full understanding of environmental carcinogenesis and of the effectiveness of intervention procedures requires a highly cross-disciplinary approach, as all aspects from the nature of the exposure to the evaluation of human health effects and susceptibility need to be considered. The multidisciplinary nature of this work includes amongst others the disciplines of analytical and synthetic chemistry, molecular biology, food science, epidemiology, risk assessment and ethics. No single laboratory is capable of tackling the whole problem alone. ECNIS however provided the glue to bring together many of the top European institutes with a high degree of specialisation in individual relevant areas, and began the process of developing strategies for the combined use of these techniques, with the ultimate intention of making them available for pan-European cancer molecular epidemiology studies, i.e. studies of populations from different regions of Europe with different climates, pollution levels and dietary habits.
While the efforts of the ECNIS NoE met with a high degree of success, as acknowledged by all the annual Reviews which the project underwent, as well as by Interim Impact Assessment of Networks of Excellence (NoEs) within the Food Quality and Safety Programme (Report of March 2009) this was only the first stage of the process of creating a strongly integrated and viable European research network. Having drawn together the most relevant parties towards this task and also having identified the major gaps in available data and biomarker validation, it was realised as necessary to cement the integration on a more permanent. This idea has become a major goal of the ECNIS^2 project, which has received granting under FP7 call, aiming at continuing the integrative and coordinative works initiated during ECNIS network with an ultimate goal of transforming network into a virtual centre, the European Centre for Research and Education on Cancer, Environment and Food (ECRECEF).

Workpackage 1

INTEGRATION OF AVAILABLE RESOURCES AND SETTING UP QUALITY STANDARDS

Peter Farmer, WP1 Leader

The Network comprised 15 workpackages, which were divided into: Integrating activities (WP1-4), research activities (WP5-12), spreading of excellence (WP13, 14), management (WP15). The integrating activities were designed to bring together the resources and expertise available within Europe to allow full exploitation of the potential of molecular epidemiology in environmental cancer research. WP1 is responsible for integration of the available resources and activities, setting up quality standards and quality indicators for the comparison and assessment of data sets from different laboratories and developing a strategy for the use of biomarker methodology in collaborative human studies. These WP objectives were in accord with the first of the overall ECNIS objectives 'To overcome the fragmented nature of research in areas related to carcinogenesis caused by diet, the environment, occupation, or lifestyle, as well as exposure assessment, within Europe'.
All ECNIS partners were involved in WP1.

Panel of Experts for Methodology Standardisation

To ensure achievement of the objectives of WP1, a Panel of Experts for Methodology Standardisation[1] was established at the beginning of the programme to oversee the setting of quality standards and the comparison and standardisation of methodologies. The establishment of an ECNIS quality management system was essential so that standards could be set that would allow meaningful comparison of results between laboratories and ensure the high quality of data for dissemination outside the network. The Panel of Experts for Methodology Standardisation also contributed to the management of the core facilities and considered the arrangements for these after ECNIS.
Details of the quality criteria to be recommended for chemicals were developed at early workshops and at dedicated videoconferences, with the lead taken by Albrecht Seidel, BIU, on behalf of the Panel of Experts for Methodology Standardisation. A document was circulated for comment and, after incorporating amendments and suggestions from partners, was prepared for posting on the public website.
The final document is an integral part of the Integration and Resources link on the ECNIS website. Collaborating partners are strongly encouraged to use chemicals that fulfil the criteria, whether from the core facility or from commercial sources.

Surveys of equipment, techniques and projects

Detailed knowledge of the resources of Partners was crucial to the effectiveness of the Network and the best use of the materials and expertise available. In addition, identifying the projects being undertaken by Partners and identification of any areas that are underrepresented enabled better evaluation of joint research proposals and future planning and avoidance of duplication of effort. The establishment of links with organisations and groups outside ECNIS was facilitated by a knowledge of the programmes and projects under way elsewhere. To meet these needs, surveys of equipment, techniques and projects of ECNIS members and of activities globally were undertaken in the first year of the programme in association with WP2. Seventeen surveys were used to gather information on available techniques and an additional 21 surveys gathered information on ECNIS research projects.

[1] Peter Farmer (University of Leicester), Ari Hirvonen (FIOH, Helsinki), Jagadeesan Nair† (DKFZ, Heidelberg), Franz Oesch (University of Mainz), David Phillips (ICR, Sutton), Dan Segerbäck (Karolinska Institutet), Albrecht Seidel (BIU, Grosshansdorf), Frederik-Jan van Schooten (Maastricht University), Paolo Vineis (Imperial College, London)

The original survey results and the reports[2, 3] describing them can be accessed via the ECNIS website http://www.ecnis.org.

Core facilities

The development of core facilities was intended to promote the availability of technologies within the network that might be too expensive for an individual group to justify purchasing, or would require specialised expertise. They would also provide specialist materials that might be difficult or expensive to obtain commercially or were not of an acceptable or consistent standard. The sharing of resources, effort and expertise was hoped to increase the efficiency and cost-effectiveness of the work of the network.

The nature and feasibility of the proposed core facilities was the subject of much discussion at early workshops and videoconferences, taking into account the results of the early surveys of partners' resources and comments made at the annual review. The idea of a 'virtual' core facility for technologies was raised and the benefits to partners of collaboration versus providing a service were discussed. Finally, it was decided to set up three core facilities: chemical standards and reference materials (overseen by Albrecht Seidel, BIU), antibodies (Marcus Cooke, University of Leicester) and a virtual core facility for analytical techniques (Peter Farmer, University of Leicester), The first two core facilities require a major effort in chemical synthesis, which is performed at BIU. BIU has extensive expertise in the synthesis of metabolites of carcinogens and their DNA adducts and in the preparation of EU reference materials and pure PAHs.

A priority list of eight chemical standards and reference materials to be synthesised was compiled after an extensive process of consultation with partners. The list included standards for use in ^{32}P-postlabelling studies and nucleotides and nucleosides for characterisation of the antibodies to be produced by the Antibody Core Facility.

For antibodies partners were principally interested in modifications of DNA and, after consultation as described above, the following priority list was produced: 1,N^6-Etheno-2'-deoxyadenosine-5'-O-hemisuccinate; N^2-Ethyl-2'-deoxyguanosine-5'-O-hemisuccinate; N^2-(2'-Deoxyguanosin-8-yl)-2-amino-1-methyl-6-phenylimidazo[4,5-b]-pyridine(dG-C8-PhIP)-5'-O-hemisuccinate; 5,6-Dihydroxy-5,6-dihydrothymine (thymine glycol or dTg)-5'-O-hemisuccinate; 8-oxo-7,8-dihydro-2'-deoxyguanosine-5'-O-hemisuccinate; 1-thyminebutanoic acid cyclobutane dimer (dT<>dT). Three of these antibodies are currently in production.

An inventory of the technical resources already available among partners was thought to be of value to those looking for project collaborators or training. From a list of potential techniques, a short list, GC-MS, ICP-MS, LC-MS, NMR, Proteomics, Metabonomics, Microarray, ^{32}P-postlabelling and Genotyping, was compiled and partners who had indicated that they possessed the relevant techniques in the initial surveys were contacted to see whether they were prepared to share these techniques. The information obtained was compiled and circulated to all partners for input. The results were posted on the ECNIS website in 2008 with an update in 2009[4]. The data can be browsed by technique to determine which laboratories own specific equipment, whether or not it is available to others and, if so, the number of samples that can be processed and the cost.

[2] ECNIS infrastructure and capabilities. WP6 Internal Report 1; June 06

[3] ECNIS partner current and planned projects, WP1 Internal Report 1, Aug 2006

[4] http://www.ecnis.org/index.php?option=com_docman&task=cat_view&gid=104&Itemid=140

Interlaboratory validation

Multilaboratory studies are crucial to the purpose of ECNIS; hence it is important that data from collaborating laboratories can be compared and/or pooled. Within WP1, trials were carried out to compare techniques in different laboratories and to identify reasons for any variation found, to improve throughput and to allow establishment of recommended protocols where possible. These included:

- ITEPA – improving the throughput and efficiency of the ^{32}P-postlabelling assay
- ESCULA – European Standards Committee of Urinary (DNA) Lesion Analysis
- ECVAG – the ECNIS Comet Assay Validation Group
- Phenotypic DNA repair assays
- Genotyping

After consultation with partners protocols were produced for the ^{32}P-postlabelling assay and the Comet assay.

Workshops

Four workshops were held relating to establishing infrastructure for large-scale human studies. The first was held on 'Methodology Standardisation' in Athens in January 2006. The subject of the second workshop held in Heidelberg in September 2006 was 'Strategic plans for core facilities and quality standards and quality indicators'. WP1 also held a workshop on 'Standardised protocols' in Maastricht, February 2007 and on 'Methodology standardisation' in Athens in November 2007. Further communication on these topics was by regular videoconferences.

With regard to implementing large-scale human studies, WP1 organised a workshop on 'Practical considerations for use of biomarker methodology in collaborative human studies' in Barcelona, March 2008, one on 'Progressing from transitional to large-scale molecular epidemiology studies' in Cavtat, Croatia, and one on 'Prioritising, planning and implementing large-scale human studies', in Leuven, in March 2009.

A workshop on 'Achievements of WP1 and prospects for future use of ECNIS facilities was held at the final ECNIS meeting in Lodz, Poland. This included presentations on the ITEPA, ESCULA and ECVAG interlaboratory trials and the lessons learnt from them, the status of the core facilities, and prospects for the future.

Dissemination

For dissemination detailed reports of the workshops are available to partners on the ECNIS internal website. A series of articles on the workshops, written for the ECNIS Newsletter, which is distributed to stakeholders, are available on the public website.

A dedicated link on the ECNIS website, 'Integration', provides information on the antibodies and chemical standards and reference material being produced by the core facilities. The ECNIS quality criteria for chemicals and recommendations for the ^{32}P-postlabelling and comet methods can be downloaded from the site. Links are also provided to the work of ESCULA, and the guidelines being developed for reporting molecular epidemiology studies based on the STROBE initiative and a framework for evaluate human observational studies for quantitative risk assessment.

The many peer-reviewed publications arising from ECNIS-funded studies are listed at: http://www.ecnis.org/index.php?option=com_content&task=view&id=295&Itemid=151

The varied channels by which the work of WP1 is disseminated ensure that information can be readily accessed by biomonitoring experts, risk assessors and managers, regulators, public health practitioners, research funders, industry and the general public.

The activities of ECNIS will, as they continue and develop in ECNIS^2, increase the applicability of biomarker technologies in population studies, support multidisciplinary collaborative research efforts and, through the practical experience gained, make a valuable contribution to the development of environment and food related cancer research strategies in Europe.

Workpackage 2

WP2: INTEGRATED ORGANIZATION AND MANAGEMENT OF KNOWLEDGE AND INFORMATION FLOW

Robert Klarecki, WP2 Leader

Nowadays internet network is one of the most growing sources of up-today information in any field. The scientists constitute the large target for data spreading in the internet. In case of the scientific consortiums where the members are distributed over the whole Europe (or even the world) there exists the need for appropriate means of data exchange. The internet, with such services as e-mails, web servers, workgroup places and many others offers a very useful solution. In the time of internet, the idea of "global village" has been implemented to the full length – no borders, no time consuming, "on-desk" data transfer, video- and tele-conferencing regardless where the participants are.
ECNIS network activity was focused to prepare the mechanisms which allow to spread any ECNIS information to public internet users and to support ECNIS members in their group work. Beside the typical internet applications (i.e. e-mail, website), there are some ECNIS specific services running for the project members, i.e. voting server, questionnaires server and workgroup internal server.
All partners were involved in the Workpackage 2.

The Information Technology is not the goal itself but only a toolkit for achieving the scientific research goals. But it really may be helpful and ECNIS NoE is proud of some of the achievements:

1. Unified network for exchange of ECNIS information – several different sources of information were combined together to form a single place to access them all in a unified manner. And the whole system has flexible architecture, allowing all authorized users to modify content of the ECNIS Web services directly from the web browser without involving webmasters. As a result all ECNIS Partners and many other interested users (more than 500 were registered in the ECNIS Portal's database) gained easy access to a huge number of documents and other forms of information (more than 1100 articles were published within the system). All the ECNIS Partners actively used all IT tools prepared for them - increasing the overall ECNIS Team effectiveness.
2. Unique Secure Internet Voting system – designed by Netix on individual demand of ECNIS NMB, allowed all ECNIS Members to easily vote over the Internet using their own personal computers equipped with standard web browser. There was no need to meet in the same place or even in the same time to take part in a voting. The technology implemented in the application provided the highest level of encryption, thus making the voting secure, reliable and indisputable.

3. Noticeable time savings as a result of the ECNIS Videoconferencing Network implementation - Successful implementation of multi-point videoconferencing system provided ECNIS participants with capabilities of natural interaction, discussing issues and solving problems in a highly efficient manner. The precise simulation using all the collected statistics (frequency of meetings, number and locations of the participants, etc.) shows that the total travelling costs would exceed the value of the ECNIS videoconferencing equipment right after 1.5 year from the project beginning. It is rather not appropriate to estimate the ROI (Return On Investment) for a scientific research but the time saving is irrefutable. Of course, there are more important benefits of decreased travelling, like increasing personal safety and reducing the environmental "foot print". But there is another observation indicating the importance of the videoconference meetings, especially multi-point meetings: the personal schedule of every involved scientist is extremely busy for many months ahead and it is really difficult to find a common time available for conventional meeting (travelling across the Europe usually takes 2 days). The videoconference takes only 2 or 3 hours and there is no need to leave the Institute. In many cases there were scientists wishing to take part in a videoconference even when they were out of the Institute or even abroad. In that cases Netix engineers used every available communication paths (mobile phone, Skype) to provide ability to participate in the videoconference – but even if the form of presence of that person was limited to audio only, the meetings were really effective. One of the bright examples was the last Gender Issue Panel videoconference, where one of the participating woman was able to take part in the discussion with debaters in distant European countries during her maternity leave, using her notebook with Skype and a web camera at home, still being able to take care of her lovely child. The total duration of the 46 multipoint meetings was 53 hours and 16 minutes.

4. ECNIS Repository (http://ecnis.openrepository.com) is an electronic platform for storing and providing access to digital documents dealing with the matters of environmental hazards for cancer. It is an Open Access service. It enables reading, copying and printing full texts of the publications. Ensures efficient propagation of the scientific research results. The authors may deposit their works in the Repository through the editor (in the Scientific Library of the Nofer Institute of Occupational Medicine - NIOM) or directly on-line. The author submits his/her work in the form of a pre- or postprint. The ECNIS Repository is registered in the Directory of Open Access Repositories (OpenDOAR), Registry of Open Access Repositories (ROAR) and in the DRIVER Project - a shared platform for document repositories of the European Research Area. Publications were collected in three Collections, which are distinguished by the formal nature of the documents: Articles (186), Chapters (31), Reports (7)

Workpackage 3
JOINT TRAINING AND MOBILITY PROGRAM

Paolo Boffetta, WP3 Leader

WP3 was one of the four workpackages dealing with integrating activities. These activities were designed to bring together the resources and expertise available within Europe to allow full exploitation of the potential of molecular epidemiology. WP3 did this through the organisation of joint training activities and sharing of laboratory facilities across ECNIS member institutions. These were achieved through three main activities: (i) training fellowships, (ii) training courses and workshops and (iii) providing opportunities for PhD students to attend and present their work at scientific conferences. Training fellowships funded researchers to spend a period of time in another laboratory/institution, through which both knowledge and technologies could be shared. The organisation of training courses and workshops aided the sharing of knowledge and expertise between ECNIS scientists and institutions.

WP3 was led by partner 22, the International Agency for Research on Cancer (IARC) with the contribution of other partners.

Training fellowships

Training fellowships were awarded to researchers at ECNIS institutions to spend a period of between 2 weeks and 6 months at another ECNIS institution, to allow the sharing of knowledge, expertise and laboratory facilities. During each of the 5 years of ECNIS, training fellowships were advertised within ECNIS member institutions and on the ECNIS website, inviting researchers to apply. Applicants agreed a research proposal with their home and potential host institutions for their application. Applications were independently reviewed and scored by senior scientists at IARC, Imperial College London, the Institute of Cancer Research (UK), Athens University, Nofer Institute of Occupational Medicine (Poland) and Vrije Universiteit Brussels (Belgium). This selection committee then met (via telephone conference) to discuss scores and decide on fellowships to be awarded.

Over the 5 years a total of 19 training fellowships were awarded, funding a total of 49 months of research (an average of 10 weeks per fellow, up to a maximum of 6 months). Examples of the topics of research include “Mediterranean diet and risk of gastric adenocarcinoma”, “EPHX1 gene modify and non-malignant pulmonary diseases”, “Glutathione conjugates of PAHs and CACO-2 cells”, “Using aggregated evidence from observational studies to assess benzene leukemia exposure response curve” and “The role of nicotinic acetylcholine receptor in lung cancer.”

The training fellows were awarded to researchers at various levels of their scientific careers, with a greater focus on those beginning their careers. Seven training fellowships were awarded to PhD students, 8 to post-doctoral fellows and 4 to junior/mid-career scientists. Typically, training periods were spent in another laboratory that had equipment or expertise not available in the fellow’s home institution.

The experiences of the fellows during their training experience were evaluated in year 4. The fellows evaluated their fellowship period through completion of a questionnaire asking about their experience, and scoring it based on various criteria (knowledge gained, skills acquired, ability to speed up research, support in host institution, potential of future collaboration). There was an

overwhelming positive response to this questionnaire by nearly all fellows. They found the program to be 'good' or 'very good' and that the period was beneficial to them. For many (70%), their research benefitted from new technologies in the host institutions, for example use of Affymetrix technology and new techniques in proteomics. Most fellows felt that their research gained momentum from the exchange period, e.g. by learning new statistical software or methods to analyze pooled genetic data. Some fellows specifically said that they felt their research would not have been possible without the program. Fellows were asked what were the best and worst features of the exchange period and how these could be improved. The best features included an efficient focused use of time and establishing research collaborations. Some fellows felt that the knowledge they gained was not only useful for themselves, but that they would be able to transfer this to their colleagues back in their home institutions. The effects of this exchange program therefore go beyond the fellow concerned.

Training workshops and courses

Workshops and courses were held throughout the 5 years. They were organised by ECNIS scientists working throughout the network, advertised on the ECNIS website and emailing list and open to attendance to all ECNIS researchers. An average of about 20 courses and workshops was held each year. The courses varied from shorter one or half-day workshops which were often in connection with methods developed within other workpackages, to longer full-week courses. A major ECNIS-funded one-week training course on Molecular Epidemiology was held each year, at Imperial College London. Not only a useful opportunity for face-to-face learning, but this course also contributed to workpackage 13 on the dissemination of knowledge to the scientific community, through adapting it for online learning available to interested researchers who could not attend.

Courses covered a very wide range of topics and research methods needed by ECNIS researchers, from exposure assessment, molecular and genetic epidemiology to statistical methods. Examples of course topics are: Oxidative stress - Disease, Methods and Concepts; Standardization and validation of the comet assay for the measurement of DNA damage and DNA repair phenotype; Methods and guidelines for the Development of spectral mutation databases in cancer; Advanced Course on A Critical Review of Environmental Mutagenesis and Carcinogenesis; - Novel Biomarkers and Techniques for Large Prospective Studies.
All together over 550 students took part in training workshops and courses.

Opportunities for PhD students

A particular focus on training for PhD students has implemented through the organisation of PhD oral and poster presentations at annual meetings of ECNIS and at workshops. For the annual meetings, PhD students were invited to submit abstracts and the best five were selected to be presented orally. The abstracts were evaluated by the same selection committee that selected the training fellowships. Some of the meetings where sessions for PhD students were programmed include the International Symposium on Integrative Molecular Cancer Epidemiology (IARC France, July 2008), the ECNIS 4th annual meeting in Leuven, Belgium (March, 2009) and a workshop on 'Biomarkers and Cancer' in Porto, Portugal (September, 2009).

Workpackage 4

CONSTRUCTION OF A KNOWLEDGE DATA BASE ON MOLECULAR EPIDEMIOLOGY AND CANCER (MEC)

Paolo Vineis, WP4 leader

The objective of WP 4 was the setting up and implementation of a knowledge data base on Molecular Epidemiology and Cancer (MEC). The database MEC has been established during the first two years and a pooled analysis of DNA adduct studies has been successfully completed. Work during the third and fourth year was focused on collecting biomarker data from ECNIS partners with the aim of pooling data when feasible. The MEC software was updated and disseminated. A Bayesian statistical tool for meta- and pooled analyses was developed and a workshop was organized on the theme. In addition the MEC database was extended by inclusion of other biomarker data, partly from other data sets (NIEHS, EPA and EBI).

WP4 was lead by partner ICL, UK with contribution from: ICO , Spain; FIOH, Finland; NIEH, Hungary; National Hellenic Research Foundation, Greece; DKFZ, Germany; IRAS, Netherlands, UM, Netherlands; Collegium Medicum, Poland; NIOM, Poland; University of Copenhagen, Denmark; DKFZ, Germany; ISI Torino

Work performed and end results

We have completed the development of the concept of MEC, of the tools for its implementation, a demonstration project for the pooling of data (DNA adducts, paper published in Carcinogenesis, 2008), and a demonstration project on meta-analyses based on DNA repair (paper published in JNCI, 2009). We have developed a strategic document which describes the procedures that have been followed in the creation of the central database. MEC currently contains data from 19 datasets belonging to 15 European laboratories. Collateral methodological initiatives have been taken (e.g. workshop on GWAS: Vineis et al, Mutagenesis, 2008).

We have currently in the MEC datasets from ECNIS partners on oxidative DNA damage, dietary biomarkers, DNA adducts, bladder cancer, and air pollution. We are currently rapidly enriching the MEC, and these efforts will be intensified during ECNIS^2 project. Finally, MEC will be extended to other biomarkers: inclusion of DNA repair data base, inclusion of literature searches and original data on specific biomarkers to be agreed upon, and links to other more complex biomarkers databases such as transcriptomics, proteomics and metabolomics will be made. This will be done partially by including biomarkers available from other data sets (NIEHS, EPA, EBI) and partially on the basis of the partners' data bases.

The MEC database stores, organizes and links all the pedigree/individual, genomic, phenotypic and disease status information used in gene mapping studies. We organized data as follows:

1) Three main databases to store imported data ready for analyses: these tables share some common data (e.g. SNP and gene information, biomarkers description, covariates and so on), but are kept distinct in function of their origin. We maintain a database of human peer-reviewed publications with their results, which collects data in a format immediately available to meta-analyses; then we also maintain other two sources of raw data, the first to store biomarkers from partners' projects and to map data to standard measures, the latter to store (ongoing test) data from GWAS.

2) A document manager (DMS) to archive original datasets with author level access control. This application is not focused on data analyses, but only on storage and conservation.
3) A bibliographic tool (set up on a per project criterion) to integrate data with study information and references.
4) A set of statistical tools: R code developed for meta-analyses and integrated in the web application, and SAS scripts for data pooling and regression (externally run)
5) A local copy of external biological databases. These tables can be accessed as a source for annotating results or directly in the analytical phase to integrate feature exploration.

In addition we produced a MEC handbook which is a comprehensive document summarising all features, potentialities, data, and results coming from the MEC database. To allow meta- and pooled-analyses, we have developed and implemented a website (http:// www.episat.org), and an application (EPISAT, Epidemiological Information Storage and Analysis Tool) that allows researchers to:

1. Store, maintain and retrieve epidemiological information and databases.
2. Analyse and compare summary information.

Over the years of activity within ECNIS we published 3 papers on data coming from the MEC database, whose main results are outlined below:

"DNA adducts and cancer risk in prospective studies: a pooled analysis and a meta-analysis." (Carcinogenesis. 2008 May;29(5):932-6. Epub 2008 Mar 14.)
Bulky DNA adducts are biomarkers of exposure to aromatic compounds and of the ability of the individual to metabolically activate carcinogens and to repair DNA damage. Their ability to predict cancer onset is uncertain. We have performed a pooled analysis of three prospective studies on cancer risk in which bulky DNA adducts have been measured in blood samples collected from healthy subjects (N = 1947; average follow-up 51-137 months). In addition, we have performed a meta-analysis by identifying all articles on the same subject published up to the end of 2006, including case-control studies. In the pooled analysis, a weakly statistically significant increase in the risk of lung cancer was apparent (14% per unit standard deviation change in adduct levels, 95% confidence interval 1-28%; using the weighted mean difference method, 0.15 SD, units higher adducts in cases than in controls). The association was evident only in current smokers and was absent in former smokers. Also the meta-analysis, which included both lung and bladder cancers, showed a statistically significant association in current smokers, whereas the results in never smokers were equivocal; in former smokers, no association was detected. The results of our pooled and meta-analyses suggest that bulky DNA adducts are associated with lung cancer arising in current smokers after a follow-up of several years.

"A field synopsis on low-penetrance variants in DNA repair genes and cancer susceptibility." (J Natl Cancer Inst. 2009 Jan 7;101(1):24-36. Epub 2008 Dec 30.)
Several genes encoding for DNA repair molecules implicated in maintaining genomic integrity have been proposed as cancer-susceptibility genes. Although efforts have been made to create synopses for specific fields that summarize the data from genetic association studies, such an overview is not available for genes involved in DNA repair. We have created a regularly updated database of studies addressing associations between DNA repair gene variants (excluding highly penetrant mutations) and different types of cancer. Using 1087 datasets and publicly available data from genome-wide

association platforms, meta-analyses using dominant and recessive models were performed on 241 associations between individual variants and specific cancer types that had been tested in two or more independent studies. The epidemiological strength of each association was graded with Venice criteria that assess amount of evidence, replication, and protection from bias.
Thirty-one nominally statistically significant (ie, P < .05 without adjustment for multiple comparisons) associations were recorded for 16 genes in dominant and/or recessive model analyses (BRCA2, CCND1, ERCC1, ERCC2, ERCC4, ERCC5, MGMT, NBN, PARP1, POLI, TP53, XPA, XRCC1, XRCC2, XRCC3, and XRCC4). XRCC1, XRCC2, TP53, and ERCC2 variants were each nominally associated with several types of cancer. Three associations were graded as having "strong" credibility, another four had modest credibility, and 24 had weak credibility based on Venice criteria. Requiring more stringent P values to account for multiplicity of comparisons, only the associations of ERCC2 codon 751 (recessive model) and of XRCC1 -77 T>C (dominant model) with lung cancer had P <or= .0001 and retained P <or= .001 even when the first published studies on the respective associations were excluded. This synopsis offers a model to survey the current status and gaps in evidence in the field of DNA repair genes and cancer susceptibility, may indicate potential pleiotropic activity of genes and gene pathways, and may offer mechanistic insights in carcinogenesis.

"Bulky DNA adducts in white blood cells: a pooled analysis of 3600 subjects" (Cancer Epidemiol Biomarkers Prev. 2010 Oct 4. [Epub ahead of print])

This paper considers the epidemiological contribution of DNA adducts as an example of markers for use in chemoprevention studies, and highlights the potential biases inherent in the conduct of epidemiological studies with molecular markers. Although adducts have been interpreted mainly as biomarkers of exposure, 'bulky' DNA adducts such as those measured by 32P-postlabelling or ELISA in white blood cells are more correctly interpretable as markers of cumulative unrepaired DNA damage. The latter concept can prove useful in cancer epidemiology, since it is consistent with existing knowledge on the importance of duration of exposure in the etiology of chemically-induced cancers. Increasing evidence suggests that in addition to prolonged exposure to genotoxic chemicals, inter-individual variability in carcinogen metabolism and DNA repair is predictive of cancer risk. Also from this point of view, measurements of 'bulky' DNA adducts can be useful as biomarkers for studies in populations, since they express the amount of carcinogen linked to DNA after repair, taking into account individual repair capacity. Finally, we suggest a theory of causality based on the work of Wesley Salmon and the concept of 'propagating mark', which is particularly attractive for molecular epidemiologists.

DNA adducts and vitamins (in press)

There is some evidence that dietary components that are rich in antioxidant and vitamins are inversely associated with DNA adduct levels induced by environmental carcinogens such as polycyclic aromatic hydrocarbons, although the epidemiologic data are inconsistent. This study addresses the association between vitamins, DNA adducts and smoking. A combined analysis of individual data on the association between bulky DNA adducts and dietary vitamins was conducted. A Medline search was performed to identify studies on healthy subjects in which smoking and vitamins intake information were available, and bulky DNA adducts were measured in peripheral blood with 32P-postlabelling. Eight published studies met the eligibility criteria, and individual data from 7 data sets including 2758 subjects were obtained. GSTM1 and GSTT1 were also available on all the subjects. Vitamin E was inversely significantly associated with DNA adducts after adjustment for possible confounding factors. Vitamins A and C were not independent predictors of DNA adducts. A stratified

analysis showed that vitamin A had a significant inverse association with DNA adducts in ever smokers only. This result is relevant to planning any future chemo-preventive interventions directed to high risk subgroups of the population, for cancer prevention.

The objective of WP 4 was the finalisation and implementation of a knowledge data base on Molecular Epidemiology and Cancer (MEC) incorporating 1) information on exposure, including nutrition and cancer chemoprevention, 2) biomarkers of exposure, 3) biomarkers of individual susceptibility, 4) cytogenetic and other genotoxic damage, and suggestions to incorporate and to link other more complex biomarkers dataset such as 5) transcriptomics (DNA microarrays, SAGE etc), proteomics and metabolomics have been made. The same database also contains the data sets of 6) molecular epidemiology studies in such a way that MEC would enable their evaluation according to a formal and common protocol, as well as facilitate their pooling with the results of other studies.
Today, the Molecular Epidemiology of Cancer Database (MEC) is a repository of datasets of molecular epidemiology that has been set up to address several important topics arising in cancer research: (a) the predictive value of existing biomarkers, measured in large scale epidemiological studies; this is explored through well-conducted meta- and pooled analyses of the existing data; (b) biomarker validation, through the comparison of different laboratories and techniques. These uses of the MEC need to be considered in the light of the new challenges posed by biomarker research.

Workpackage 5
SCIENCE MONITORING AND REVIEW (SMR)

Soterios Kyrtopoulos, WP5 Leader

While ECNIS, as a FP6 Network of Excellence, had as its main objective the promotion of viable integration of European research in the area of environmental carcinogenesis, the maintentance of high scientific standards in the research activities conducted within the network, and the formulation of a long-term research strategy that was in line with international developments, was also given high priority. This task was assigned to WP5 ("Science monitoring and review; SMR") which aimed to focus on the "excellence" part of the Network's aims.

The specific objectives of WP5 were:
To follow progress worldwide in the area of environmental cancer and its modulation by diet and genetic susceptibility, and provide support to ECNIS in the formulation of its research strategy in this area
To follow and assess the progress of ECNIS research, ensuring that they retain a high quality, are in harmony with ongoing developments and adequately respond to emerging challenges
To conduct an internal assessment of ECNIS papers, reports and projects

While the core of the SMR Task Force consisted of the leaders of research WPs (WP6-12), all ECNIS partners participated in the activities of WP5. The overall objective of WP5 was to help maintain a high quality of science within ECNIS by a) monitoring and assessing the research and other scientific activities of the network, b) following scientific progress and emerging issues worldwide in the area of ECNIS interest and providing guidance for the formulation of the network´s research policy.

To achieve its objectives, at the outset of the project the SMR TF prepared guideline and policy documents for the assessment, conduct and reporting of collaborative research activities within the network, as well as for the evaluation and publication of ECNIS reports. It was also active in putting into effect these regulations in connection with the evaluation of research activities and reports produced during this period.

To facilitate the formulation of research strategy, WP5 organised a series of workshops at which the state of science (including emerging issues and opportunities) in specific areas of biomarker research was reviewed, problems and bottlenecks were identified and ways to overcome them proposed. In this context, the SMR TF was instrumental in formulating the directions of research activities conducted within ECNIS, including the selection of specific priorities for the various calls for research projects published by ECNIS and the evaluation of the achievements of these projects.

Research activities within ECNIS

At the outset of the project the foundations for the operation of research were laid through a number of activities, including the mapping of partner interests, projects, expertise and infrastructures, the identification of immediate research priorities by the various workpackages and the initiation of collaborative research projects. These activities served the long-term aim of building on partner complementarities to create an integrated network with long-term prospects of viability which would, at the same time, act as a leading force internationally in terms of conducting high-quality research and drawing the lines of future research policy in the area of environmental carcinogenesis.

Guidelines for the conduct of research within ECNIS, which included procedures for the evaluation and reporting of research projects, were formulated. Based on this background, collaborative research activities were conducted in the form of two types of projects: projects partly funded from the budget distributed to the various partners ("type A" projects) and projects partly funded through a mechanism of calls for relevant proposals oriented in specific priority areas ("type B" projects). During the 5 years of ECNIS activity, 3 calls for "type B" projects were published, leading to the conduct of 24 projects.
The SMR Task Force supervised the evaluation and selection procedures in both calls for type B projects published so far. Following a first call for type B projects near the end of the first year, 10 projects were evaluated positively. A second call was published during the second year which, in contrast to the previous one, was based on a specific set of priority topics selected during a strategic research planning meeting, as a result of which 9 projects were granted. Finally in last 2 years a small number mostly follow-ups of previously granted projects was supported following an open call.
All projects submitted intermediate and final progress reports.

ECNIS Reports and publications

A policy document regarding the publication of ECNIS Reports was formulated at an early stage of the project. This document provided guidance regarding the fate (publication as an internal document or for open circulation, in printed form or on the website) of each type of document (ECNIS Reports, Review, Workshop Report etc) produced by ECNIS and defined an appropriate procedure for evaluation prior to publication. This policy was followed for all documents published and involved peer review of all reports by experts from within or from outside the network, depending on the type of report and its mode of publications. During the 5 years of ECNIS 7 reports were published in the ECNIS Reports series.

In addition to the above, a large number of scientific publications arising from ECNIS activities (reviews, experimental or population studies conducted in the context of ECNIS projects) were published in international, peer-reviewed journals. In all, 236 papers acknowledging the support or involvement of ECNIS have been published.

Research strategy

Following the mapping, during the project's first year, of the interests, expertise and infrastructures of the ECNIS partners, and the evaluations of the state of science conducted within the individual WPs, steps were taken towards the development of a long-term research strategy for the network.

A "strategic planning meeting" to discuss ECNIS research strategy and define immediate priorities was organised in September 2006, at which the prospects of future ECNIS research, particularly in the context of FP7, were discussed and general objectives defined. In this context, and with the aim of preparing for a move towards large-scale molecular epidemiology studies over the next few years, five specific priorities were identified, which formed the basis of a subsequent call for collaborative research projects.

During the project's duration WP5 organised a number of workshops to review the state of science and identify emerging trends and opportunities
Finally, in the context of the development of the research strategy of ECNIS and the improvement of the network's links with the rest of the European research community, and in accordance with the

Technical Annex, steps were taken by the Management Office for the creation of ECNIS Collaborative Centres. For this purpose, the SMR Task Force prepared a policy document setting out the criteria for the selection of such centres and the procedures for the evaluation of applications.

ECNIS Review

After deliberations between the partners in the early phase of the project, and based on the experience gained during the first year of the network's operation in relation to the production of reviews and scientific reports, the objective of ECNIS Review was redefined, relative to the originally stated aim, as the production of an annotated bibliographic database of research on biomarkers of environmental carcinogenesis.

For the preparation of the database, a strategy for searching Medline, using suitable search strings, partly based on the corresponding search string employed in the EPA Biomarkers Database and adapted to the specific interests of ECNIS, was developed as described in the previous progress report. This search focuses on experimental or field studies on the development, validation and application of biomarkers of exposure to environmental carcinogens, biomarkers of effect and genetic susceptibility, and modulation by the environment, food or lifestyle of cancer risk or related biomarkers. The search included studies of cancer epidemiology, even if not involving biomarkers, whereas studies on environmental presence of carcinogens, exposure assessment, toxicity evaluation and mechanisms of carcinogenesis were not covered at this stage unless they included a biomarker component. The initial output of such a search was manually screened to remove false positives, leading to a final selection of 500-800 publications each year. Following retrieval along with all their associated MEDLINE keywords and abstracts, these publications were classified into different areas (multiple classification employed when necessary) roughly corresponding to the topics covered by different research WPs of ECNIS. Subsequently publications were further screened for suitability for annotation with standardised sets of information fields in addition to those accompanying the original references. These standardised sets of information fields were identified after consultation with ECNIS partners with appropriate expertise and contain important items of information of use for potential users in a form which will facilitate the publications' usefulness in evaluating the state of science in specific areas.

The database was uploaded initially on the internal ECNIS website and subsequently on the ECNIS Repository section of the website, and partners were invited to make use of it, proposing ways for improvement or further development. The feedback obtained from partners indicated that, while the potential usefulness of the database was recognised, there was need for significant improvements, especially in relation to the standardisation of the annotation procedures (selection of terms, use of standardised language etc).

Having succeeded to a significant degree in the objective of forging strong links between its partners and of acting as a platform for the launch of new research initiatives, and following the approval of the FP7 proposal for a follow-up project, the major challenge lying ahead is to establish structures and activities that can ensure the long-term viability of a research network which can conduct world-class research and chart a strategy for future research aiming at the prevention of environmentally related cancers.

The most important difficulty in achieving the major NoE objective of the creation of a long-lived research consortium is the absence (with the exception of the European Union) of opportunities for significant funding support of such multi-national platform.

Workpackage 6

DEVELOPMENT AND VALIDATION OF BIOMARKERS OF EXPOSURE AND OF BIOINDICATORS OF DISEASE FOR USE IN EPIDEMIOLOGY

Peter Farmer, WP6 Leader

Workpackage 6 was one of the Research Activities workpackages of ECNIS. The Joint Research Programme of the Network was intended to promote execution of high-quality research by making use of the multidisciplinary expertise and infrastructure of the partners, as well as providing the opportunity for conducting molecular epidemiology research at the pan-European scale.
Research Activities WPs were focused on the exploitation of technological and scientific innovation in nutrition and molecular cancer epidemiology, with an ultimate use for cancer risk. The main objectives of WP6 included planning for integration and research for biomarkers of exposure and bioindicators of early effects of carcinogens, and for their implementation in human disease. In particular WP6 was responsible for

- defining the state of validation and applicability of biomarkers of carcinogen exposure and bioindicators of disease in molecular epidemiology that were relevant to ECNIS,
- promoting new opportunities for collaboration and synergy, formulation and conduction of new projects,
- developing the strategies for integration and research in the area of the development and validation of biomarkers and for their implementation in human studies,
- investigating new technologies for biomarkers of carcinogen exposure and effect.

ECNIS partners 1, 2, 4-14, 16-19 are involved in WP6.

Review of biomarkers of carcinogen exposure and bioindicators of disease and examination of their state of validation and applicability in molecular epidemiology.

The first objective of WP6 that was addressed in years one and two was to find out the current state of validation and applicability of biomarkers of carcinogen exposure and bioindicators of disease in molecular epidemiology.
A state of the art review was written by 29 contributors from the ECNIS partners on biomarkers of carcinogen exposure and early effects. The purpose of this review was to summarise the current situation regarding the types and uses of biomarkers of exposure and effect for the main classes of food-derived genotoxic carcinogens, and to consider some aspects of the intercomparison between these biomarkers. The biomarkers of exposure and early effects of carcinogens that have been most extensively developed are those for genotoxic agents and for compounds that generate hydroxyl radicals and other reactive radical species, and it is on these that this review was mostly concentrated. The main areas covered were sensitivity and specificity of techniques for the identification of biomarkers, oxidative DNA damage, specific biomarkers related to food, long lifetime biomarkers and correlations amongst biomarkers. One major overall conclusion was the need for further validation of biomarkers.
A second review was written by 21 contributors from the ECNIS partners on the state of validation of biomarkers of carcinogen exposure and early effects and their applicability in molecular epidemiology. For the potential of biomarkers to be realised, it is essential that they undergo the critical process of validation. Biomarker validation encompasses two different levels: firstly, the analytical and operational methodology, and secondly the inherent ability of biomarkers to reflect the chemical nature, level and duration of an individual's exposure and/or the degree of disease risk. This review

focuses on the state of validation of the most important biomarkers of exposure to food-related carcinogens or their early effects and identifies the gaps in knowledge that remain.
Both of these reviews were published as part of the ECNIS report series.

Surveys of partners resources and research

The ECNIS programme was designed to bring together the resources and expertise of its partners to enable the undertaking of collaborative projects and facilitate large-scale molecular epidemiology studies. This was addressed in conjunction with WP1 by partners completing on-line questionnaires gathering information on available techniques and research capacities, current and planned projects in the field of biomarkers of carcinogen exposure and bioindicators of disease, and major on-going research efforts in the field of biomarkers of carcinogen exposure and bioindicators of disease within as well as outside Europe.
Seventeen surveys covered equipment, techniques and resources. Topics included: ^{32}P-Postlabelling, ELISA, Mass spectrometry, FISH, Comet assay, Genotyping, 'Omics, Dietary components; Animal models, Chemical standards and Antibodies. Twenty-one surveys gathered information on projects in which ECNIS partners were involved and WP6 prepared a report of projects on biomarkers of carcinogen exposure and bioindicators of disease. Awareness of similar work being undertaken internationally was important to ECNIS so as to enable links to be made with other scientists and to allow the best use of global resources. Hence, information on research efforts relevant to ECNIS was compiled by WP1 from the websites of government bodies and agencies, national and international charities and non-governmental organisations and WP6 provided additional information to this.

Conduct of research

Type B projects on biomarker development and validation exercises were the main research activity of WP6 partners. The funded projects that were particularly relevant to WP6 included studies on biomarkers for alcohol, PAHs, N-nitroso compounds and mycotoxins, and investigations on DNA repair phenotype, transgenic animals, immunological markers, selenium, biomarkers of long term exposure, genetic and epigenetic alterations in plasma DNA, and mechanistic factors.
The list of funded type B projects is given on ECNIS webpage (under Research) and these are decribed in more detail in deliverable D6.12 'The final Report of WP6 activities during years 2005-2010'.
In summary, a number of the first call projects were concerned with the development and validation of biomarkers, including work on collagen adducts in lung as a biomarker of cumulative exposure to tobacco smoke; the role of endogenous formation of N-nitroso compounds in gastrointestinal carcinogenesis; the use of urinary 8-oxo-7,8-dihydro-2'-deoxyguanosine as a non-invasive biomarker of oxidative damage to DNA (ESCULA); methods for detection of genetic and epigenetic (methylation) changes in DNA extracted from the plasma of healthy subjects and cancer patients; and the study of the use of transformed lymphoblastoid cell lines as a surrogate for peripheral blood mononuclear cells in DNA repair assays. Other Type B projects addressed mechanistic issues underpinning biomarker development, such as the biological pathways affected by benzo[a]pyrene and the dioxin TCDD and the induction of oxidative stress by PAHs and its modulation by food components. The emphasis of ECNIS on diet was represented by three further projects, exploring the mechanism by which fatty foods promote intestinal cancer, the short-term effects of selenium supplementation on global gene expression in humans, and the relationship of glutathione-S-transferase genotype (and hence ability to eliminate isothiocyanates from e.g. cruciferous vegetables) with lung cancer in a case-cohort embedded in EPIC.

The second-round Type B projects included studies of alcohol consumption and the use of acetaldehyde adducts as a biomarker of exposure, a search for immunological markers of non-Hodgkins lymphomas, a study of the contribution of diet, cell turnover and DNA repair to the production of urinary products of oxidatively damaged DNA, the role of exposure to PAHs in the high incidence of oesophageal squamous cell carcinoma in a province of Iran, and the development of biomarker-based estimates of cancer attributable fractions and their application to specific agent-cancer associations. Three second-round Type B projects involved inter-laboratory trials of methodology: an interlaboratory trial of the ^{32}P-postlabelling assay (ITEPA) for use in molecular epidemiology was carried out; the ECNIS Comet Assay Validation Group (ECVAG) investigated variations in procedures and the levels of DNA damage and repair found by different trial members; and phenotypic nucleotide excision repair assays were developed and validated for molecular epidemiological studies

The third call focussed on projects related to the ECNIS main goals, based on work done in the context of type B projects granted during previous calls. The analytical methods (^{32}P-postlabelling and LC-MS/MS) developed within the previous ECNIS type B project were used to validate the usefulness of N^2-ethylidene-dG as a biomarker of alcohol consumption. The stability and repair of this DNA adduct were studied in normal and repair deficient cell lines and the stability in humans was tested in an intervention study. Two projects continued the work of ECVAG and ESCULA. The former developed and tested reference conditions for the comet assay, assessed variation within and between laboratories and in different countries and continued development of an internal standard. The second aimed to improve intra-assay and inter-assay agreement, to investigate intra-individual variability and to optimise sample collection and normalisation. In a mechanistic study, new transgenic mouse models were used to study the metabolism of environmental and dietary carcinogens, specifically CYP-mediated xenobiotic metabolism. In addition, a novel mass spectrometry based method for the detection of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)-DNA adducts was developed that could be used in this model. Work also continued on the factors influencing the high incidence of oesophageal squamous cell carcinoma in a province of Iran. The relationships between dietary information and urinary biomarkers of two mycotoxins, fumonisins (FB1) and deoxynivalenol, were investigated.

Workshops

A major effort within WP6 was the arrangement of workshops designed to promote the understanding of the validation of biomarkers of exposure and effects in humans and to discuss new biomarker developments. Twelve such workshops were held:

- Biomarkers of carcinogen exposure and early effects. (Athens month 9)
- Strategy on development and validation of biomarkers of carcinogen exposure and bioindicators of diesease. (Heidelberg month 17)
- Urinary biomarkers. (Maastricht month 22)
- Validation exercises. (Athens month 32)
- Validation of biomarkers of exposure and effect in humans (including suitability for use in transitional/pilot studies). (Barcelona month 35)
- New developments: biomarkers of complex mixtures and use of 'omics' technology. (Cavtat month 41)
- Epigenetics biomarkers in cancer molecular epidemiology, jointly with WP5. (Leuven month 46)
- Outcome of type B projects'. (Leuven month 47)

- ü Clinical significance of oxidative damage to DNA. (Bydgoszcz month 50)
- ü Future priorities/needs for developing biomarkers of exposure, effect and chemoprevention. (Porto month 53)
- ü Mechanistic insights and use of biomarkers for improved carcinogen risk assessment of mixtures, jointly with WP 7 and 10. (Porto month 53)
- ü Summary and achievements of type B projects and assessment of sensitivity and validation of new biomarkers jointly with WP5 and WP8. (Lodz month 60)

Conclusion

The activities of WP6 have led to a greater understanding of the achievements of biomarkers in the field of human carcinogenesis and have provided up to date information to ECNIS members and other scientists on new developments. The thorough review of biomarkers of diet-related carcinogens in the first ECNIS report set the scene for the work of WP6 in developing biomarkers of exposure and effect. This was complemented by ECNIS volume, also prepared by WP6, which surveyed the state of readiness of these biomarkers for use in molecular epidemiological studies. The two reports provided a starting point for the collaborative work of the network. In parallel with the preparation of these two reports, the contribution of WP6 to the online surveys of resources and expertise, and on-going projects also facilitated the planning of new work on the development of biomarkers. The information provided to WP1 on global projects, cohorts and networks added to the value of this inventory of potential collaborators within Europe and beyond.

Many of the Type B projects funded by ECNIS were relevant to the objectives of WP6, including work on biomarkers of N-nitroso-related compounds, oxidative damage to DNA, DNA repair, and alcohol exposure. Other projects developed higher through-put methods or aimed to reduce interlaboratory variation in methods, both essential for the successful application of biomarkers to large-scale human studies such as those envisaged for ECNIS^2. Validation exercises in conjunction with WP1 have led to several methods being thought to be acceptable for future human molecular epidemiology studies, which may be considered in ECNIS^2. These methods include measures of oxidative DNA damage in urine, the Comet assay, ^{32}P-postlabelling for DNA damage, phenotypic DNA repair assays and genotyping.

The workshops organised by WP6 provided a venue for presentation of progress in the development and validation of biomarkers of exposure and effect, including results from the Type B projects. They enabled problems to be discussed and experience shared. Other multidisciplinary workshops introduced new techniques or enabled specialists in different fields to share their expertise, setting a pattern for the future in ECNIS^2.

Partners have been kept informed of WP6 progress by comprehensive reports posted on the internal website. The Type B projects have resulted in numerous peer-reviewed papers, also listed on the ECNIS website. Wider dissemination of the work of WP6 has been accomplished through the ECNIS reports and via articles on the workshops written for the ECNIS Newsletter. These endeavours have ensured that the achievements of WP6 in developing biomarkers of exposure and effect have been made available to a wider audience.

Workpackage 7

DEVELOPMENT AND VALIDATION OF BIOMARKERS OF INDIVIDUAL SUSCEPTIBILITY

Ari Hirvonen, WP7 Leader

While the studies on gene-environment and gene-gene interactions have provided interesting information on the regulation of various enzyme activities, and in some cases also on how the enzymatic activity could associate to cancer risk, it is usually difficult to judge from them which is the 'real phenotype' that should be compared to the genotype. However, it should always, even under the most complicated influence of endogenous and exogenous factors, be possible to understand the relationship between the genotype and the phenotype. For this, a complete understanding of the gene regulation is necessary. Therefore, one important goal of ECNIS WP7, responsible for development and validation of biomarkers of individual susceptibility, was to gather better knowledge about genotype-phenotype associations. The focus was decided to be on the phase I and phase II xenobiotic metabolizing enzymes (XMEs) and DNA repair enzymes of potential relevance in individual susceptibility to environmentally-induced cancer. First, the state-of-the-art of genotype vs. phenotype studies was extensively reviewed. Based on this review, a plan was made for future experimental studies on the phenotypic significance of variation in XME, and also DNA repair, genes. Some preliminary studies were also initiated on this topic.

WP7 also aimed to rapid dissemination of preferred genotyping techniques among the participants and other scientists performing genotyping of human cancer risk genes. For this, a quality control project was conducted to validate methods and equipment currently used for genotyping approaches within ECNIS laboratories. The results of this project clearly indicated that although some of the commonly used methods for determination of the genotypes of human cancer risk genes give fully comparable results, some methods are less accurate. This means that some SNPs are assessed with substantial error with these methods. This can subsequently result in attenuation of the statistical relation between the polymorphism and disease occurrence.

Taking all the data gathered by WP7 into consideration, it was difficult to give preference to any of the methodology that was in use in the ECNIS laboratories. In fact, the medium-throughput methodologies, that were not included in the above mentioned comparisons, were ultimately considered as the best choices for the future ECNIS studies. WP7 also provided a principle of selecting genetic polymorphisms that must be analysed in population studies to be conducted by ECNIS in relation to the specific exposures involved and the specific biomarkers of exposure and effect.

One of the main goals of WP7 was to formulate a long-term strategy of ECNIS research in the area of experimental studies on development and validation of biomarkers of susceptibility. The suggested long term strategy includes the following main goals: 1) further studies on the genotype-phenotype relationships to increase our knowledge on the genetic basis of increased susceptibility to genotoxic compounds; 2) design of studies which provide more effective routes to the detection of the large number of susceptibility genes; 3) independent replication of the findings of ECNIS partners in other large population samples; 4) establishment of quality control schemes and standards for the genotyping and phenotyping methods used within ECNIS.

Surveys

Two surveys were conducted by WP7. The survey of the genotyping methods in use among ECNIS Partners was conducted at the early stages of the work of WP7. The results of the survey enabled optimal use of resources and aided joint research proposals and future planning.
The subsequent survey on availability of bioinformatic skills in ECNIS, on the other hand, revealed that the widest bioinformatical experience exists among data mining, database searching and the use of different databases. The microchip data handling and sequence alignment and analysis were quite popular tasks as well. Least experience appeared to exist in the use of structural biology tools, gene mapping and finding, and secondary structure prediction.

Some interest was also in acquiring education in haplotype analysis and motif search. Knowledge in SQL-programming, protein folding and Genehunter software was also requested by individual partners. This information is anticipated to be very useful in planning the future work and educational needs in ECNIS^2.

Inter-laboratory trial

To date, many different methods and equipment exist to determine the genotypes of low penetrance genes. The various methodologies may, however, sometimes give divergent results in different laboratories or with different equipment. To examine this, WP7 conducted, as a Type A project, an inter-laboratory trial to assess: 1) whether the different methodologies used in this network give similar results for a given genotype; 2) whether the same genotyping methods give comparable results in different participating laboratories. Altogether nine partners took part to some or all parts of this quality control project.

The results of the trial clearly indicated that although some of the commonly used methods for determination of the genotypes of human cancer risk genes give fully comparable results, some methods are less accurate. This means that some SNPs are assessed with substantial error with these methods. This can subsequently result in an attenuation of the statistical relation between the polymorphism and disease occurrence.

On the other hand, the trend in the genotyping area has in recent years been towards higher throughput methodologies. Consequently, the 'medium-throughput' applications like Sequenom, utilizing MALDI-TOF mass spectrometry in the analysis of nucleic acids, and the TaqMan® OpenArray™ Genotyping System, were ultimately considered as the best choices as methods in the future studies on environmental cancer risk, nutrition, and individual susceptibility.

Workshops

Eight workshops were arranged by WP7 (Table 1), some of them as joint workshops with other WPs. The workshops involving partners from all ECNIS disciplines provided a good environment for discussing the technological issues like quality criteria for the genotyping analyses, pros and cons of the currently used genotyping methods, and technological innovations.

The other important issues discussed included the use of new approaches like systems biology to environmental carcinogenesis and the related biomarkers. In the workshops ECNIS specialists and outside speakers were also able to share their knowledge in risk assessment, e.g., in discussing the

mechanistic insights and use of biomarkers for improving risk assessment of mixtures. Since the assessment of the health risks of chemical mixtures is currently a burning topic at EU, the workshop was very timely and important initiative of ECNIS.

The outcomes of the two workshops on dietary habits/modulation and genetic pathways as cancer risk factors, on the other hand, are anticipated to be very important for the future work in ECNIS[2].

WP7 Workshops:

- ü Functional impact of genetic variation in genes of relevance to environmental carcinogenesis; 27 February 2007; Maastricht, The Netherlands
- ü AFTER GWAS: an exercise in problem solving (co-organized by WP7 and WP8); 12 October 2007; Venice, Italy
- ü Technological innovations for SNP genotyping and haplotype approaches in cancer studies; 8 February 2008; Turin, Italy
- ü Dietary habits and genetic pathways as cancer risk factors; 3-4 March 2008; Barcelona, Spain
- ü Pros and cons of the currently used genotyping techniques; 13 October 2008; Helsinki, Finland
- ü Systems biology approaches to environmental carcinogenesis and related biomarkers (co-organized by WP5 and WP7); 23 August 2009; Firenze, Italy
- ü Mechanistic insights and use of biomarkers for improving risk assessment of mixtures (co-organized by WP6, WP7, and WP10); 22-23 September 2009; Porto, Portugal
- ü How is dietary modulation of cancer risk influenced by genetic polymorphisms; (co-organized by WP7 and WP9); 16 April 2010; Lódz, Poland

Reviews and reports

In addition to workshop reports, five reviews or reports on specific topics of interest to ECNIS were produced by WP7.

Report on 'ECNIS plans for high throughput genotyping and selection of relevant genetic polymorphisms that might be associated with environmental toxicity'

One of the important issues in population studies in relation to specific exposures is the selection of relevant genes to be studied for a given exposure. Therefore, a framework, comprising five partners, was developed for harmonized and rational selection of the genetic polymorphisms that should be analysed in population studies to be conducted by ECNIS in relation to the specific exposures involved and effect being examined. The report produced by the framework suggests general principles of selecting genetic polymorphisms to be analysed by high throughput methods in population studies conducted by ECNIS.

Report on 'Long-term strategy in the area of development and validation of biomarkers of individual susceptibility'

The ultimate goal of WP7 was to formulate a long-term strategy of ECNIS research in the area of experimental studies on development and validation of biomarkers of susceptibility. The suggested long term strategy includes the following main goals: 1) further studies on the genotype-phenotype relationships to increase our knowledge on the genetic basis of increased susceptibility to genotoxic compounds; 2) design of studies which provide more effective routes to the detection of the large number of susceptibility genes; 3) independent replication of the findings of ECNIS partners in other large population samples; 4) establishment of quality control schemes and standards for the genotyping and phenotyping methods used within ECNIS.

Review on 'State of the art of genotype vs. phenotype studies'

The purpose of this review was to summarise the current situation regarding the genotype-phenotype studies of the phase I, phase II and DNA repair enzymes of potential relevance in individual susceptibility to environmentally-induced cancer. Functional effects of certain gene variations can of course be studied directly by assessing the actual enzyme activity of the variants. However, indirect assessment of phenotypic effects can also be obtained by studying their effects on later end-points like DNA damage and cancer risk. These end-points were therefore also considered in the review when appropriate.

From the review it is clear that the most challenging problems in the characterization of the human drug metabolism phenotype stems from the fact that most of the catalyzing enzymes are expressed in a tissue specific manner leading to great differences between tissues in the activation and inactivation of carcinogens. Moreover, a complete understanding of the gene regulation is necessary to understand the relationship between the genotype and the phenotype. Based on the review, except for very few simple cases, we unfortunately seem to be far from this goal at the moment.

Report on 'Comparison of direct and indirect methodologies for the assessment of a cellular DNA repair phenotype'

The main conclusion of the report was, that although most of the currently used methods for the assessment of a cellular phenotype are relatively simple, and have a good potential for identifying individuals with reduced DNA repair capacity, it is not possible to give any general recommendations. The choice of the assay depends on the scientific question researchers have and on which exposure they want to address. Furthermore, it is not possible to investigate all different DNA repair pathways with one single method. As far as cancer predictability is concerned, only the cytogenetic assays have been shown to be predictive, but are labour-intensive. Moreover, the relationship between genotypes and phenotypes for DNA repair should be evaluated for cancer risk prediction.

Report on 'Inter- and intralaboratory comparison of genotyping methods and equipment'

An inter-laboratory trial was conducted by WP7 to assess: 1) whether the different methodologies used in this network give similar results for a given genotype; 2) whether the same genotyping methods give comparable results in different participating laboratories. The outcomes of this trial were already described earlier (see 1.2. Inter-laboratory trial).

Report on 'Coverage of HapMap for the genes and SNPs of interest in ECNIS'

The selection of the genes and SNPs of interest of ECNIS had already been done earlier in the above mentioned ECNIS Type A project on 'Inter- and intra-laboratory comparison of genotyping methods and equipment'; altogether 19 SNPs and two gene deletion polymorphisms were included in this trial. The SNP coverage mapping was done by using HapMap Genome Browser (Phase 1, 2 and 3 - merged genotypes and frequencies) –version. Based on the search HapMap covers very well the genes and SNPs of interest in ECNIS. Database has been linked to NCBI and UCSC -databases and works with rs-number or gene name based only. This means that only the SNP information needs to be updated and checked for occasions where rs-numbers has been changed. It is also recommended to always use the rs-numbers with the typical amino acid SNP description to prevent miss-classifications and errors. Usage of rs-numbers would also speed up the use of HapMap.

Dissemination

The workshops organised by WP7 enabled participants to be updated on progress in developing quality criteria and the inter-laboratory trials of genotyping methods. Through the multidisciplinary workshops, both ECNIS partners and external scientists have been able to broaden their knowledge of the issues involved in the use of biomarkers in human population studies. Detailed reports of the

workshops and quality control project are available to partners on the ECNIS internal website. In addition, articles on the workshops, written for the ECNIS Newsletter, which is distributed to stakeholders, are available on the public website.

Conclusions

The specific objectives of WP7 in ECNIS were: 1) to optimise the use of the network's genotyping resources; 2) to develop a framework for harmonised selection of combinations of carcinogen exposures, biomarkers and genetic polymorphisms to be examined in molecular epidemiology studies; 3) to promote harmonized execution of experimental studies on the phenotypic significance of variation in xenobiotic metabolising enzymes and DNA repair genes; 4) to develop plans for coordinated establishment of new methods for DNA repair genotyping and high throughput genotyping, including strategies for choosing multiple polymorphisms to be evaluated for cancer risk; 5) to develop a database for recommended genotyping methods with WP4. All of these objectives were achieved except the development of a database for recommended genotyping methods. This objective was decided to be dropped since the trend in the genotyping area is towards higher throughput methodologies, which were also recommended to be used in the future ECNIS studies. Therefore, development of the originally planned database was not considered rational anymore.

In summary, the activities and outcomes described in this report are anticipated to have well fulfilled the goals of WP7, and, at least partly, are expected to continue and develop in ECNIS^2.

Workpackage 8

IMPLEMENTATION OF BIOMARKER TECHNOLOGY FOR CANCER PREVENTION

Paolo Vineis, W8 leader

ECNIS focused on the utility of biomarkers of exposure as well as bioindicators of disease to characterize the influence of diet and hereditary factors on environmental cancer risk. One of the main objectives was to develop and standardize procedures for cancer risk assessment, while identifying significant data gaps as well as to provide directions for future developments.
The objective of WP8 was to address the application of biomarker methodologies in the context of population studies. Its activities focused on a) the exploitation of data and samples, available among the ECNIS partners, for conducting further research and b) the development of theoretical tools for the design, conduct and evaluation of biomarker-based studies.

Partners involved

ICO , Spain; FIOH, Finland; NIEH, Hungary; National Hellenic Research Foundation, Greece; DKFZ, Germany; IRAS, Netherlands; UM, Netherlands; Collegium Medicum, Poland; NIOM, Poland; UC, Denmark; ISI Italy

Work performed and end results

1. Validation and applicability of biomarkers for molecular epidemiology and evaluation of their contribution to the understanding of environmental carcinogenesis

The works of WP8 in the field of epidemiological concepts of biomarker validation resulted with the ECNIS series review entitled (ECNIS Reports Vol. 3) " Epidemiological concepts of validation of biomarkers for the identification/quantification of environmental carcinogenic exposures (Edited by Paolo Vineis and Valentina Gallo).

The aim of this report was to review concepts of biomarker validation and assess the current status of validation mainly with regards to the use of biomarkers in molecular epidemiology. The first part of the report describes the epidemiological criteria of biomarker validation in population studies. Then some chapters address newer problems encountered in the introduction of intermediate biomarkers into use, in the management of missing data, in causality assessment for biomarker and genetic data, and in the study of phenotype-genotype correlations.
The final part applies criteria of validation to some of the main biomarkers used today in molecular epidemiology (DNA adducts, oxidative damage to DNA , urinary 1-hydroxypyrene, markers for heterocyclic aromatic amines, and N-nitrosocompound adducts). We have found that there are some important gaps of knowledge that deserve attention. Most validation studies have dealt with analytical validation, like reproducibility and repeatability. Some studies also considered validity in terms of sensitivity and specificity in comparison with a me studies also (which, however, does not exist for avant-garde markers). Very few studies considered clinical validity, i.e. the ability to predict disease, or the relationship between a decrease in marker and a decrease in disease risk. The latter gaps are challenges for future research, with the following goals:
1. To develop a validation strategy, i.e. to identify those validation criteria that are essential before any marker is introduced into epidemiological practice.
2. To conduct pooled analyses to peruse the existing data and fill the gaps (for example, the pooled analysis of DNA adducts we show in Chapter 3).

3. Finally, when pooled analyses are insufficient, to conduct field research to obtain original data on biomarker validity, for example within the existing, large prospective population studies.

Based on this work a paper was elaborated: "Validation of biomarkers for the study of environmental carcinogens: a review" by Gallo V, Khan A, Gonzales C, Phillips DH, Schoket B, Györffy E, Anna L, Kovács K, Møller P, Loft S, Kyrtopoulos S, Matullo G, Vineis P on Biomarkers 2008;13:505 It was concluded that:

- a high-sensitivity method is available for the measurement of 1-hydroxypyrene in urine,
- little is known about intra-individual variation of DNA adducts measurements, but measurements have a good repeatability, irrespective of the technique used for their identification; reproducibility improved after the correction for a laboratory factor,
- there is consensus on validation of biomarkers of oxidative damage DNA based on the comet assay and chromatographic measurement in blood,
- urinary measurements by chromatographic assays were well validated, and ELISA-based assays appear to lack specificity,
- immunoassays for the quantification of adducts of N-nitroso compounds are useful for large epidemiological studies, given their sensitivity, the small amount of DNA required, and their potential for rapid and high-throughput analysis.

2. Standardized format for the design, conduct and reporting of molecular epidemiology studies

In recent years the methods of epidemiology have considerably expanded encompassing sophisticated exposure and outcome assessment techniques based on biomarkers. Biomarkers can be widely defined as measurements that are based on DNA, RNA, protein, or other metabolites involved in human physiology and their deviations in disease. Biomarkers may be measured as single items or many of them can be measured concurrently at the same time, including high throughput simultaneous measurements of hundreds or even thousands of markers. The expectation is that the inclusion of biomarkers can overcome some of the limitations of other epidemiological approaches, where measurements are often problematic, error-prone, poorly defined, and remotely connected with disease causation and outcome. In this regard, biomarkers have been used mostly as exposure variables, but also as covariates and outcomes. The use of biomarkers has led to the development of a new, rapidly expanding field, molecular epidemiology. Despite enthusiasm about the prospects of molecular epidemiology the inclusion of biomarkers poses a number of new problems, such as the reliability of measurements, special sources of bias, and special study design issues. There is much room for inappropriate use, and also reporting is often far from being complete and accurate and selective reporting of positive results poses a considerable threat to the validity of this literature. Suboptimal reporting may also lead to exaggerated claims about the translational potential and clinical utility of these findings. Given the importance of the field and the threats of suboptimal reporting, we have proposed some recommendations for strengthening the reporting of molecular epidemiology studies. We differentiate two levels of uses of biomarkers: molecular epidemiology studies (transitional studies, nested case-control and case-cohort studies, and other formal designs) and applications of validated biomarkers within routine settings. The proposed recommendations are conceived for the first type of context; however, for the sake of completeness, core items have been identified within the checklist to be applied to any setting involving biomarker measurement. The current recommendations are built on the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) statement, simultaneously published in 2007 in different medical journals.

The general aim of STROBE is improving the quality of reporting observational studies through providing general reporting recommendations for descriptive observational studies and studies that investigate associations between exposures and health outcome. However, recent advances in molecular biology, the availability of vast amount of data coming from high throughput techniques (and consequent changes and improvement in terms of epidemiology, statistical analysis and study design) pose the need for implementing these recommendations specifically for molecular epidemiology studies. Genetic associations in particular are a field that has special characteristics and guidance on the reporting of genetic association studies has been included in a recent separate statement (STREGA). These recommendations are intended to be applied to other types of molecular markers. The manuscript containing the STROBE-ME recommendations has been submitted to few journals for simultaneous publication "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Molecular Epidemiology STROBE-ME" Valentina Gallo, John Ioannidis, Peter Farmer, Giuseppe Matullo, David Phillips, Bernadette Schoket, Ulf Stromberg, Christopher Wild, Paolo Vineis.. This will ensure a large coverage of the scientific community, following the example of the previous STROBE papers. Once the article will be finalized, the authors will invite journal editors to adopt the recommendations for papers published in their journals.

3. Finalization of pooled analyses on suitable biomarkers in MEC

Within the MEC database, we have performed a pooled analysis of three prospective studies on cancer risk in which bulky DNA adducts have been measured in blood samples collected from healthy subjects (N = 1947; average follow-up 51–137 months). In addition, we have performed a meta-analysis by identifying all articles on the same subject published up to the end of 2006, including case–control studies. In the pooled analysis, a weakly statistically significant increase in the risk of lung cancer was apparent (14% per unit standard deviation change in adduct levels, 95% confidence interval 1–28%; using the weighted mean difference method, 0.15 SD, units higher adducts in cases than in controls). The association was evident only in current smokers and was absent in former smokers. Also the meta-analysis, which included both lung and bladder cancers, showed a statistically significant association in current smokers, whereas the results in never smokers were equivocal; in former smokers, no association was detected. The results of our pooled and meta-analyses suggest that bulky DNA adducts are associated with lung cancer arising in current smokers after a follow-up of several years.

Relying on the experience of the pooled analysis on DNA adducts that has shown that the biomarker can predict the onset of lung cancer prospectively, we aimed at extending the finding to other biomarkers.

4) Report on measurement of biomarkers in cohort studies based on the principle of calibration

While the application of biomarkers of exposure provides valuable information on personal exposure, it suffers from the disadvantage of often requiring amounts of biological material (e.g. serum, DNA) which exceed those that can be made available by most biobanks. Furthermore, the corresponding analyses are also often costly and time-consuming. This constitutes a limitation to the exploitation of existing biobanks (EPIC, UK-Biobank) which would otherwise constitute a valuable resource for the study of environmental disease etiology with many hundreds of thousands of samples in Europe alone. (Omics may be an exception to the need for large volumes). Therefore there is a need to find ways to minimize the volume of biological samples used, the number of analyses and their costs. This

is the same problem already tackled by nutritional epidemiologists when a trade-off between accuracy of measurements (e.g. with 7-day diaries) and costs was sought. The solution adopted in the case of diet-borne exposures was to use a less accurate tool (e.g. Food Frequency Questionnaires) in the whole cohort, and calibrate the measurements thus obtained with the more accurate measures taken in a subset. Calibration is in fact a way to correct misclassification by applying a correction factor (or "de-attenuation factor") derived from a subset of the whole cohort. The same concept suggests an integration between longitudinal prospective studies and case-control or cross-sectional studies.
On this basis we propose a mixed model for conducting exposure assessment within longitudinal studies:
i) Use of GIS (or questionnaire)-based exposure assessment
ii) Exposure biomarker measurements in subsets of the general population of same areas or in subsets of the cohorts
The philosophy of calibration consists in using a more accurate tool for exposure ascertainment than would be possible in the whole cohort. Data derived from the accurate measurement (i.e. less affected by measurement error) are then used to "calibrate" the estimates in the whole population. This approach has been mainly used in the context of nutritional studies. For example, Bingham et al calibrated estimates of fibre intake using a 24-hour recall instrument to adjust measures based on a food frequency questionnaire.
The "meet-in-the-middle" philosophy has been described elsewhere and derives from very practical problems we encounter in epidemiology, i.e. the usual lack of repeat samples. Discovering new biomarkers for disease risk with high-throughput approaches such as metabonomics poses serious design issues. With a case-control study design markers of clinically overt disease can be identified, but not pre-clinical markers or markers associated with exposure. The latter require pre-diagnostic biological samples, i.e. prospective cohort studies. In the context of the latter, the analysis of samples collected years before the disease onset (at least for chronic diseases) is likely to be more related to exposure, while measurements close to the disease onset will be more oriented towards early diagnosis/early damage. It is possible that there is partial overlap between the two types of markers, what we call the "meet-in-the-middle" approach. The rationale of this strategy is under development at Imperial College in studies on metabonomics.
One of the main challenges in molecular epidemiology is how to model time. Usually statistical models applied to omics serve the purpose of identifying signals, separating them from noise, while little has been done in chronic diseases to model time into the exposure-biomarker-disease continuum. Recently, Sandro Galea has proposed to use mathematical approaches for infectious diseases as a model also for chronic diseases. Instead of looking at biomarkers synchronically, as usually done, we should look at them diachronically. In addition, the concept of "epidemic curve" should be mimicked, i.e. the onset of diseases should follow exposure (in the population) according to a meaningful time pattern that has to do with "induction-latency"
As a result of works carried out in the WP8 a handbook on calibration methodology has been produced, encompassing the challenges posed by the methodological issues.

Brief description of the methodologies and approaches employed

A research plan on available samples using biomarker methodologies in partner laboratories was developed, and the existing data sets and the opportunities they offer for integrated European research were analysed. Some priorities were identified, including the conduct of pooled analyses on DNA adducts, DNA repair, genotype-phenotype correlations, and dietary information and biomarkers.

Based on this progress, the following specific steps for WP8 were:

1. Conduct descriptive analyses on the anonymous data sets provided by the partners. These analyses will be circulated and will serve for a "survey" of biomarker availability and levels in European countries.
2. Select markers and biological samples to exchange and analyse, based on the following three possible purposes:
   2.1. Validation, including inter-laboratory comparison.
   2.2. Development of new techniques, such as high-throughput methodologies for DNA adducts
   2.3. Completion of analyses to complement those already performed in some but not all the laboratories.
3. Facilitate the integration of suitable and validated biomarkers into large epidemiological studies. Based on the conclusions of workshops held during the preceding period, a modality of measurement based on calibration, as done in dietary studies, has been developed.
4. A proposal of standardized format for the design, conduct and reporting of molecular epidemiology studies, based on the Strobe initiative, whose development has started, has been completed.

Potential impact of the project on its industry or research sector

The use of biomarkers and bioindicators extends the resolution of classical epidemiology

The utilization of biomarkers of exposure may considerably improve the resolution of conventional approaches by reducing exposure misclassification and decreasing the time between exposure and the appearance of an observable effect. This approach can also enhance the biological credibility of a detected statistical association by providing mechanistic evidence. Further, information derived from the use of biomarkers for genetic variability obtained by genotyping, and bioindicators of associated phenotypic differences that influence susceptibility to cancer is of paramount importance in the interpretation of epidemiological data. The latter type of information is critical for the protection of highly susceptible human subpopulations.

By providing a virtual centre of excellence, ECNIS will create the momentum and critical mass to take maximum advantage of the successful use of molecular biology in epidemiological studies, thereby improving the resolution of classical epidemiology.

Bridging the gap between research areas

Recent developments in natural sciences have favoured a high degree of specialization that has often occurred at the expense of seeking more generalized knowledge. This trend has inter alia generated highly sophisticated and automatized technical tools that have a tremendous potential. However, the indiscriminate use of high-tech implements has often resulted in the generation of heaps of data that are difficult to interpret because insufficient attention was paid to the underlying fundamental biological problems, the assessment of which requires an integrated input from various fields of expertise. The ECNIS network covers a number of different areas, and by developing collaboration and exchange of ideas between researchers representing different areas of specialization, transfer of technology and know-how between disciplines it creates a fertile environment for true innovation.

Providing support for the development of functional foods

The development of relevant biomarkers that have been validated in humans and that can be used for screening in development of functional foods (nutraceuticals, therapeutic foods, designer foods) represents the main potential economic and technological gain from the ECNIS network activities. There is a rapidly growing market for functional foods, and a considerable amount of evidence has accumulated during the last decade indicting that the presence of anticarcinogenic or antimutagenic agents in fruits and vegetables has an important role in modulating the cancer incidence in human populations. However, as already mentioned, it has been extremely difficult to demonstrate beneficial effects for specific food constituents, even when they do occur. This major problem has repeatedly been pointed out by national health authorities in response to claims of cancer prevention for such products. Thus, in contrast to the situation in the US, by law or voluntary agreement, European industry may not capitalize on general results obtained e.g. by comparing cancer incidence rates in populations with different dietary habits and market functional foods based on claims for cancer prevention.

ECNIS offers a unique opportunity to provide better basis for dietary advice formulation, functional food development and further chemoprevention trials. By utilisation of relevant biomarkers, the concepts presented in this NoE will provide a short-cut in identifying individual chemical components in the diet that protects against human cancers. Monitoring of biomarkers associated with early effects leading to cancer in intervention studies is of particular interest in this context. This opens up the possibility for European industry to substantiate previously made claims, as well as to promote the development of new and more effective products and enhance the competitiveness in the functional food sector. Not only will this type of information assist the food industry sector to develop functional foods, but it will also help promote agricultural production of crops that have beneficial health effects with respect to lowering the cancer incidence at major sites. Industry input will be assured by co-operation that has already been initiated with the food industry sector.

Workpackage 9
MECHANISMS OF MODULATION OF CANCER BY DIETARY FACTORS

Björn Åkesson, WP leader

The objectives of WP 9 were to strengthen research on biomarkers reflecting dietary exposure to anticarcinogenic food components and identify knowledge gaps, to integrate research on carcinogenic and anticarcinogenic compounds and their interaction in different models of colon carcinogenesis, to stimulate research on the mechanisms of the protective effects of food components on carcinogenesis, to develop cross-links between human intervention studies on anticarcinogenic dietary compounds within and outside ECNIS and to follow and interpret reports on human dietary intervention studies to provide a better basis for dietary advice formulation, functional food development and further chemoprevention trials.

Many partners inside and outside ECNIS contributed to these activites including: NIOM, DKFZ, UC, KI, NHRF, ULEIC, Collegium Medicum, UM, ULUND, JOGU

To reach the objectives a number of different activites were performed as summarised in the following.

ECNIS projects

Beside a number of Type A projects run by the partners ECNIS funds were set aside to support collaborative projects, Type B. In the first call WP9 members were active in five of ten approved proposals: UC, ULUND, KI, DKFZ (2), UM, JUGO as shown by the following list.

1. DKFZ (J. Lineisen), UM (T deKok): Validation of NNOC-related DNA adducts and assessment of their determinants in the general population (also WP 6).
2. JUGO (F. Oesch): Molecular dissection and potential cross-talk of the biological and genetic pathways affects by benzo(a)pyrene and dioxin (TCDD) (also WP 10).
3. ULUND (B. Åkesson), UC (L. Dragsted): Short-term effects of selenium on global gene expression in humans using selenium-rich milk and different selenium supplements (see ref Ravn-Haren et al. 2008).
4. DKFZ (J. Lineisen): A mendelian randomization study of cruciferous vegetables and lung cancer within the EPIC cohort study (also WP8).
5. KI (J. Rafter, S. Pettersson): Is PPARd the ”fat sensor” that mediates the promotion of intestinal cancer by high fat diets?

A Working group was also appointed with the task to propose new research on mechanism of action of diet in the models of colon carcinogenesis including the action of probiotic bacteria. This action was partly based on the evaluations made in the WP9 Review and at workshops (see below).

A working group was also active on the subject of the role of the intake of cereals for the risk of cancer. The aim was thus to discuss epidemiological data on the association of cereal intake in relation to cancer risk, the molecular mechanisms of action of different compounds in cereals on carcinogenesis-related processes and public health perspectives. In addition a workshop was organised (see below).

An example of a Type C project partly emerging from ECNIS is the work of ULUND and UC in the SYSDIET network, a Nordic Centre of Excellence in Food, Nutrition and Health. The topic of the network is "Systems biology in controlled dietary interventions and cohort studies" planned to run during the period 2007-2012 with 12 partners (www.sysdiet.fi).

Reviews: Biomarkers of exposure to and mechanisms behind the anticarcinogenic action of selected dietary components

A major part of the work in WP9 has concerned the preparation of different reviews, which was performed in several steps. First a state-of-the-art review on the use of biomarkers reflecting dietary exposure to anticarcinogenic food components was assembled (Åkesson, Mercke 2007). The review was prepared after extensive consultation among the partners. It contained 14 chapters divided between two main themes "Mechanistic aspects of anticarcinogenic dietary effects" and "Evaluation of dietary biomarkers in relation to dietary prevention" and 21 authors from ten partners contributed. The review was evaluated by external experts before publication (Åkesson, Mercke 2007). The review served several purposes among them 1) as an inventory of ECNIS and non-ECNIS research on the mechanisms of action of anticarcinogenic food components (e.g. antioxidants, polyphenols, trace elements, vitamins, probiotics and other components) to stimulate opportunities for collaborative research, 2) as a background for the launching of joint research projects concerning mechanistic studies of anticarcinogenic food components, and 3) as a collection of data of novel biomarkers of nutritional status for anticarcinogenic food components.

In the next step this review was used to prepare revised papers intended for an international journal. They were published in the May 2008 Supplement of European Journal of Nutrition and contained 7 chapters divided between two main themes "Vitamins and selenium" and "Bioactive components in foods" and 21 authors from 11 partners contributed. This effort involved intensive consultation and communication among partners and several previous texts were merged into stronger papers. This seems to be the first supplement published by the ECNIS network in an international journal.

Workshops

Within WP9 as many as 9 workshops were organized:

1. Workshop on mechanisms of protective effects of diet on cancer risks and cancer-related biomarkers (Athens, 2006).

The methodological possibilities and challenges concerning the validity of different biomarkers to document the protective effects of food components was the topic of a workshop with nine presentations from 7 partners and one invited speaker. The following topics were reviewed. Overview of mechanisms and issues (Margaret Manson, Leicester), Models for assessment of chemopreventive efficacy (Clarissa Gerhauser, Heidelberg), Intervention studies of nutrients with respect to oxidative stress (Lars Dragsted, Copenhagen), Role of ARE in chemoprevention (John Hayes, Dundee), Nutritional modulation of DNA repair (Ad Knaapen and Frederick Jan van Schooten, Maastricht), Cancer chemopreventive potential of Spirulina (Theodore Sotiroudis, Athens), Antioxidant status and DNA breaking - The results of an intervention study (Jolanta Gromadzinska and Wojciech Wasowicz, Lódz), Importance of dietary Se in cancer prevention (Björn Åkesson, Lund), and Perspectives for combination chemoprevention (Theo de Kok (Maastricht). The workshop served several purposes 1) as an inventory of research within the ECNIS community, 2) as a background for the launching of joint research projects concerning mechanistic studies of anticarcinogenic food components, 3) as a basis for the preparation of position papers on new biomarkers of nutritional status and improved

methodologies to study their mechanisms of action, and 4) as a collection of data of novel biomarkers of nutritional status for anticarcinogenic food components.

2. Workshop on mechanism of action of diet in the models of colon carcinogenesis (Athens, 2006).

Research on the action of carcinogenic and anticarcinogenic compounds in different models of colon carcinogenesis was reviewed. The following seven presentations from 4 partners and 3 invited speakers were given. Novel receptor-mediated mechanisms for effects of diet on colon carcinogenesis (Sven Pettersson, Stockholm), Dietary factors and genetic susceptibility as determinants of mutation and methylation of cancer genes in sporadic colorectal carcinomas (Piet van den Brandt, Maastricht), Signalling functions of bioactive lipids in the gut in relation to colon cancer (Rui-Dong Duan, Lund), Chemopreventive phytoalexins? - Cytotoxic effects of 2-arylbenzofuran phytoestrogens on human cancer cells (Michael N. Alexis, Athens), Mechanisms of action of diet in the AOM-rat model of colon carcinogenesis (Giovanna Caderni, Florence), Identification of mechanisms at the genome level for protection against colon cancer by vegetables (Simone van Breda, Maastricht), Antioxidant vitamins and cancer risk. Is oxidative DNA damage a relevant biomarker? (Peter Moller, Copenhagen), and Dietary phenolic phytochemicals to counteract colon carcinogenesis (Joseph Rafter, Karolinska). The aim was to facilitate the introduction of novel concepts, stimulate the cross-fertilisation between projects and researchers and initiate the formulation of new projects. Improved designs and possible obstacles for studies on the interaction of different types of compounds was evaluated, e.g. concerning different components occurring in the intestinal lumen proposed to be related to colon cancer (low-molecular weight compounds, bioactive lipids, polymers, microorganisms).

3. Workshop on the use of genomic methods for studies of the relations between diet and cancer.

The workshop was held March 3, 2008 at the Annual ECNIS meeting in Barcelona. A joint ECNIS-NuGO committee performed the planning: John Mathers (NuGO, chair), Theo de Kok (ECNIS), Ellen Kampman (NuGO), Joseph Rafter (ECNIS, co-chair), Ian Johnson (NuGO), and Jakob Linseisen (ECNIS). It got very good attendance and was highly appreciated. Several potential project ideas and possible collaborations were initiated. The following talks were presented. A genome wide association scan identifies three colorectal cancer susceptibility loci (Albert Tenesa, University of Edinburgh), Interactions between genetic polymorphisms and diet in influencing CRC risk (Ellen Kampman, Wageningen University/ NuGO/), Mitochondrial mutations – a potential novel biomarker of diet-related bowel cancer risk (John Mathers, Newcastle University /NuGO/), Use of proteomics to develop novel biomarkers of vulnerability to cancer in the alimentary tract (Ian Johnson, Institute of Food Research, Norwich/ NuGO/), Statistical techniques for classifying patient groups in large "omics" datasets - an example from gene methylation data (Jack Dainty, Institute of Food Research, Norwich/ NuGO/), Receptors mediating microbe-host crosstalk in the gut (Velmurugesan Arulampalam and Sven Pettersson, Karolinska/ECNIS/), Proteomics and transcriptomics reveal molecular mechanisms underlying the selective apoptosis induction of dietary flavone in transformed colonocytes (Uwe Wenzel, Justus-Liebig-University Giessen, Giessen), Dietary regulation of genomic instability in the colon (GraemeYoung, Flinders University, Australia), and Modulation of gene expression profiles by vegetables in colonic tissue from mice and human adenoma patients ((Theo de Kok, University Maastricht /ECNIS/).

4. Workshop on the mechanisms of protective effects of selenium regarding cancer.
The workshop held March 4, 2008 at the Annual ECNIS meeting in Barcelona. It was planned by B. Åkesson (ECNIS, chair), L. Dragsted (ECNIS) after consultations with J. Hesketh (NuGO) and J. Keijer (NuGO). The program was as follows. Epidemiologic studies of the association between selenium and different forms of cancer (Piet van den Brandt, University of Maastricht /ECNIS/), Polymorphisms in selenium-related genes and susceptibility to cancer (John Hesketh, University of Newcastle /NuGO/), Role of selenoproteins in carcinogenesis. (Regina Brigelius-Flohé, DIfE, Potsdam /NuGO/), Lessons from two decades of short-term selenium supplementation studies (John R. Arthur, Rowett Research Institute, Aberdeen /NuGO/), Selenium and health – a Danish perspective (Lars O. Dragsted, University of Copenhagen /ECNIS/), 20-year experiences from the nationwide selenium fertilization programme in Finland (Georg Alfthan, National Public Health Institute, Helsinki), and Design and outcomes of long-term selenium anti-cancer trials (Philip Taylor, NCI, U.S.A). The workshop got good attendance and was highly appreciated. Several potential project ideas and possible collaborations were initiated.

5. A joint WP 9-10-11 workshop on Environmental carcinogenesis: Mechanistic progress allowing improved risk assessment and prevention by nutrition modification.
The workshop was held at the Annual meeting March 16-18, 2009 in Leuven. The lectures included the following topics. Green tea and breast cancer (Gail Sonenshein, Boston, USA), The formation of acrylamide in foods (Leif H. Skibsted, Copenhagen, Denmark), Acrylamide and glycidamide related biomarkers of toxification, detoxification and genotoxicity (Gerhard Eisenbrand, Kaiserslautern, Germany) and Exposure to acrylamide and glycidamide in the general population (Hubert Vesper, Atlanta, USA).

6. Workshop on the Role of intake of cereal foods for the risk of cancer.
The workshop was held in Malmö April 24, 2009 and 39 participants from 8 countries attended. State-of-the-art knowledge was reviewed as well as knowledge gaps, and the needs regarding methodology development and design of future studies was discussed. The following talks were given. Introduction on cereals and health (Gunilla Önning, Biomedical Nutrition, Lund University), Cereals, dietary fibre and cancer risk: the epidemiological evidence (Jakob Linseisen, DKFZ, Heidelberg), Intake of whole grain products and risk of breast, colorectal and prostate cancer in the Danish EPIC cohort (Rikke Egeberg and Anne Tjønneland, The Danish Cancer Society, Copenhagen), Plant foods, plasma enterolactone and breast cancer - with a focus on estrogen receptor status and genetic variation (Emily Sonestedt, Lund University), Physiological functionality and health effects of rye products (Kaisa Poutanen, VTT, Helsinki), Effect of beta-glucans on glucose metabolism (Martine Laville, CRNH Rhône-Alpes, Lyon), Progression of prostate cancer related to energy flux, obesity and plant food (Leif Holmgren and Göran Hallmans, Umeå University), Development and application of genomics markers in dietary intervention studies (Theo de Kok, University of Maastricht), and Development of health-promoting liquid oat products (Rickard Öste, Lund University). A separate report in a Swedish food journal was written (Ulmius, 2009).

7. Workshop on the Relationship between vitamin D and cancer.
New scientific data indicate that a low vitamin D nutritional status may be a risk factor for several types of cancer and also other chronic diseases. Other data suggest that the vitamin D status in several populations and groups may be lower than previously anticipated. Another interesting line of research is the role of the tissue distribution of the vitamin D receptor and gene polymorphisms in

this receptor for cancer risk. To review this field a workshop was organised. To further strengthen and expand the collaboration with the sister NoE NuGO this event took place at the NuGO week Aug 31-Sep 4, 2009 in Montecatini. The preliminary program was developed in collaboration with B. van Ommen, K. Cashman (NuGO) and J. Linseisen (ECNIS). The topics covered were as follows. Determinants of vitamin D status; desirable range of intake; effects of food fortification (Kevin Cashman, UCC, IE), Vitamin D and cancer prevention: biological mechanisms (Michael Sitrin, University at Buffalo, USA), Role of genetic variation in selected genes (Kristina Åkesson, Malmö University Hospital, ULund, SE), Vitamin D and cancer: observational studies (Jakob Linseisen, Helmholtz Zentrum München, DE), and Experiences from vitamin D intervention studies/ RCT (Philippe Autier (IARC-WHO, FR).

8. Workshop on the Role of intestinal microorganisms for the risk of cancer.

This workshop was held together with the EU project TORNADO (J. Rafter, Karolinska) at the Annual Meeting in Lódz, April 2010. The aim was to bring the participants up to date on present knowledge regarding role of gut bacteria in cancer (with focus on colon cancer). This was done within a framework covering such issues as: general consequences for the host of 'host-microbe crosstalk'; gut microbes and inflammation; inflammation and cancer; state-of-the-art methodology; metabolic aspects of gut bacteria; role of pathogenic bacteria; human clinical trials. The workshop was well attended and its quality appreciated by numerous participants. Particularly, putting the subject of the workshop into the larger context of 'host-microbe interactions' was much appreciated. The precise mechanisms by which the gut bacteria impact on colon cancer have not yet been pinpointed. However, it does appear likely that effects of the bacteria on the inflammatory response in the gut may be more important than hitherto believed in this context. A better understanding of the overall mechanisms underlying 'host-microbe crosstalk' and the consequences of this for gut homeostasis is essential if we are to better understand how the bugs are contributing to carcinogenesis. The following topics were reviewed. Introduction (Joseph Rafter, Karolinska Institutet, Stockholm), Significance of host – microbe crosstalk for the host: Role of intestinal micro-organisms in gut homeostasis (Velmurugesan Arulampalam, Karolinska Institutet, Stockholm), Analysis and modulation of gut microbiota - implications for gut health (Arjan Narbad, IFR, Norwich), Inflammation and preneoplastic lesions in colon carcinogenesis - a role for gut bacteria? (Giovanna Caderni, University of Florence), Bacterial butyrate formation and impact of alternative diets on microbial metabolism in human studies (Petra Louis, Rowett Institute, Aberdeen), Can bacterial genotoxin contribute to carcinogenesis? (Teresa Frisan, Karolinska Institutet, Stockholm), and SYNCAN clinical trial: probiotics and colon cancer prevention (Joseph Rafter, Karolinska Institutet, Stockholm).

9. Workshop on How is dietary modulation of cancer risk influenced by genetic polymorphisms?"

The work to increase the collaboration with WP 7 was continued by organising this joint workshop at the Annual Meeting in Lódz, April 2010. This also formed part of the efforts to continue the ECNIS activities beyond the 5th year. The program was as follows. Vitamin K: dietary intake, genetic variation in key enzymes, and cancer risk (Jakob Linseisen, Helmholtz Zentrum München), Nutritional status and genetic polymorphisms related to folate and breast cancer risk (Ulrika Ericson and Elisabet Wirfält, Department of Clinical Sciences in Malmö, Lund University), Selenoprotein polymorphism and selenium status in relation to cancer risk (Lutz Schomburg, Charité - Universitätsmedizin Berlin), Selenium, GPx1 activity and GPx1 polymorphism - a study of gene-diet interaction in humans (Ewa

Jablonska, Nofer Institute of Occupational Medicine, Lódz) and Gene-environment interaction research in the Netherlands Cohort Study (PA va den Brandt, Maastricht).
For most of the workshops summary reports have been written for the ECNIS Newsletter in addition to the formal reports.

Contacts with other EU and international projects

As mentioned previously a number of contacts have been maintained with other EU projects and other international platforms including co-organisation of workshops and other events. A summary is given below.

1. NuGO, co-organisation of workshops on genomic methods (no. 3), cancer prevention by selenium (no. 4) and vitamin D and cancer (no.7).
2. Nordic CoE SYSDIET, co-organisation of workshop on Cereal Intake and Health (no. 6).
3. Link to TORNADO project (Karolinska), workshop no. 8.
4. Contribution of material to EFSA activity on Selenium content of foods.
5. Link to Bolivian-Swedish project on Plants in nutrition and medicine (ULUND).

Other activities

An activity was initiated concerning the preparation of a database on on-going and planned human intervention studies on anticarcinogenic dietary compounds and regimens within and outside ECNIS and some progress has been made (P. Mercke, ULUND). Moreover, we established conctact with the sister NoE NuGO in which Gunilla Önning, ULUND and others accumulated a similar database on human studies. Further work has been made within that database. Gunilla Önning also contributes to a monograph on the Design of human studies (Önning et al, 2009).
Linked to workshop no. 4 on Mechanisms of protective effects of selenium regarding cancer, contacts were established with a so-called Focus Team in the sister NoE NuGO (leader J Hesketh, Newcastle). This led to the planning of an epidemiological study of the relationship of selenium status to the risk of prostate cancer (Steinbrecher et al, 2010). In a human intervention study the effects of an antioxidant supplement including selenium on different variables on antioxidant status were investigated (Rytter et al, 2010).

Dissemination

The WP9 review has been published in its first form as an ECNIS monograph (Åkesson, Mercke 2007) and in its second form as a supplement to an international journal (Åkesson, Kyrtopoulus 2008).
Most workshops have been summarised in the ECNIS Newsletter. Some material has also been published in Swedish food and nutrition journals aimed for scientists, employees at food companies and journalists (Önning et al 2008, Ulmius 2009).

Conclusion

The different actions summarised above have been used for several purposes. They have served as an inventory of research within the ECNIS community. They also formed the background for the launching of joint research projects concerning mechanistic studies of anticarcinogenic food components. They were also developed into the preparation of position papers on new biomarkers of nutritional status and improved methodologies to study their mechanisms of action. In general we have observed strong links and a good synergy between different activities such as holding of workshops, progress of Type B projects and writing of reviews and other papers. A major effort has been devoted to collaboration with other international projects which has been of benefit for ECNIS and helped to establish ECNIS as a player on the European arena.

Workpackage 10

MECHANISTIC RESEARCH TO SUPPORT CANCER HAZARD AND RISK ASSESSMENT

Cornelia Dietrich and Franz Oesch

WP 10 Partners:
University of Mainz, National Hellenic Research Foundation, Maastricht University, Karolinska Institute, University of Dundee, Vrije University Brussels, Biochemical Institute for Environmental Carcinogens, Institute of Cancer Research, International Agency for Research on Cancer

The overall objectives of WP 10 were:

a) To investigate the influence of the mechanism of carcinogenic action on the dose-response relationships and life stage- and species-specific effects of carcinogens
b) To gain a better understanding of the mechanism of mixture carcinogenicity and promote mechanistically-based cancer risk assessment of mixtures
c) To investigate the impact of different mechanisms of carcinogenic action on the choice of hazard and risk assessment strategy

Chemical carcinogenesis is a multistep process, involving procarcinogen activation to a genotoxin and induction of mutations in critical genes, the processes that favour the growth of initiated cells which, after clonal expansion, eventually give rise to a tumor. Cellular defense mechanisms counteract carcinogenesis at multiple levels e.g. carcinogen metabolism, DNA repair, cell cycle arrest and/or apoptosis. The sum of several processes finally determines whether a compound acts via a threshold or linear response mechanism. Since animal cancer bioassays are time consuming, expensive and lacking in sensitivity, there is a serious need for surrogate biomarkers for hazard and risk assessment. The development of relevant biomarkers depends crucially on an improved understanding of the mode of action of carcinogens, something that for many agents of relevance to human cancer is largely unknown. WP 10 has tackled this problem by combining forces of many teams with different but complementary expertise.
The following fundamental questions were addressed in research, in workshops and state-of-the-art reviews:
-What are the dose-, species- and age-dependent alterations in gene expression caused by xenobiotics?
-How do dose, species and age influence DNA-adduct formation and mutation induction by carcinogens?
How do dose, species and age influence the shape of dose-response curves concerning proliferation and/or apoptosis?
-Which are the genes regulating susceptibility to carcinogens and how do they influence the dose-response curve?
How does the potency of mixtures of carcinogens relate to that of individual components?

The progress of WP 10 within the first year was fortunately extremely successful. Overall, the participants of the WP were highly engaged which is reflected in five, instead of initially planned two, WP 10 meetings. Lively discussions and interactions led to the fulfillment of all deliverables and milestones within the first 12 months and spawned several grant applications. Truly, within the first 12 months the partners grew as a team creating synergistic research proposals and harmonizing their research efforts in order to provide a platform for future competitive research, exchange, integration

and training of scientists and students. Moreover, to reach out to the public the WP has used several routes such as scientific publications, lectures, workshops, press releases and internet releases. Within ECNIS WP 10 has tightened its bonds to other WPs (especially WP 1, 9, 11, 14) and thus established itself as an integral and vital part of the network.

Integration, collaborative research and training had made substantial progress during the second ECNIS year (month 13-24) in WP10. Thirteen type A projects, three type B projects and two type C projects were actively worked on during month 13-24 involving exchange, training and integration of many students and researchers. The State-of-the-art-review on "Mechanisms of chemical carcinogenesis as basis for improved risk assessment with regards to dose response relations and potential thresholds using benzo[a]pyrene and dioxin as prototypes for a DNA-damaging tumour initiator and a non-genotoxic tumour promoter, respectively" intended as a publicly available review (published in the ECNIS Reviews Series) was completed. It presents the current state of knowledge as well as gaps in our knowledge concerning the important problem of the mechanistic basis for dose responses of biochemical and biological consequences of the exposure to chemical carcinogens to vary from linear to non-linear and possibly even to non-monotonic, i.e. possibly having practical or even absolute thresholds. A Workshop on mechanisms of chemical carcinogenesis and their impact on hazard and risk assessment with special emphasis on the action of mixtures and individual susceptibilities was held in month 22 (February 2007) in Maastricht and provided a basis for a Position paper on "Carcinogenic mechanisms: Mechanisms of mixtures and individual susceptibilities" intended as WP10-internal, written basis for discussion and decision on which will be the most important and the most reward promising topics in this particular area for WP10 collaborative research.
Two WP10 meetings were held during the second year (Heidelberg, September 2006 and Maastricht, February 2007) to coordinate the cooperative work and optimize the progress. All Deliverables and Milestones planned for the second ECNIS year were completed within the second ECNIS year with the exception of the position paper "Carcinogenic mechanisms: Mechanisms of mixtures and individual susceptibilities" which was planned for month 24. Postponement of the completion was decided during our last WP10 meeting in order to allow all authors the inclusion of the material learned during the WP10 Workshop on "Mechanisms of chemical carcinogenesis and their impact on hazard and risk assessment and utility of biomarkers: Mechanisms of mixtures and individual susceptibilities" since this Workshop which was initially planned for month 26 was now held earlier in month 22 which should allow for a tolerable delay in the completion of the Position Paper when opportunity is given to all authors to include the Workshop material.

Integration, collaborative research and training had made substantial progress during the third ECNIS year (month 25-36) in WP10. Twelve type A projects, four type B projects and two type C projects were actively worked on during month 25-36 involving exchange, training and integration of many students and researchers. A position paper on "Mechanisms of chemical carcinogenesis as basis for improved risk assessment with regards to mechanisms of mixtures and individual susceptibilities" was completed.
A joint workshop with WP11 was held in month 30 (October 2007) in Ingelheim near Mainz: How can mechanisms help improving integrated risk assessment? As seen and proposed from the side of mechanisms ("offers") and from the side of the risk assessors ("needs/wishes").

A second WP 10 workshop took place in month 36 (April 2008). It focused on mechanisms of chemical carcinogenesis and their impact on hazard and integrated risk assessment with emphasis on species and gender differences as well as developmental and aging determinants.
Two successful advanced courses were held. The first took place in month 29 (September 2007) in Basel before the EEMS meeting: „A critical review of environmental mutagenesis and carcinogenesis".The second advanced course took place in month 35 (March 2008) in Mainz before the spring meeting of the German Toxicological Society: Mechanistic Basis for Improved Risk Assessment of Carcinogenic Mixtures, March 2008).
One work package meeting was held in month 29 (September 2007) in Basel with the aim to coordinate the cooperative work and optimize the progress.

Integration, collaborative research and training have made substantial progress during the fourth ECNIS year (month 37-48) in WP10. A very successful workshop on "Circadian rhythms and chemical carcinogenesis: potential link" was held in Cavtat, Croatia, Sept. 21, 2008. The main organizers were invited as guest editors for a special issue in Mutation Research to compile a series of reviews based on the different presentations of the workshop.
An advanced course on "Stem cells in chemical carcinogenesis" was held in Mainz, March 9.
To foster interactions between work packages a joint workshop together with WP9 and 11 was organized in Leuven, March 2009. All deliverables and milestones planned for the fourth ECNIS year were completed within the fourth ECNIS year.

Integration, collaborative research and training have made substantial progress during the fifth ECNIS year (month 49-66) in WP10. A special issue in Mutation Research Genetic Toxicology & Environmental Mutagenesis on the ECNIS workshop „Circadian rhythms and chemical carcinogenesis: potential link" was published. A very successful joint workshop (WP 6, 7 10) on "Mechanistic insights and use of biomarkers for improved carcinogen risk assessment of mixtures" was held 21-23 Sept. Porto, Portugal. The workshop was divided into two sessions held on 22 and 23 September, respectively. Nine speakers contributed to the workshop, which was attended by 80 or more participants each day. The first session was chaired by Barbara Oesch, University of Mainz, who gave an introduction highlighting the importance of circadian rhythms in determining susceptibility to carcinogenesis and optimal response to treatment. This was followed by presentations given by Jan Topinka, Institute of Experimental Medicine, Prague, on Genotoxicity of PAH mixtures and organic extracts from urban air particles; Andreas Zeller, Hoffman-La Roche, Basel, on Risk assessment of genotoxins with non-linear dose–response curves: the case of EMS; Theo de Kok, Department of Health Risk Analysis and Toxicology, Maastricht University, on Development and validation of genomics markers for chemopreventive effects of phytochemicals in human studies; Albrecht Seidel, BIU, Grosshansdorf, on Interactions in PAH mixtures regarding their carcinogenic and DNA-binding activities; Michael Schwarz, Tübingen, on some theoretical considerations on cancer risk resulting from simultaneous or sequential exposure to more than one cancer risk factor; and Hana Pohl, ATSDR, U.S. Department of Health and Human Services, on Predictions of binary chemical interactions: the role of toxicity mechanism and genetic variability.

Workpackage 11
INTEGRATED RISK ASSESSMENT

Hans Kromhout, WP11 Leader

The aim of this work package was to develop a strategy for Integrated Risk Assessment (IRA) in the context of environmental carcinogens. A big challenge for quantitative risk assessment is to assess the effect of low level exposures on human health. This is mainly due to large uncertainty regarding the human dose-response relationship at the low dose region. Current risk assessments usually deal with this uncertainty by applying uncertainty factors to an observed significant effect level or by extrapolation of the dose-response relationship into low-dose regions. Full integration between evidence from animal bioassays, human epidemiological studies and mechanistic studies will allow better characterization of dose-response relationships and will result in less uncertainty in risk assessment. Biomarkers might be especially valuable tools for the integration of these types of evidence. Potential advantages of biomarkers for risk assessment are hazard characterization at lower dose levels, providing insight in the shape of the dose response curve at the low dose region, and identification of susceptible subpopulations. The development of an approach for IRA directly contributed to the ECNIS objective of 'Contributing to policy development and evaluation of human carcinogens'

Partners involved

20 IRAS - Utrecht University
Partners contributing 1, 4, 5, 6, 11, 14, 17, 22

Work performed

The activities of work package "Integrated Risk Assessment" resulted in a set of tools, approaches, and reviews that provide tools for the implementation of IRA.

Prioritization of carcinogens on socio-economic criteria

Because IRA will likely be very resource intensive we developed an approach in which we explored the possibility to prioritize potential carcinogens based on socio-economic criteria. Such a prioritization will contribute to direct research activities towards IRA of agents that are most relevant to the population at large. To determine which agents should be prioritized for IRA was a complex task, since the outcome of the risk assessment itself is the best indication of the potential socio-economic impact resulting from exposure to the agent. Prioritization was based on a combination of hazard assessment, disease incidence and exposure prevalence. The result of the exercise showed that although information on hazards and disease incidence are available that exposure information is limited. Although some (outdated) exposure information was available for occupational exposure, no information was available for consumer and environmental exposures. An expert meeting was only partly successful to fill these gaps. Although we were able to produce a preliminary prioritization of carcinogens for IRA, apparently very limited knowledge is available with regard to the number of people that are environmentally exposed. Much more insight into non-occupational exposures is needed to improve the weight of evidence for this type of exercise.

Guidelines to Evaluate Human Observational Studies for Quantitative Risk Assessment

Careful evaluation of the quality of human observational studies (HOS) is required to assess the suitability of HOS for IRA. In particular, the quality of quantitative exposure assessment is a crucial

aspect of HOS that are to be considered for QRA. We developed guidelines for the evaluation of HOS for IRA and applied these guidelines to case-control and cohort studies on the relation between exposure to benzene and acute myeloid leukemia (AML). The guidelines consisted of 20 evaluation criteria. A specific focus of the framework was on the quality of exposure assessment applied in HOS. Seven HOS on the relation of benzene and AML were found eligible for evaluation. Of these studies five were found suitable for QRA and were ranked based on the quality of the study design, the conduct and reporting on the study. The developed guidelines facilitate a structured evaluation that is transparent in its application and harmonizes the evaluation of HOS for IRA. With the application of the guidelines it was possible to identify studies that are suitable for the IRA of benzene and AML and rank these studies based on their quality. Application of the guidelines in IRA will be a valuable addition to the assessment of the 'weight of evidence' of HOS for IRA.
This work resulted in a publication in Environmental Health Perspectives (December 2008):
Vlaanderen J, Vermeulen R, Heederik D, Kromhout H; ECNIS Integrated Risk Assessment Group, European Union Network Of Excellence. Guidelines to evaluate human observational studies for quantitative risk assessment. Environ Health Perspect. 2008 Dec;116(12):1700-5.

Extending the evaluation of study quality with a tool to evaluate temporal coverage of occupational history by exposure measurements

In occupational epidemiology, differences in the temporal coverage of the exposure history by available exposure measurement data may affect the uncertainty of exposure estimates. In the reporting of results of studies, greater attention should be paid to the extent to which exposure assessments require extrapolation outside the timeframe for which exposure measurements are available. We proposed a simple graphical method that can be used to visualise the temporal coverage of exposure history with exposure measurements and the extent of temporal extrapolation needed. We constructed a graph that displays the accumulated work history years for which exposure had to be assessed in each calendar year. Years for which exposure measurements were available were shaded. The proportion of work history years covered by exposure measurements and the proportion of work history years accrued before the first measurements are summarized. When available, the actual number of measurements available in each calendar year was shown. We demonstrated the application of the graphical tool in three nested case-control studies that reported on leukemia in relation to low-level benzene exposures in the petroleum industry. Considerable differences in temporal coverage between the studies were illustrated, which may have resulted in differences in the reliability of the retrospective exposure estimates derived for these studies.
This work resulted in a publication in Occupational and Environmental Medicine (September 2010):
Vlaanderen J, Fransman W, Miller B, Burstyn I, Heederik D, Hurley F, Vermeulen R, Kromhout H. A graphical tool to evaluate temporal coverage of occupational history by exposure measurements. Occup Environ Med. 2010 Sep;67(9):636-8.

Integrating the approach to evaluate study quality into hazard identification: Meta analysis on Occupational Benzene Exposure and the Risk of Lymphoma Subtypes

The use of occupational cohort studies to assess the association of benzene and lymphoma is complicated by problems with exposure misclassification, outcome classification, and low statistical power. We performed meta-analyses of occupational cohort studies for five different lymphoma categories: Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), multiple myeloma (MM), acute lymphocytic leukemia (ALL), and chronic lymphocytic leukemia (CLL). We assessed three study quality

dimensions to evaluate the impact of study quality variations on meta-risk estimates: stratification by the year-of-start of follow-up, stratification by the strength of the reported AML association, and stratification by the quality of benzene exposure assessment. The meta-analysis provided support for an association between occupational benzene exposure and risk of MM, ALL, and CLL. The evidence for an association with NHL was less clear, but was likely complicated by the heterogeneity of this group of diseases.
This work resulted in a publication in Environmental Health Perspectives (September 2010):
Vlaanderen J, Lan Q, Kromhout H, Rothmann N, Vermeulen R. Occupational Benzene Exposure and the Risk of Lymphoma Subtypes: a Meta-Analysis of Cohort Studies Incorporating Three Study Quality Dimensions. Environ Health Perspect. 2010 Sep 29.

Integrating the approach to evaluate study quality into a quantitative exposure response analysis for benzene and leukemia

Previous evaluations of the shape of the benzene leukemia exposure response curve (ERC) were based on single or small sets of human occupational studies. Integration of evidence from all studies available that are of sufficient quality combined with flexible meta-regression models is likely to provide a better insight into the functional relation between benzene exposure and risk of leukemia. Meta-regression models were fitted to 30 aggregated risk estimates extracted from nine human observational studies. Sensitivity analyses were performed to assess the impact of a-priori assessed study characteristics on the predicted ERC. The flexible model showed a supralinear shape at cumulative exposures below 100 ppm-years, although this model fitted the data only marginally better than a linear model (P=0.06). Stratification based on study design and jackknifing indicated that the cohort studies had a considerable impact on the shape of the ERC at high exposure levels (i.e. >100 ppm-years), but that predicted risks for the low exposure range (i.e. <50 ppm-years) were robust. Although limited by the low number of studies and the large heterogeneity between studies, the inclusion of all studies of sufficient quality combined with a flexible meta-regression method provides the most comprehensive evaluation of the benzene-leukemia ERC to date.
This work resulted in a publication in Environmental Health Perspectives (April 2010):
Vlaanderen J, Portengen L, Rothman N, Lan Q, Kromhout H, Vermeulen R. Flexible meta-regression to assess the shape of the benzene-leukemia exposure-response curve. Environ Health Perspect. 2010 Apr;118(4):526-32.

Integrating OMICS technologies in occupational and environmental health research

OMICS technologies are relatively new biomarker discovery tools that can be applied to study large sets of biological molecules. Their integration into human observational studies (HOS) has become feasible in recent years due to a spectacular increase in the sensitivity, resolution and throughput of OMICS based assays. Although, the number of OMIC techniques is ever expanding, the five most developed OMICS technologies are genotyping, transcriptomics, epigenomics, proteomics and metabolomics. These techniques have been applied in HOS to various extents. However, their application in Occupational Environmental Health (OEH) research has been limited. We explored the opportunities these new techniques provide for OEH research. In addition we explored the difficulties and limitations to the interpretation of the data that is generated by OMICS technologies. As an example, we prepared an overview of studies that used OMICS technologies to investigate human health effects of two well known toxicants, benzene and arsenic to illustrate the current status of the application of OMICS in OEH research.

This work resulted in a publication in Occupational and Environmental Medicine (February 2010): Vlaanderen J, Moore LE, Smith MT, Lan Q, Zhang L, Skibola CF, Rothman N, Vermeulen R. Application of OMICS technologies in occupational and environmental health research; current status and projections. Occup Environ Med. 2010 Feb;67(2):136-43. Review.

Integration of biomarkers of benzene exposure into a quantitative cancer exposure response analysis of benzene and leukemia

Although to date the relation between exposure to benzene and leukemia is widely recognized, uncertainties regarding the exact shape of the relation between exposure to benzene and leukemia still exist. The discussion is mainly focused on the leukemogenic mechanism of action of benzene and on the statistical models that should be used to quantitatively describe the exposure-response relation for benzene and leukemia. We hypothesize that dose-dependent changes in benzene metabolism play an important role in the leukemogenic effect of exposure to benzene. This hypothesis is based on evidence that suggests that specific benzene metabolites, and not benzene in its unmetabolized form, are responsible for the observed leukemogenic effects in combination with evidence that suggests that the production of leukemogenic benzene metabolites in humans is more efficient at low exposures than at high exposures. To test this hypothesis developed an approach for the integration of biomarkers of benzene exposure into the quantitative risk assessment of benzene and leukemia. Next we acquired raw data from two existing occupational studies and extracted the estimates of external benzene exposure that were used in the original analyses. The developed approach was used to convert the extracted exposure estimates to estimates of urinary concentrations of relevant benzene metabolites. Application of our approach in this example contributed to the further elucidation of the relation between benzene and leukemia.
This work will soon be submitted for publication

Impact of the work

Most of the tools and approaches developed in our work package have been published in the peer-reviewed literature and are currently cited by other researchers. Our guidelines to evaluate human observational studies have been successfully applied in various (regulatory) risk assessments and in the 2010 Monograph 100F evaluation of the carcinogenicity of benzene by the International Agency for Research on Cancer (IARC).

Objectives not reached

Acrylamide

The original proposal for “Integrated Risk Assessment” noted that the developed approaches and tools would be applied on a second case substance: acrylamide. In contrast to benzene, the epidemiological evidence for the carcinogenicity of acrylamide is scarce. A recent JNCI publication noted that “The findings from epidemiological studies have converged in indicating no positive association between total dietary acrylamide intake and risk of colorectal cancer, bladder cancer, esophageal cancer, and prostate cancer. Similarly, no associations have been reported with risk of oropharyngeal, laryngeal, pancreatic, and gastric cancers, although the findings for these cancers were based on results from only one study” (Mucci et al. in JNCI 2009). The scarcity of the epidemiological evidence on acrylamide precluded us to apply our methods which are generally very data intensive.

Workpackage 12
SOCIO-ETHICAL IMPACT OF BIOMARKER USE

Birgit Dumez, WP12 Leader

WP12 was dedicated to specific research on the socio-ethical impact of biomarker use. The general aim of the work was to (i) assess the socio-ethical impact of current human biomonitoring research activities and surveillance practices in the EU, (ii) to assess consistency of these practices with goals which have been part of 'European' social morality traditions (respect for human dignity, social justice, solidarity and democratic participation) with a view to identify the need for (modification of) regulations and rules and (iii) to contribute to guidelines for harmonized socio-ethical and legal approach of human biomonitoring activities in the EU, including procedures for effective and appropriate communication both a the individual level and at the collective level.

Relation to general ECNIS objectives

Ethical considerations are as intrinsically related to good research as are scientific considerations. The conduct of biomedical research involving the participation of human beings implicates a variety of ethical concerns, pertaining to such values as human dignity, bodily integrity, autonomy and solidarity, and to the balancing of these.

Overall ECNIS tackled several sensitive ethical issues when dealing with genomic differences in response to diet, identifying sensitive sub-populations. The project intended to ensure that any ethical issue, including risks for participants, was recognised and managed by researchers and that research was conducted following the highest ethical standards, in accordance with European socio-ethical values.

Practices within the project were collected and served as a basis for the identification of challenges and bottlenecks in the current framework and of possible levers for solutions. At the same time support was given on ethical and data protection problems experienced in daily life circumstances. The ERP was initiated and then further supported.

Partners involved

The work was mainly performed by the KULeuven team. All ECNIS researchers contributed however with reporting on specific experiences and challenges in their daily work. Particular collaboration was established with the Ethical Review Panel and with the project coordinator team.

The degree to which the objectives were reached

The results of the work of WP12 are brought together in ECNIS volume "Ethics and Data Protection in Human Biomarker (HBM) Studies", available on line trough the ECNIS website and addressing the 3 objectives mentioned above.

In the volume ethics and data protection in environmental health studies using human biomarkers are extensively reviewed. The question is raised whether research participants involved in human biomarker studies are adequately and equally protected throughout the whole of Europe and whether at the same time the possibilities for environmental health related research to progress are safeguarded. In other words, whether the current ethical and legal framework protects what ultimately should be protected, or whether – and, if so, to what extent - it may need rethinking to achieve its goals.

In the first part of this volume attention is given to a working definition of public and environmental health and the current ethical and legal framework is outlined. Furthermore, a short introduction is included on guiding philosophical principles when analyzing ethical issues and the problem of conflicting societal goods is explored.

In the second part, important challenges in ethics and data protection in environmental health research using human biomarkers are analyzed and discussed. Focus is on the application of the formal legal aspects of human biomarker research, on decision making processes (mainly the informed consent procedure and the function, position and significance of research ethics committees) and on communication, going shortly into the most important aspects and highlighting some of the recent developments in this field.
As much information as possible was drawn from concrete situations occurring in practice. As said above, researchers in the field shared their personal experiences and difficulties regarding these issues. Other valuable contributions came from ethicists, lawyers and social scientists in the field of public health, and from studies assessing the perception of research participants. Illustrative example cases are presented, an analysis of specific problems is made and possible steps towards improvements are discussed.
The final part summarizes the considerations and adds suggestions for possible solutions.
In the annex, relevant articles of the legal or guiding documents presented in the text are cited in full, ordered by topic.

Brief description of the methodologies and approaches employed

- Bottom up approach: a continued investigation and analysis of practices related to recruitment of study participants and collection of samples in ongoing scientific studies and programmes of the ECNIS network, including the informed consent procedure and communication of results, both at the collective and individual level. Information on diverse ethical and data protection aspects was gathered via inquiries and via formal and informal dialogues –also at bilateral level- with ECNIS researchers. Information was furthermore collected based on discussions with relevant experts at workshops and congresses both at national and European level. Besides the collection of information directly from researchers, the ethical review of the ECNIS calls on type B projects provided valuable additional information together with the discussions on the MEC DATABASE and the issue of the use of anonymous data and the interpretation of the terminology.
- Investigation of the information by a comparative analysis of determinants of ethical reasoning, created the opportunity to assess not only whether there is a justified need for rethinking the ethical framework for environmental health research using human biomarkers, but also to identify possible solutions. Proposals for solutions were subjected to the criticism of a selection of experts with different backgrounds (including researchers, philosophers and lawyers), aiming at a solid foundation and backing of the proposals. a close link with policy actions in the field was established (e.g. the EU Health and Environment Action Plan 2004-2010).
- Guidelines and support: working with different research teams learned that the focus of activities with respect to ethical analysis had to be widened to fulfill also more immediate and practical needs. The challenge consisted of elaborating very concrete and clear practical guidelines and solutions that not only guarantee the respect of ethical values, but at the same time reduce the perceived burden of (sometimes irrelevant) ethical constraints, both for the research subjects and the researchers. Most urgent practical needs were related to research performed in transnational context and to the secondary use of personal data and biological material. Furthermore, from the information collected in real life complexity, it became apparent as well that due to the specific public health context of HBM research, there is a growing need for appropriate communication strategies, at recruitment, during and at the end of a project.
- Continued investigation of legislative and regulatory context, focusing on the rights, entitlements and responsibilities of researcher and research participants. Besides general and practical advice, more detailed analysis on specific items related to differences in interpretation and implementation in EU Member States was performed and solutions outlined to facilitate

secondary use and transnational research in HBM activities in Europe. This included the development of a roadmap to comply with current legislation. The roadmap focused, from the perspective of the rights and entitlements of researcher and research subject, on the privacy legislation (based on the EU Directive 95/46/EC) and the guidelines produced by the Council of Europe from the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, its Additional Protocol concerning Biomedical Research and the Recommendation Rec(2006)4 on research on biological material of human origin, which is build on the principles from the Convention.

- Education and training: Teaching modules on ethical aspects of HBM research were developed and included in some ECNIS workshops or courses in the field of HBM research. In order to reach a wider public of relevant professionals, WP12 has contributed to the development of a video on the informed consent procedure by NewGeneris IP. This training material is based on problems and obstacles encountered in practice and confronts the practice with the theory.

Relation to the achievements of the project to the state-of-the-art.

There is no good science without good ethics. The focus on ethical issues within the project supports the value of its overall results.

Potential impact of the project on its industry or research sector.

The critical analysis of research experiences in various EU countries has shown that difficulties, ambiguities or even inconsistencies exist in the way ethical and juridical challenges are framed and being dealt with within and across countries. Overall, it is observed that in research involving human samples or data emphasis is primarily on decisional autonomy and protection of the individual's rights whilst the collective need to protect health as a public asset is relatively less valued. This is particularly striking when personal data or samples collected for a specific research purpose could be of value in a new study. This secondary use often remains very complex or almost impossible, although there are strong and recognized arguments for facilitation of such further use in the context of environmental health research where risks of improper use of data or samples are minimal and public interest comes to the forefront.

Besides presenting the general conditions in the current EU regulative and ethical framework, the analyses made and the steps to solutions suggested may (i) help to increase knowledge on the application and implementation of the regulatory context; (ii) may enrich the public debate on ethical and legal issues with respect to human biomarker studies; and (iii) may contribute to a situation where study participants are adequately and equally protected throughout Europe whilst at the same time progress in environmental health related studies is fully safeguarded.

Since its publication in spring 2010, the volume has been presented and disseminated at several occasions e.g. during meetings of the EU projects ECNIS, NewGeneris and COPHES; at the Collegium Ramazzini October 2010; at the Human Biomonitoring event in the frame of the EU presidency in October 2010, at the annual HEAL meeting in September 2010. The volume is also included in the conference material of the upcoming meeting within the EU Belgian presidency - Privacy & Scientific Research: from Obstruction to Construction - organised by the Belgian Privacy Commission on 23 November 2010. The congress focuses on various target groups, primarily the European data protection authorities, but also domestic and foreign academics and researchers. The volume is available on line trough the ECNIS website.

Workpackage 13
DISSEMINATION OF KNOWLEDGE TO THE SCIENTIFIC COMMUNITY

Paolo Boffetta, WP13 Leader

Workpackage 13 (WP13) is one of the two workpackages dealing with spreading of excellence activities. The specific objectives of WP13 are to disseminate knowledge to the scientific community and this was achieved through the organisation of three main tasks. Firstly, a fellowship scheme was run whereby fellowships were awarded to researchers external to ECNIS to spend a period of research at an ECNIS institution, or for ECNIS researchers to train at an institution external to ECNIS. The second main dissemination task was to jointly hold meetings, international symposia and workshops as satellite events to international conferences. Lastly, a web-course on molecular epidemiology has been developed.

WP13 was led by partner 22, the International Agency for Research on Cancer (IARC).

Exchange fellowships

Exchange fellowships were awarded to researchers external to ECNIS to spend a period of between 2 weeks and 6 months at an ECNIS institution, or more commonly for an external researcher to conduct research within an ECNIS institution. In principle, these are similar to the training fellowships (WP3) but with an external connection. During each of the 5 years of ECNIS, exchange fellowships were advertised within ECNIS member institutions and on the ECNIS and IARC websites, inviting researchers to apply. Applicants agreed a research proposal with their home and potential host institutions for their application. Applications were independently reviewed and scored by senior scientists at IARC, Imperial College London, the Institute of Cancer Research (UK), Athens University, Nofer Institute of Occupational Medicine (Poland) and Vrije Universiteit Brussels (Belgium). This selection committee then met (via telephone conference) to discuss scores and decide on fellowships to be awarded.

Over the 5 years a total of 22 exchange fellowships were awarded, funding a total of 66 months of research, i.e. an average exchange time of 3 months per fellow. The exchange fellows originated from a diverse range of countries, including Italy, Germany, Iran, Turkey, Norway, Poland, Hungary, Bulgaria, Spain and the Czech Republic, demonstrating the far-reaching nature of the scientific community that benefitted from this programme. Most exchange fellows were at the start of or early in their scientific careers, with 9 being PhD students, 9 postdoctoral fellows and 5 junior scientists. Typically, training periods were spent in another laboratory that had equipment or expertise not available in the fellow's home institution.

Examples of the topics of research include "Integration of biomarkers of benzene exposure into quantitative cancer risk assessment of benzene and leukaemia", "Role of nicotinic acetylcholine receptor in lung cancer", "Environmental Epigenetics – Identification of intermediate biomarkers for breast cancer and B-cell lymphoma based on DNA methylation status".

An evaluation of the fellows' experiences was carried out in year 4 via completion of a questionnaire asking about their experience, and scoring it based on various criteria (knowledge gained, skills acquired, ability to speed up research, support in host institution, and potential of future collaboration). There was an overwhelming positive response to this questionnaire by nearly all

fellows. All fellows found the program to be 'good' or 'very good' and that the period was beneficial to them. For many (70%), their research benefitted from new technologies in the host institutions, for example use of Affymetrix technology and new techniques in proteomics. Some fellows specifically said that they felt their research would not have been possible without the program. Fellows were commented that the benefits of the exchange programme included the educational experience, the building up of a network and the opportunity to collaborate with much more experienced researchers. They also appreciated the opportunity to travel and work in other institutions with different structures, to exchange scientific ideas and to learn new methods that could be brought back to their home institutions.

Organisation of meetings and international symposia

Each year international meetings or workshops alongside such meetings were organised to provide an opportunity for ECNIS scientists to interact and network with the broader scientific community specialising in their research fields. ECNIS-sponsored or led meetings were especially held alongside European Environmental Mutagen Society (EEMS) on several occasions. Links with other European scientific networks such as CONCAWE and CASCADE and international networks such as HuGeNet, were established through the organization of joint international conferences or fostering specific sessions and meetings.

Examples of the above meetings and interactions include a Symposium on "The role of environmental genotoxins in human carcinogenesis", held in 2005 at the 35th Annual Meeting of EEMS (Kos, Greece). The following year a joint ECNIS-EEMS International Conference was held between 3-7 July 2006 in Prague, Czech Republic. This was the First Annual Conference of ECNIS, held in conjunction with the 36th Annual Conference of EEMS. ECNIS promoted a number of events in the context of the 42nd Annual Meeting of EUROTOX, which was held on 11-14 September 2005 in Krakow, Poland, including the Continuing Education Course on "Molecular Mechanisms of Food Contaminants Toxicity".

An International Symposium on Integrative Molecular Cancer Epidemiology was held in Lyon France from 3rd to 5th July 2008. This was a large and successful symposium, attended by over 200 participants from institutions worldwide and was a joint initiative of IARC, EACR, AACR and ECNIS. The symposium brought together international experts, researchers and junior scientists working in molecular cancer epidemiology to discuss and exchange ideas and findings in the aetiologic and mechanistic aspects of molecular and genetic cancer epidemiology research.

Development of a web-based course in molecular epidemiology

Spreading of excellence throughout the ECNIS network was achieved not only through face-to-face courses and workshops, but also by developing material that could be utilized online, to achieve a greater reach. Initially this was achieved through web-hosting lectures that were delivered in the Molecular Epidemiology and other courses on the ECNIS website, accessible to all ECNIS members. These were later modified, formatted and integrated into a single course of Molecular Epidemiology. The final version of the course consists of 4 modules, with sub-modules as shown below.

The intention of the compiled course is that it introduces the basic concepts in molecular epidemiology and pointing the researcher to the main issues and further reading. Where appropriate cross-reference between sub-modules have been included, to allow a user to study stand-alone sub-modules, filling in their knowledge gaps as and when needed.

ECNIS web-based course in Molecular Epidemiology	
Module	Submodules
Module A: Molecular Epidemiology- concepts and essential background	Overview; Biomarkers; Study design; Biomarkers in case-control studies; Study design example – breast and lung cancer; Statistical methods in molecular epidemiology; Confounding and effect modification
Module B: Biomarkers	Biomarker Validation; Biomarkers of DNA damage; Biomarkers in nutrition; Ethics and Biomarkers
Module C: Genetics and Omics in Molecular Epidemiology	Mutation Spectra; Genetic Epidemiology; Mandelian Randomisation and causality; Omics in Longitudinal studies; Metabolomics by NMR Spectroscopy; Proteomics and Biomarker discovery
Module D: Advanced and Further Topics	Systems biology approach to epidemiology; Example: Oesophageal cancer; Infection and Cancer; Advanced Statistics

http://www.episat.org/episat/courses/

Workpackage 14
COMMUNICATION AND DISSEMINATION

Soterios Kyrtopoulos, WP14 Leader

Specific objectives of WP14 were: To organise and conduct ECNIS communication and information dissemination activities, to facilitate internal network communications, to promote ECNIS visibility and to promote the dissemination of scientific knowledge to stakeholders. The role of WP14 were to:

Ensure that the ECNIS uses appropriate and effective tools to spread information to stakeholders and for its internal communications,

Promote contacts and interaction with stakeholders and further develop interaction with them,

Produce materials and events to promote ECNIS visibility,

Produce materials and events to promote the utilisation of new knowledge by stakeholders.

ECNIS Dissemination strategy and organisation

The organisation of Dissemination activities in ECNIS were based on a) a Dissemination and Communication Office (DCO), established at partner 6 (National Hellenic Research Foundation) including DC Officer (Maria Botsivali) and secretarial support and b) a Dissemination Task Force, consisting of partner 6, partner 1 (Beata Peplonska and Robert Klarecki, Nofer Institute, primarily responsible for the operation of the website and printing of most publications), partner 24 (Lennart Moller, Leocordia Company, primarily responsible for the production of the Newsletter), and partners 14 (Bjorn Akesson, Univ. Lund) and 2 (Jagdish Nair, DKFZ) who made general contributions to dissemination activities. Other network partners were involved in dissemination activities on an ad-hoc basis.

A Framework of operation of ECNIS “Dissemination to stakeholders” activities was agreed at an early date, defining the flow of activities in the cycle of selection, processing, evaluation and dissemination of knowledge, and a series of stakeholders on whom attention would be focused was identified, including in particular stakeholders at the European level (general public, EC policy makers, industry, consumer and health professional organisations)

As the main tools for conducting dissemination activities were employed a) the project website and email news network, b) publication of brochures and newsletters, and c) participation in stakeholder events organised by ECNIS or other entities.

During the first year of the project, a training course on risk communication was held for network partners, organised by Lennart Moller, member of the ECNIS Dissemination task force.

ECNIS website:

The ECNIS website is an interactive site consisting of an open (public section) and a partners-only collaboration area.

- Operation of the public section of the ECNIS website

The ECNIS website (www.ecnis.org) was initially set up immediately after the start of the project and took its fully developed form a few months later. The website served as a major instrument for spreading information about ECNIS and related scientific progress, providing general information on

the project, its objectives, structure and partners. Additional notable sections of the public website include

a) The “Publications and Reports” section, hosting Publications (partner publications in peer-reviewed journals, of which the abstracts could be downloaded) and ECNIS Reports (which can be downloaded in full text). At a later date a sub-section dedicated to the ECNIS Repository was added to the website, which provides organised access to all partner publications, including full-text access where possible. The ECNIS Repository also hosts the ECNIS Annotated Bibliographic Database which was produced in the context of WP5.

b) The “News and Events” section, providing regularly updated information regarding upcoming events, ECNIS- organised as well as organised by others but of ECNIS relevance, including workshops, training courses and conferences. The uploading of all new items of News and Events on the website was automatically notified by email to all subscribers of the “ECNIS email-news network”. Importantly, for all important ECNIS Workshops, a report containing a summary of the proceedings (and sometimes the full presentations) was produced by the Dissemination Officer and uploaded on the News and Events section of the website.

c) The “Science Portal”, on which recent advances in the area of ECNIS interest are highlighted for the benefit of the general public and other stakeholders, was supplied with material derived from recent scientific publications of ECNIS partners. This material included not only summaries of individual publications but also popularised overview texts summarising the findings of groups of publications related to specific topics.

- Operation of the “partners only” area of the ECNIS website

The internal area of the website operates as a collaboration area, where all important working documents produced by the network are organised and stored. Examples of such documents include information on the project contract, general network documents (partner lists etc), various ECNIS reports which it has been decided to publish only on the internal website, information on type A and funded type B projects, ECNIS publicity materials (logo, brochure etc), information on ECNIS-relevant FP7 topics, presentations from the Annual General Meetings etc.

Newsletter

Newsletters were produced twice yearly throughout the duration of the project, containing information on ECNIS activities, presentation of the network partners, as well as popularised articles on environmental cancer and its causes and prevention. The ECNIS Newsletters were distributed to a large number of stakeholders and are also available for downloading from the project website. 9 issues of Newsletter were produced and distributed during the ECNIS project.

Brochures, poster and Powerpoint presentations

A colour brochure and poster were produced, along with an electronic Powerpoint presentation of the project, at the state of the project as well as, in an updated form, after the project’s mid-point, and distributed to all partners as well as to a large number of stakeholders.

Stakeholder workshops

During the project’s duration ECNIS WP14 organised 2 stakeholder workshops and participated in a large number of analogous stakeholder events organised by others.

- WP14-organised “Workshop on biomarkers and their potential in human biomonitoring and environmental health surveillance”
In view of the strong current interest in human biomonitoring and current plans for the setting up of a FP7 European biomonitoring pilot project, a Workshop on biomarkers and their potential in human biomonitoring and environmental health surveillance was organised, in collaboration with DG Research and DG Environment, in Luxembourg on 29 November 2006. The event was attended by 70 stakeholder representatives from national organisations of EU member states, the European Commission, NGOs and industry. The speakers came mainly from ECNIS but also from the European Commission as well as from two EU projects (NewGeneris and ESBIO) related to biomarkers. The Report from the Workshop, in the form of a CD including the programme and speaker presentations, was circulated to more than 200 stakeholders.

- Stakeholder workshop on “Food and environmental cancer risks for adults and children”, organised jointly by ECNIS WP14 and the NewGeneris project, Brussels, 16 March 2009. The workshop was attended by about 30 representatives of stakeholders, including DG Sanco, ILSI, CEFIC and HEAL (the Health and Environment Allicance) as well as by about 100 ECNIS scientists.

- The ECNIS Dissemination and Communication Officer participated in the EFSA European Food Safety Summit in Brussels, on November 2007, where some hundreds of people participated (high-level decision makers from member states, representatives from EU Institutions, International Organizations, NGOs, Industry, Consumers).

- The ECNIS Dissemination and Communication Officer participated in the 1st International Conference on Risk Assessment “Global Risk Assessment Dialogue”, organised by DG SANCO, Brussels, 13-14 November 2008, where some hundreds of people participated (high-level decision makers from member states, representatives from EU Institutions, International Organizations, NGOs, Industry, Consumers) and distribution of ECNIS publicity material.

- The Dissemination and Communication Officer participated in the Fifth WHO Ministerial Conference on environment and health: Protecting children's health in a changing environment, Parma, Italy, 10-12 March 2010, where she gave a presentation on “Trends in biomarkers research and their potential for biomonitoring strategies: A NewGeneris and ECNIS overview” in the context of a workshop on biomonitoring organized by the COPHES project.

- ECNIS joined CommNet, a Network of communication officers of 30 food-related EU projects. The ECNIS Dissemination Officer Maria Botsivali participated in two events organized by CommNet
- the European Food Science Day in Brussels, 18 November 2009, in which over 100 participants from a wide background participated; ECNIS information material was distributed.
- CommNet partner meeting in Brussels on 24 March 2010, followed by a meeting of FP6 Food Quality & Safety Communicators organised by DG Research.
In addition, the ECNIS Dissemination Office hosted a CommNet meeting in Athens in October 2010.

Contacts with other projects

From an early stage contacts were established between ECNIS and a large number of European projects related to environmental cancer and food safety. Particularly close collaborative contacts

were maintained with the NewGeneris project, a large FP6 integrated project which applies in the field biomarkers of direct interest for ECNIS. A number of joint ECNIS-NewGeneris workshops have been organised, including one aimed at stakeholders and co-organised by WP14.

Close contacts have also been maintained with two European biomonitoring projects, ESBIO and its successor COPHES. ECNIS activities were presented at workshops organised by both these projects, first at an ESBIO meeting in Berlin, June 2006 and subsequently at a workshop on biomonitoring organised by COPHES during the "Fifth WHO Ministerial Conference on environment and health: Protecting children's health in a changing environment", Parma, March 2010.

Other dissemination activities

- ECNIS presentation in the magazine of the European Parliament

ECNIS was presented in the European Parlament's "Parliament Magazine" on 3 occasions of the publication of special issues related to research or to cancer: 12th March 2007, 28 January 2008, 2 February 2009. The Parliament Magazine has a readership of 20,000.

- Contribution to DG Research DVD

In January 2007 the ECNIS Communication and Dissemination Officer participated in a DVD produced by DG Research with the general theme Food in Europe, where she presented ECNIS and its activities. The DVD was distributed by DG Research to a large number of stakeholders.

Achievement of objectives and impact

The main success of ECNIS has been at the level of establishing a tight European research network and of playing a key role in the evaluation of the state of science and the formulation of research strategies. The Dissemination activities of ECNIS played an important role in establishing the network as a major player in the area of environmental carcinogenesis and biomarker research in Europe and beyond. This achievement is particularly well reflected in the impressive degree of popularity of the ECNIS website, which during the 5½ years of the project's duration received over 2 710 632 hits (as compared to the 5,000 which was the initial target described in the DoW). The number of Google hits for the word "ECNIS" at the end of October 2010 was 69,000.

Workpackage 15
MANAGEMENT

Konrad Rydzynski, WP15 Leader

The goal for the ECNIS management was to establish a functional, flexible management structure to ensure efficient communication between the ECNIS participants, with EU, and different stakeholders as well as to guide the network towards its ultimate goal of world-wide recognition. Considering the potential problems involved in coordinating more than 20 institutions where many different administrative cultures were represented, the establishment of a flexible management structure was a challenging task.

The principal objectives of the NoE Management Activities were:
– To ensure management, integration and coordination of network activities.
– To conduct a comprehensive evaluation of the network´s performance, with special regard to progress towards the achievement of integration objectives, at regular intervals.
– To ensure efficient communication within the partnership network, with the European Commission as well as with external bodies by establishing a robust management structure.
– To ensure compliance with the work program as well as contractual conditions,
– To ensure that due attention has been given to gender and ethical considerations, including the fulfillment of local legislation and other requirements.
– To provide assistance to ECNIS partners regarding administration and reporting as well as potential problems.

Management Structure

The ECNIS managerial structure during the period funded by European Commission was executed on different levels:

(i) Network Governing Council (GC)
(ii) Network Management Board (NMB) with Network Management Office (NMO)
(iii) Task groups/Workpackages
(iv) Partner level

The Nofer Institute of Occupational Medicine & WHO Research Centre in Lodz, Poland, has been appointed as the Coordinating Institute of ECNIS, with professor Konrad Rydzynski as the Coordinator (CO). He was the main legal party with respect to the Commission, and represented the link between the Commission and the Consortium, i.e. the partners of the ECNIS Network.

The Network Governing Council represented the main decision making body of the whole Network. One representative from each participating institution was delegated to this body. Chaired by the Coordinator, NGC was responsible for all major decisions related to the management of the network and took full responsibility for the financial, administrative, legal and research management of the NoE. Network Governing Council meetings were organized regularly, during the Annual General Assemblies. During these meetings a crucial decisions for the network were undertaken by voting. Additionally, between the meetings the voting via internet was organized. Within ECNIS voting application enabling all ECNIS partners to take a vote virtually on every issue was developed. Using this application ECNIS NGC members selected noble scientists for the ECNIS Scientific Advisory

Committee, approved the system of the partners evaluation, inclusion of the Collaborating Centres, and replacement of the Workpackage Leaders.

The NGC was supported by the Network Management Board which represented the focal point of the network management. It was composed of the Coordinator (Professor Konrad Rydzynski), the Activity Coordinators (Prof. B. Åkesson(replaced then by Prof. Micheline Kirsh-Volders), Prof. D. Segerbäck, Prof. S. Kyrtopoulos, Prof. P. Farmer, Prof. P. Boffetta and Prof. P. Vineis) and the Executive Director of the Network Management Office (Dr Maciej Stepnik, then replaced by Dr Beata Peplonska).General NMO Manager was Dr Robert Klarrecki. Financial manager of the network was Ms Dorota Bialas M.A, then replaced by Ms Kamila Szczesniak,MSc.

The NMB took all actions to ensure proper network management. It took full responsibility for the implemention activities linked to administrative, legal, knowledge management and financial management on a network level. These activities also referred to other issues such as conflict solving, intellectual property rights assessment, innovation activities etc. The NMB took the major decisions between GC meetings – e.g. approval of new projects to be funded by the network or to be proposed for funding. NMB meet as many as 22 times during 5 years. Besides hundreds of e-mail messages were circulating between NMB members.

During first year of ECNIS operation The Science Advisory Committee, and three panels: Panel for Experts on Methodology Standardization, Ethical Review Panel and Panel for Gender Issues were set up within the Network.

The Science Advisory Committee consisted of external scientists of high reputation, who covered areas relevant to ECNIS. Its current members are:
Dr. H. Autrup, University of Aarhus, Denmark
Dr. S. Bingham†, Medical Research Council, Dunn Human Nutrition Unit, Cambridge, United Kingdom
Dr. M. Fenech, CSIRO Health Sciences and Nutrition, Adelaide, Australia
Dr. J. Milner, National Cancer Institute, NIH/DHHS, Rockville, Maryland, USA
Dr. F. Perera, Columbia University, USA

The preparation for the ECNIS Panel of Experts for Methodology Standardization set up was initiated at kick-off meeting. The final list of members was agreed upon during the ECNIS NMB meeting in Kos Island (July, 2005).
The Panel of Experts for Methodology Standardization brings together prominent scientist, with expertise in various fields of relevance to quality assurance of methodologies. Its current members are:
Dr. P.B. Farmer, University of Leicester, United Kingdom
Dr. Ari Hirvonen, National Institute of Occupational Health, Helsinki, Finland
Dr. Jagadeesan Nair, German Cancer Research Centre, Heidelberg, Germany
Dr. Franz Oesch, Johannes Gutenberg University, Mainz, Germany
Dr. David Phillips, Institute of Cancer Research, United Kingdom
Dr. Dan Segerbäck, Karolinska Institutet, Stockholm, Sweden
Dr. Albrecht Seidel, Biochemical Institute for Environmental Carcinogens, Prof. dr Gernot Grimmer Foundation, Grosshansdorf, Germany
Dr. Frederik-Jan van Schooten, Maastricht University, Netherlands

Dr. Paolo Vineis, Institute for Scientific Interchange Foundation, Torino, Italy

The two Panels: Panel for Gender Issues, and Ethical Review Panel were established.

Annual meetings:

The NMO with cooperation with hosting Partners organized kick-off meeting and 5 annual meetings.

A KICK-OFF MEETING took place early after initiation of ECNIS in Warsaw (25, 26.05.2006). This event brought together more than 130 scientists representing all of the Network's partners, together with EC and Polish officials participating as the invited guests. The kick off meeting event was described in the report, and was published in the International Journal of Occupational Medicine and Environmental Health: Stepnik M, Kazmierczak K. Kick-off meeting of ECNIS Network of Excellence. (Report) Int J Occup Med and Environ Health, 2005; 18(30): 281-286.

First ECNIS Annual Meeting – Prague, July 2-6, 2006 was organized in conjunction with the "36th Annual Meeting of the European Environmental Mutagen Society". Some formal meetings, eg. Science Advisory Committee meeting, Network Governing Council meeting, and Reviews meeting took place at this occasion. During General Assembly activities coordinators presented the achievements and progress of ECNIS during the first year since it was launched.

SECOND ECNIS ANNUAL MEETING - Maastricht, 25-28 February 2007, attended by more than 130 scientists - committee approved

During the meeting the progress of all the work packages was discussed, special workshops took place, a poster session was organized, while the Network Management Board and Network Governing Council held also their meetings. All 15 Workpackages of ECNIS presented their progress and plans for the next 18 months, followed by discussion with all the members.

During the workshops ECNIS scientists as well as invited speakers had the opportunity to discuss a variety of issues including: urinary biomarkers, the databases on biomarkers, standardized protocols, mechanisms of chemical carcinogenesis, functional impact of genetic variation in genes of relevance to environmental carcinogenesis, development and organization of teaching modules on ethical aspects of human biomonitoring research modules. A lot of young researchers and students had the opportunity to present by posters or orally their exciting results in projects conducted in the ECNIS framework.

THIRD ECNIS ANNUAL MEETING - BARCELONA, 3-5 March 2008 (160 scientists participants)

Several WPs organized special seven workshops with a rich topics covering all fields of ECNIS research area (biomarkers, epidemiology, nutrition and cancer, susceptibility, diet antioxidants, gene-environment interactions, environmental pollutants, nanoparticles, carcinogenic reaction mechanisms, -omics, cancer incidence etc):

Fourth ECNIS Annual Meeting - Brussels, Leuven - on 16-18 March 2009 (130 participants)

The first part of the Meeting was held on 16 March, at the Royal Academy Palace, Brussels, and was open to the public. During the morning a half-day stakeholders' workshop on "Food and environmental cancer risks for adults and children" was held, jointly organized by ECNIS and the NewGeneris Integrated Project. This was followed on the afternoon of the same day, and at the same

location, by the first part of the Annual General Meeting of the ECNIS consortium, during which the WP leaders presented an update of progress achieved during the preceding year as well as their plans for the following year. On the following 2 days the Meeting moved to the Faculty Club, Leuven, where a total of 7 workshops and a session dedicated to presentations by Ph.D. students were held.

FIFTH ECNIS ANNUAL MEETING - 15-16 April 2010, Lódz, Poland (80 participants)
During 2 days of the meeting 5 workshops were organised by different Workpackages and held as parallel sessions. In addition, a poster session was organized with 11 posters presented. The scientific Workshops covered important developments in the areas of biomarkers and summary of the achievement within the workpackages. (e.g. achievements of WP1 and prospects for future use of ECNIS facilities; achievements in biomarkers of environmental carcinogenesis), overview of the MEC and strategy and recommendations for reporting molecular epidemiology results, with a concept of STROBE-ME presented. Interesting works were presented on the data on influence of the genetic polymorphism on dietary modulation of cancer risk. Separate workshop was organized on relatively new and not clear yet role of intestinal microorganism for the risk of cancer.
In order to facilitate an efficient communication flow between ECNIS members as well as to communicate on ECNIS related events and activities an e-mail network at NMO was worked out based on the address data collected from each partner. The list of e-mail recipients has been created in the first month of ECNIS operation, and was being updated on a regular basis. The first version of ECNIS website presumed to be both a tool of internal and external communication was implemented as early as in the May, 2005 (www.ecnis.org). The first version of the service news was introduced at the ECNIS workspace in August, 2006.

System of partners evaluation and budgeting system
During the second year of ECNIS the effectiveness of main organisational structures i.e. Network Management Board and Network Management Office was further intensified in order to speed the process of Network integration and to coordinate incoming activities and secure their timely accomplishment. The two major issues related to the Network (system of partners evaluation and budgeting system) were finally solved.

The Financial Task Force (FTF) formed in September, 2006, of 5 ECNIS members (2 NMB members, 2 Partners, NMO representative) namely: Paolo Boffetta (IARC), Soterios Kyrtopoulos (NHFR), Ari Hirvonen (FIOH), Hans Kromhout (IRAS), and Kamila Szczesniak (NIOM) elaborated clear rules of the budgeting system, and indicated the necessary revision of the Partners Evaluation System. The proposal of the FTF was then approved by NMB and finally by Network Governing Council by voting held during Annual Meeting in Maastricht 27th of February, 2007.
Within ECNIS an original system for evaluation of the partners performance in the integration process was developed. Such important values were summed up for each Partner as: a)Contributions to science integration, b)Providing input to the ECNIS knowledge database on Molecular Epidemiology and Cancer (MEC), c)Creation and maintenance of core facilities supporting molecular epidemiology research within ECNIS, d)Establishment of common inventories of, and tissue banks for biological samples, e) Common publications (with ECNIS®) score based on Impact Factor IF of the journal (CC). f) Writing a chapter for an ECNIS report, g) Participation in the Research projects (ECNIS - type A; type B, type C), h) Exchange of researchers, i) Contributions to technical integration: Input to the ECNIS website and ECNIS e-mail news network (ECN-EWS), j) Contribution to public website, k) Contributions to education : organization or participation in the specialized training courses. Starting

from ECNIS year 2, this system was used for the purpose of the budget distribution in this way distributing more fund for the most active partners.

ECNIS Collaborating Centres

The process of integrating the Collaborating Centres into the structure of ECNIS was carried out and finalized in years 2-3. There were five candidates that sent their applications and supporting letters according to the procedural request. The Network Management Board members have carefully reviewed the applications and assigned scores to each of the candidates assessing the candidate's fulfillment in following categories: 1. Relevance to ECNIS, 2. Quality of the Group, 3. Potential collaborations

Four out of five candidates for CC were approved by NGC, namely

– Institute of Experimental Medicine AS CR, Prague, Czech Republic
– Molecular Epidemiology Unit of the University of Leeds, UK
– National Institute of Health, Government Institution, Porto, Portugal
– University of Manchester, Manchester, UK

National Institute of Health, Government Institution, Porto, Portugal was hosting a set of ECNIS workshops in the autumn, 2009.

Conflict of interest with tobacco industry

One major problem emerged concerning the policy of some partner institutions regarding their relationships with the tobacco industry, collaboration between ECNIS partners and subsequent threat of withdrawal of some of the partners from the Consortium.

In recent years, Europe has taken a more restrictive road in relation to tobacco industry. The EU convention, as well as the general discussion on research funding from the tobacco industry, has influenced a number of research institutions to set up new policy commitments, with decisions not to accept funding from the tobacco industry.

The field of research of ECNIS, namely biomarkers of exposure, effect and susceptibility to environmental carcinogens, is particularly sensitive in this respect, since several groups of these carcinogens are also present in tobacco smoke and in smokeless tobacco products. Due to IARC policy concerning conflict of interest with tobacco industry, no collaboration of IARC is allowed with partners having financial support from tobacco industry. Variations of these policy rules exist for several other, but not all ECNIS partners. The issue emerged in conjunction to the ECNIS funded projects whereas several partners having various policies regarding tobacco industry were to operate together. "An ECNIS working group to elaborate policy on conflict of interest" was set up, chaired by Ulf Görman (chair of Ethical Review Panel) with participation of Paolo Boffetta, Micheline Kirsch-Volders, and Peter Farmer

The working group for a policy on conflict of interests has developed a policy document (which was then adapted by NGC by voting during NGC meeting in Barcelona Disclosure statements from partners were collected.

Core Group of Networks of Excellence

ECNIS has joined the group of Core Group of Networks of Excellence, and ECNIS coordinator Prof. Konrad Rydzynski participated actively in the meetings and actions of the group. The Core Group consisted of 7 Networks of Excellence (CASCADE, CO2GEONET, ECNIS, EUROGENTEST, GA2LEN, GRACE, IMISCOE), representing different thematic priorities of FP6. The Core Group's initiatives to raise awareness of the uncertain future of Networks began in April 2007. By October

2008 over 70 Networks had confirmed their support for its objectives and aims, as set out in the 'Opinion Paper' issued by the Core Group. The Core Group organised the 'Open Forum on the future of Networks of Excellence' on 20 November 2007 and took the initiative in organising a 'Lunch Debate on the Future of NoEs' in the European Parliament on 26 February 2008 hosted by Prof. Jerzy Buzek MEP. The Core Group aimed at raising awareness of the uncertain future of FP6 NoE. The group prepared a letter to Commissioner Janez Potocnik (sent on 4th of March, 2009). The letter addressed the final report prepared by "Expert Group on the future of Networks of Excellence" and "silence" from the Commission towards recommendations from "Wise Man Group".

The extensive search for funding outside ECNIS was performed on a regular basis. Within found rising activities, apart from competitive calls, the co-coordinator purchased the access to Community of Science (COS) database. COS is a leading provider of information resources to researchers. Unfortunately majority of funds announced in COS are offered mainly for benefit of American research institutions as founds are provided by American Foundations and companies. So far there were no funding opportunities found which might be applicable to ECNIS. Due to low effectiveness of search through COs it was decided to cease COS subscription.

In response to European Commission 7th Framework Programme call in Activity 2.4 Other Activities: KBBE.2010.4-01: Strengthening the implementation of durable integration in FP6 Networks of Excellence Call: FP7-KBBE-2010-4. a proposal for ECNIS^2 was elaborated titled: "ECNIS^2: towards ECNIS Centre for Research and Education on Cancer, Environment and Food". The proposal was driven by an idea of extending ECNIS for 2 years in order to have additional time and resources for forming the basis of the durable structure, with the ECNIS Centre for Research and Education on Cancer, Environment and Food (ECRECEF), being a continuation of ECNIS. ECNIS^2 has included most of the network partners (20 out of 25 in the original network organization). Our proposal has been selected among other recommended for funding.

ETHICAL REVIEW PANEL (ERP)

The role and tasks of ERP

The main role of ERP was to ensure that all research within the ECNIS Network of Excellence complies with relevant national and EU legislation and follows common ethical guidelines. The ERP advised on the ethical considerations and ethical standards applied within the network.

ERP had an advisory role, with the task to give advice to researchers on concerns that they need to take into account in designing their projects in order to fulfil relevant ethical requirements, among else demands that national bodies may have for giving permit for the project in question. It has also been understood that ERP had the task to give the Network Management Board (NMB) advise when it comes to funding or withholding funding for a certain project with respect to its ethical aspects. These two tasks have been carried through by making ethical evaluations of all research projects funded by ECNIS and communicating these evaluations to researchers as well as the NMB. A third task of ERP was to control that adequate permits have been received on the national level by collecting and storing these permits. Finally ERP had an educational task.

An overview of the work of ERP

ERP was set up during spring 2006. Initially elected members of ERP were Paul Brennan, Ludwine Casteleyn, Birgit Dumez, Ulf Görman, Constantine Sekeris†, Peter Whittaker, and Kinga Polanska, secretary. Paul Brennan, Ulf Görman, Constantine Sekeris† and Peter Whittaker were external in relation to ECNIS. Ludwine Casteleyn and Birgit Dumez were also members of WP 12.

ERP had its first meeting in Brussels on May 5, 2006. This was followed by a second meeting in connection to the ECNIS meeting in Prague, July 2–6, 2006. At this meeting Ulf Görman was elected chairman of ERP. It was also clear that Paul Brennan wanted to redraw from ERP, and based upon personal reasons, it was decided that Peter Whittaker should become a corresponding member of ERP.

At a third meeting with the ERP in Leuven on August 30–31, 2006, the working procedures for ERP were set up, and a number of crucial questions were discussed:

- Ethical review of the first call for ECNIS funded projects (type B projects), granted by ECNIS in July 2006.
- Procedure for the ethical review of ECNIS funded projects, second call.
- Draft for an Ethical Application Form to be used in connection to the second call for projects.

The Ethical review of the projects funded in the first call was finalised on September 26, 2006. The ethical application form was finalised on October 30, 2006, and subsequently distributed together with the second call for projects.

At a fourth meeting with ERP in Athens December 21, 2006, the ethical review of the applications in reply to the second call for projects was discussed. This review was finalised January 6, 2007, and distributed to researchers for additional information and answers to specific questions.

At a fifth meeting with ERP in Maastricht February 26, 2007, the responses from researchers to the ethical review of the second call were discussed and evaluated. This was finalised in a second ethical review of the second call, dated March 17, 2007.

At the 6th meeting in Lódz September 30–October 2, 2007 ERP made plans for the ethical review of the third call for projects and prepared a revision of the Ethical Application form.

ERP was asked to make an ethical review of the plans for setting up a central database with data collected from ECNIS partners, named the MEC Database. At the 7th meeting in Barcelona March 4, 2008, ERP agreed on a review of this effort, finalised on April 16, 2008, where ERP recommended the MEC database to be collected with completely anonymous data. The MEC database has since then been successfully set up. This work is described in the report from WP 4.

At its 8th meeting in Leuven, October 16, 2008, ERP discussed the ethical review of the third call for projects. This review was finalised on December 8, 2008.

At its 9th meeting in Leuven March 18, 2009 and its 10th meeting in Lódz April 15–16, 2010, ERP finished its tasks, among else by checking that all permits for research projects had been adequately reported to ERP.

Ethical examination of research projects

The task to examine projects from an ethical point of view has been limited to the projects supported financially by ECNIS, i.e. the type B projects. As the first call for projects and the decision for funding of these projects had already been carried through when ERP started its work, the examination of these projects was limited to giving advice to each researcher on how to handle ethical questions raised by their project. The procedure for the second and third call involved advices and direct questions for additional information to researchers as well as evaluations of these answers, before giving a final advice to NMB, whether ERP found any obstacles for carrying through the project in question. Unless ERP considered it reasonable that a project should be able to receive relevant ethical permits from domestic authorities, ERP did not recommend ECNIS funding for this project.

As part of the evaluation process, ERP initiated a dialogue with the researchers on the ethical aspects of their projects. In most cases the projects were considered well handled from an ethical point of view, in several cases after additional information, in a few cases after some revision, and in one case after a major review. One project was never realised after the ethical review.

The task to collect and store permits

The task to collect and store permits from national authorities has been carried through successively after each call for projects. A final check was made in 2009 to make sure that all documents were collected and in order. All projects that had been granted support from ECNIS have received approval from national ethical review authorities, when applicable.

The educational task

The educational task of ERP has been fulfilled

- through presentations of ethical issues and the work and tasks of ERP at all ECNIS annual meetings,
- through presentations by members of ERP at some workshops arranged by ECNIS,
- and through a Workshop on ethical questions at the ECNIS Annual meeting in Leuven March 18, 2009.

INTEGRATING THE GENDER ASPECTS IN RESEARCH AND PROMOTING THE PARTICIPATION OF WOMEN

The general aim of the GIP actions was to address the gender equality in science in line with the European research Area, the Science and Society action plan of the Commission and the decisions on FP6, Priority 5. On the one hand, the place and role of women in science and research at European level need to be reinforced and increased. On the other hand, our Network of Excellence, ECNIS, dealt ultimately with the health of human beings, and therefore provided special opportunity to consider, when relevant, sex differences and gender differences linked to the research itself.

Within ECNIS, a Gender Action Plan (GAP) was elaborated with a similar double focus on 1) the contribution of women to the research activity and 2) the consideration of gender aspects in the research itself, where appropriate.

To raise gender awareness and to ensure this GAP was implemented, a Panel for Gender Issues (GIP) has been established. The members of the GIP were:
Prof. Inger Lovkrona, ULUND, Lund, Sweden (chair)
Dr. Birgit Dumez (University of Leuven)
Prof. Mischelina Kirsch-Volders(Vrije University of Brussels)
Prof. Bjorn Akesson (Lund University)- resigned
Dr. Bernardette Schoket (Fodor József National Center for Public Health)
Dr. Jolanta Gromadzinska (Nofer Institute of Occupational Medicine)
Joined the panel in the fourth ECNIS year:
Prof. Ulla Vogel, Copenhagen (DTU),
Dr Amelie Plymoth, Lyon (IARC),
An Jamers, PhD student, Leuven (KULEUVEN)
Dr Barbara Oesch, Mainz (JUGO)
Livia Anna, PhD student

Following GIP´s Action Plan, presented at the AM in Barcelona March 2008, GIP has focused on the following activities:

I. A questionnaire to collect data on the local level
II. Activities targeting junior scientists
    a. Guidelines for mentorship program
III. Gender aspects in research
    a. Workshop on gender research in ECNIS at AM 2009
IV. Activities targeting postdocs and senior women scientists
    a. Leadership program

The questionnaire

The questionnaire was responded by almost all partners and provided the panel with information and data on gender issues at the local level: number of women and men in ECNIS, plans and policies, information about rules for parental leave etc., which all were very usable and gave us a basis for analysis and further activities. Each partner has also selected a contact person for the panel to communicate with.
No severe problems regarding gender issues were experienced and reported, according to the answers.
Women and men in ECNIS

The reported number of doctoral students are: 72 women and 32 men. Among the senior researchers women are in minority - 27 to 39 men; and among the leaders it is reported 9 women to 21 men. (The numbers are approximate due to some inconsistencies in the answers and two partners did not answer.) This pattern - high share of young women on the Ph D level and a low share of women in senior and leader positions – is not unique for ECNIS but represent a general development within the academy. Women´s participation in higher education and postgraduate studies is increasing. However, women tend to disappear from the academy during the postdoc period, a phenomenon called the "leaky pipeline". Or, women do not proceed at all in the academy after completed postgraduate studies.

Guidelines for mentorship program

ECNIS´ mentorship program is a tool to encourage junior women scientists to stay and advance in the academy.

Designing Guidelines for mentorship programs was GIP´s main task during spring 2008. The Guidelines were distributed to all partners in the fall 2008.

In the Guidelines GIP suggested that

- every Ph D students – women and men - should be offered the opportunity to have a mentor; although we will give priority to female doctoral students.
- The female doctoral students should be informed about available female mentors as a first option.
- Senior women scientists should be encouraged to take on the role of mentor.
- ECNIS´ mentorship program is open for both sexes
- Priority should be given to female doctoral students

The partners were requested to respond to the Guidelines, to comment and to inform about the local implementation.

The response rate was unfortunately poor, only 6 partners responded. All the same, some conclusions could be drawn :

- Some partners had their local institutional mentorship program which they are satisfied with. Opinions varied if an additional ECNIS mentorship program was desirable or not.
- The university partners, in general, had their own successful university mentor scheme.
- Partners prefered personal contacts between mentor and mentee (traditional mentorship).
- Mentorship activity should not be restricted to women only but should cover both genders.

The panel assumed that small-size ECNIS partners may still take an advantage of the ECNIS-based mentorship program. It was a very important and we considered it a progress that a mentorship program has been introduced in ECNIS. We encouraged ECNIS partners to initiate local mentorship programs if not in existence yet, and made ECNIS mentorship program visible locally. Partners were encouraged to adopt flexibly those elements of mentorship activities that suit the best to their institutional organizational and cultural circumstances.

The Guidelines were published on ECNIS´ website:
(http://www.ecnis.org/index.php?option=com_content&task=view&id=1233&Itemid=96),
and information on the mentorship programme was included in the ECNIS newsletter(issue 6).

Gender aspects in research

GIP organized two workshops at the AM in Leuven, 2009:

Gender related susceptibility to mutagens/carcinogens. Chaired by M. Kirsch-Volder (VUB). Five papers we presented. The main issues of the workshop were described in the ECNIS Newsletter (no 9).

Academic leadership and gender. Inger Lövkrona presented a Leadership program for senior scientists and postdocs within ECNIS. Announcement and call for application was issued at end of May.

Leadership program for postdocs and senior scientists within ECNIS

Rationale

Women still form a minority voice in important decision-making committees in the academy and are less likely than their male counterparts to chair decision-making or policy-formulating committees. Existing mentorship program of ECNIS offered by GIP is considered a tool to promote doctoral students, especially young women, to successfully become senior scientist. In the future far more women are expected to be available for leader positions in ECNIS institutions and in the academy, than at present. ECNIS will benefit from this and in the future the whole EU.

The ECNIS leadership program developed aimed at speeding up the process and encourage ECNIS researchers, especially women, to be educated to be able to take on leadership positions within ECNIS, and beyond. The objective was to develop leadership skills in higher education, in administrative leadership as well as strategic leadership. The leadership program being proposed by ECNIS was inspired by a program called AKKA, that Inger Lövkrona – with two colleagues - designed and implemented at Lund University, Sweden. The program started in 2004 for senior women scientists and was originally created as an action to increase the number of women in leading positions at the university. In programs I and II, 30 women participated in each program. Almost all of the participants of these two programs have been offered and have accepted high decision-making positions.

AKKA´s basic leadership concept is that leadership can be learned. A knowledge-based leadership is different from the traditional leadership concepts, which argues that individuals are “born” leaders. A knowledge-based leadership provides the tools for conscious leadership, which is applicable in practice.

ECNIS leadership program

The program was designed to learn about research on leadership, academic organization and gender studies and to provide knowledge about:

- Academic organization structures and cultures
- Academic leadership
- Personal leadership

The program aimed at:

- Increase the number of women leaders within ECNIS and beyond
- Empower women in the academic community
- Increase self-reliance and leadership abilities
- Make women and women´s competence visible in the academic community.
- Give a broader understanding of the gendered constructions of the academy and leadership

Unfortunately, there was only a minor interest within ECNIS to participate in the programme. After the first announcement in May only two applications were received. A new announcement was launched at the end of August, with one more applicant after the deadline. GIP summarized that the interest for the program was weak this year and decided to cancel the course.

Plan for using and disseminating the knowledge

A. Publications acknowledging ECNIS

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13. Arlt VM, Gingerich J, Schmeiser HH, Phillips DH, Douglas GR, White PA. Genotoxicity of 3-nitrobenzanthrone and 3-aminobenzanthrone in MutaMouse and lung epithelial cells derived from MutaMouse. Mutagenesis. 2008 Nov;23(6):483-90.
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234. Zamora-Ros R, Andres-Lacueva C, Lamuela-Raventos RM et al. Estimation of dietary sources and flavonoid intake in a Spanish adult population (EPIC-Spain). Journal of the American Dietetic Association. 2010;110(3):390-398.
235. Zamora-Ros R, ndres-Lacueva C, Lamuela-Raventos RM et al. Concentrations of resveratrol and derivatives in foods and estimation of dietary intake in a Spanish population: European Prospective Investigation into Cancer and Nutrition (EPIC)-Spain cohort. Br J Nutr. 2007;1-9.

236. Zijno A, Porcedda P, Saini F et al. Unsuitability of lymphoblastoid cell lines as surrogate of cryopreserved isolated lymphocytes for the analysis of DNA double-strand break repair activity. Mutation Research. 2010;1(2):98-105.

B. Sessions, workshops organized at international conferences

23-25 MAY 2005 WORKSHOP ON COMMUNITY-SPONSORED RESEARCH ON ENVIRONMENTAL CANCER RISKS AND REGULATION.
"Cancer risk and the environment. Fighting fragmentation of European cancer research through networking." Report published in International Journal of Occupational Medicine and Environmental Health, 2005; 18(3): 281 — 286

4th of JULY 2005 EEMS 2005 ANNUAL MEETING OF THE EUROPEAN ENVIRONMENTAL MUTAGEN SOCIETY "ENVIRONMENT AND HUMAN GENETIC DISEASE - CAUSES, MECHANISMS AND EFFECTS" KOS ISLAND, GREECE
Symposium 1: Role of environmental genotoxins in human carcinogenesis (sponsored by ECNIS)
Chairs: Konrad Rydzynski (Nofer Institute, Lodz) and Helmut Bartsch (German Cancer Research Centre, Heidelberg).
List of presentations:

- Konrad Rydzynski Presentation on ECNIS
- Paolo Boffetta (IARC, Lyon): Human cancer from environmental exposures: the epidemiological evidence
- David Phillips (Institute of Cancer Research, UK): Role of environmental genotoxins in human carcinogenesis: evidence from DNA adducts
- Monica Hollstein (German Cancer Research Centre, Heidelberg): A cell immortalization assay to investigate mutation signatures in the human p53 gene sequence
- Seymour Garte (Genetics Research Institute, Milan): Metabolic genes as markers of biochemical susceptibility: A mechanistic approach

Interactive workshop 1: Teaching/training in genetic toxicology (sponsored by ECNIS)
Chairs: James Parry (University of Swansea) and Krzysztof Szyfter (Polish Academy of Sciences, Poznan)
Tutors, presentations:

- J. Parry / E. Parry, Univ. of Swansea: Test system selection and application
- M. Kirsch-Volders, Free University, Brussels / S.A. Kyrtopoulos, National Hellenic Research Foundation, Athens: Biomonitoring of genotoxins and carcinogens
- E. Massey, BAT, Southampton / A. Lynch, GlaxoSK, Ware: Metabolism of genotoxins and carcinogens
- I. Mitchell, Chilfrome Consultants, UK / D. Lovell, Univ. of Surrey: Data analysis

11-14 SEPTEMBER 2005 KRAKOW, POLAND; 42ND CONGRESS OF THE EUROPEAN SOCIETIES OF TOXICOLOGY, EUROTOX 2005
11 September, 2005 Continuing Education Courses
Molecular Mechanisms of Food Contaminants Toxicity (in collaboration with ECNIS)
Course Leader: Joseph Rafter (Department of Medical Nutrition, Karolinska Institute, Stockholm, Sweden)
1. Introduction by J. Rafter
2. "General overview of persistent organic pollutants in food" by P.O. Darnerud (National Food Administration, Uppsala, Sweden)

3. “Infections and food contaminants” by N.G. Ilbäck (National Food Administration, Uppsala, Sweden).
4. “Molecular mechanism of dioxin action” by I. Pongratz (Department of Biosciences, Karolinska Institute, Stockholm, Sweden)
3. “Risk-benefit from consumption of baltic herring: molecular aspects” by P.O. Darnerud (National Food Administration, Uppsala, Sweden)

Monday, 12 September 2005 Plenary Session (in collaboration with ECNIS)

Chairs: Konrad Rydzynski (Nofer Institute of Occupational Medicine Lodz, Poland), Corrado Galli (University of Milan, Italy)

1. “Biomarkers in environmental carcinogenesis research: Striving for a new momentum” by S. Kyrtopoulos (National Hellenic Research Foundation, Athens, Greece)

13 September 2005, S4 Genetics and Individual Susceptibility (in collaboration with ECNIS)

Chairs: Paolo Vineis (Imperial College London, UK and University of Torino, Italy), Wojciech Wasowicz (Nofer Institute of Occupational Medicine, Lodz, Poland)

1. “Single and multiple genes as determinants of individual susceptibility” by P. Vineis
2. “Genetic basis of toxic reactions to drugs and chemicals” by I. Cascorbi (Institute of Pharmacology, University Hospital Schleswig-Holstein, Kiel, Germany)
3. “Ethical implications of genetic profiling for susceptibility” by K. Vahakangas (Dept. of Pharmacology and Toxicology, University of Kuopio, Finland)
4. “How will genetics affect the use of drugs in individual patients?” By A. Hirvonen (Biomonitoring Laboratory, Finnish Institute of Occupational Health, Helsinki, Finland)
5. “Concordance of the acetylation status between human NAT2 phenotypes and deduced genotypes of seven single nucleotide polymorphisms (snps) analysed by real-time PCR” by H. P. Rihs (BGFA, Ruhr University Bochum, Bochum, Germany)
6. “Genetically determined susceptibility to toxicants: Implications of ethnicity” by K. Golka (Institute for Occupational Physiology, University of Dortmund, Germany)

2 September 2006, International Conference on Environmental Epidemiology & Exposure (ISEE/ISEA), Paris (ECNIS session)

Chair: Paolo Vineis , Imperial College, London, UK

PROVISIONAL PROGRAMME

1. Palo Vineis and Peter Farmer - Introduction to ECNIS and its goals
2. Peter Farmer- Technological advancements in biomarkers of exposure and early response
3. David Phillips – High-throughput techniques for the measurement of DNA adducts
4. Paolo Vineis – Validation of new biomarkers and the creation of a European database of biomarkers for epidemological research
5. Paolo Boffetta – The integration of biomarkers into multicentre studies on cancer and the environment
6. To be defined – Perspectives: developing new high-throughput technologies for proteomics and metabonomics

http://www.paris2006.afsset.fr/

29-30 September 2006, Heidelberg, Germany

Biomarker of Exposure and Cancer Risk: DNA Damage and DNA Adduct Detection

ECNIS-sponsored Workshop on Biomarker of Exposure and Cancer Risk:

DNA Damage and DNA Adduct Detection
http://www.ecnis.org/images/stories/ecnis/documents/ecnis_gum_dkfz_workshop_2nd.pdf

Participation in the Conferences

- Geneva Symposium 10 – 11 November 2005

Fondation Brocher

"Value and Risks of genetic Data Collections"

Abstract: Value and risk of genetic data collection: rethinking commonly used concepts such as privacy and informed consent.

Jelle De Schrijver, Birgit Dumez, Karel Van Damme, Ludwine Casteleyn

Center for Human Genetics, Katholieke Universiteit Leuven, Belgium

http://www.brocher.ch

14 February 2006, FIOK Institute Seminar

- B. Schoket: About ECNIS
- Lisbon 19 - 21 March 2006

ESBIO Conference on "State of the art of Human Biomonitoring within Europe"

Abstract/poster: "Socio-ethical impact of biomarker use" – Environmental cancer risk, nutrition and individual susceptibility (ECNIS)

Birgit Dumez, Lien Van Hamme, Ludwine Casteleyn, Karel Van Damme

Center for Human Genetics, Katholieke Universiteit Leuven, Belgium

http://conference.hbm-inventory.org

- Mainz 3 April 2006

Spring Meeting of the German Society of Experimental and Clinical Pharmacology and Toxicology: THE THRESHOLD OF TOXICOLOGICAL CONCERN PRINCIPLE, Participants and discussants of ECNIS: Prof. Dr. Franz Oesch and Prof. Dr. Barbara Oesch

2-6 JULY 2006 - EEMS 2005

36th ANNUAL MEETING OF THE EUROPEAN ENVIRONMENTAL MUTAGEN SOCIETY

"FROM GENES TO MOLECULAR EPIDEMIOLOGY"

PRAGUE, CZECH REPUBLIC

- Symposium 1:

FOOD MUTAGENS IMPACT ON HEALTH (ECNIS)

Chairpersons:

Beatrice Pool-Zobel, F.Schiller University, Jena, Germany

Konrad Rydzinski, Afofer institute of Occupatinal Mediane, Lodz, Poland

Beatrice Pool-Zobel

F.Schiller University, Jena, Germany

Evaluation of genotoxicity and antigenotoxicity by food-derived compounds in human colon, prostata, breast and blood cells using novel genomics and transcriptomics-base methods

Rashmi Sinha

NIH-National Cancer Institute, Rockviiie, MD, USA

Cooked and preserved meat carcinogens and cancer

Jakob Linseisen

Technicai University of Munich, Munich, Germany Meat cooking, heterocyclic amines and cancer risk

Joseph Rafter

Karolinska Institutet, Novum, Stockhoim, Sweden
Anticardnogenic activity of probiotic bacteria
Miriam Poirier
National Cancer Institute,NIH, Bethesda, MD, USA
Formation of polycyclic aromatic hydrocarbon - DNA adducts in human leukocytes
David DeMarini
US Environmental Protection Agency, Research Triangle Park, NC, USA
Inhibition of fried meat-induced DNA darnage: Use of cruciferous vegetables, yougurt, and chlorophyllin in a dietary intervention study in humans
Kazuaki Kawai
University of Occupational and Environmental Health, Kitakyushu, Japan
Detection of 8-OH-dG, ribonucleoside 8-OH-Gua and free base 8-OH-Gua in fish food products
Suzanne Jeurissen
Wageningen University, Wageningen, Netherlands
Identification of the human cytochrome P450enzymes involved in the bioactivation of the herb-based carcinogens estragole and methyleugenol

- Symposium 2:

NUTRIGENOMICS (ECNIS)
Chairpersons:
Fred F. Kadlubar, National Center for Toxicoiogical Research, Jefferson, AR, USA
Bjorn Akesson, Lund University, Lund, Sweden
Gunter Kuhnle
MRC-Dunn Human Nutrition Unit, Cambridge, U.K.
Interaction of nutritional and genetic factors in colorectal cancer
Bjorn Akesson
Lund University, Lund, Sweden
The effects of cereal components on the propertles and proliferation of colon cancer cells
Lynnette Ferguson
University of Auckland, Auckland, New Zealand
Nutrigenomics and inflammatory bowel disease
Sven Pettersson (presented by Joseph Rafter)
Karolinska Institutet, Novum, Stockhoim, Sweden
Host-microbe crosstalk
Theo de Kok
Maastricht University, Maastricht, The Netherlands
Profiling of gene expression modulation in human lymphocytes is not sensitive marker for exposure to Ah-receptor agonists

- Symposium 3:

NEW KNOWLEDGE FROM BIOMARKERS OF EXPOSURE(ECNIS)
Chairpersons:
Peter B. Farmer, Leicester University$_t$ Leicester, U.K.
Radim J. Sram, Institute of Experimenta! Mediane AS CR, Prague, Czech Rep.
David Phillips
Institute of Cancer Research, Sutton, U.K.
The use and limitations of DNA adducts in determining human exposure to carcinogens and the aetiology of human cancers

Giinther Speit
University of Ulm, Uim, Germany
Systemie genotoxic effects of formaldehyde detected in biomonitoring studies and evaluation of their plausibility in an ex vivo approach
Peter B. Farmer
University of Leicester, Leicester, U.K.
The potential of mass spectrometry for the detection of DNA damage
Frederik-Jan Van Schooten
Maastricht University, Maastricht, The Netherlands
Biomonitoring of inhalatory exposures: from invasive to non-invasive methods
Johanna Haglund
Stockhoim University, Stockhoim, Sweden
Phosphate adducts - a potential biomarker?
Sophia Pavanello
Univer$ityof Padova, Padova, /ta/y
Gene-exposjre interaction on anti-benzo[a]pyre nediolepoxide-B[a]PDE-DNA adduct formatior in lymphocytes of humans
Sarolta Gundy
National Institute ofOncology, Budapest, Hungary
Cytogenetic biornarkers to assess the genetic damage induced in chronic alcoholics with malignant, premalignant, and non-malignant diseases

- Symposium 4:

EPIGENETIC MECHANI5MS IN CARCINOGENESIS (ECNIS)
Chairpersons:
Zdenko Herceg, IARC, Lyon, France
Peter J. Stambrook, University of Cincinns W, Cincinnatti, OH, USA
Zdenko Herceg
IARC, L/on, france
Epigenetic mechanisms of regulation ofcellular processes and tumorigenesis
Steven Belinsky
Lovelace Respiratory Research Institute, A!buquerque, NM, USA
Targeting of genes for silencing by promoter hypermethylation: Influence of environmental exposures
Peter J. Stambrook
University of Cincinnatti, Ondnnatti, OH, USA
Mutation, cell cycle and apoptosis: Preserving genomic integrity in somatic and embryonic stem cells
Yasuhito Yuasa
Tokyo Medical and Dental University, Tokyo, Japan
Epigenetic epidemiology of gastric cancer
Jan Vondracek
Institute of Biophysics, Brno, Czech Rep.
The dual role of AhR in genotoxic and nongenotoxic mechanisms of toxidty of erwironmental PAHs in liver epithelial cells
Katarzyna Urbanek
National Institute ofHygiene, Warsaw, Poland
Effect of phenobarbital on the level methylation of promoter region og P16 gene in rat liver

- Symposium 5:

OXIDATIVE STRESS RESPONSES (ECNIS)

Chairpersons:

Regina M, Santella, Columbia University, New York, USA

Silvio de Flora, University of Genoa, Genoa, Italy

Jagadeesan Nair

German Cancer Research Centra Heidelberg, Germany

Oxidative stress response: Lipid peroxidation induced DNA damage and repair in cancer-prone inflammatory diseases

Regina M. Santella

Columbia L/rwerstfy, New York, CO, USA

Oxidative stress and breast cancer

Steffen Loft

Univers!ty of Copenhagen, Copenhagen, Denmark

Oxidative DNA damage and risk of cancer

Silvio de Flora

University of Genoa, Genoa, Itaiy

Oxidants and antioxldants in tne prevention of mutation-related diseases

Hiroshi Ide

Hiroshima Univer$ity, Hiroshima, Japan

Repair of DNA lesions induced by oxidative and nitrosative stress

- Symposium 6:

RISK ASSESSMENT (ECNIS)

Chairpersons:

Rob Baan, IARC, Lyon, France

Paolo Vineis, Imperia! College London, London, U.K.

Paolo Vineis

Imperia! College London, London, U.K.

The contribution of the ECNIS network to the validation of markers for risk assessment

Yasunobu Aoki

National Institute for Environmenta! Studies, Tsukuba, Japan

Evaluation of in vivo mutagenicity using transgenic animals

Hans Kromhout

University of Utrecht, Utrecht, The Nethertands

Progress with integrated risk assessment?

Lee Byung-Mu

Sungkyunkwan University, Suwon, Korea

Toxikokinetic pattern of phtalic acid for risk assessment approach

Ryeom Tai-Kyung

Korea Food and Drug Administration, Seoul, Korea

Human exposure assessment of hetenocyclic amines in foods

James E.Trosko

Michigan State University, East Lansing, MI, USA

Crises in the chemical genotoxidty paradigm: Stem cells, cell-cell communication and systems biology as ignored concepts

Christopher Portier

National Toxicology Program, Research Triangle Park, NC, USA
Looking to the future: Where will "Omics" and systems biology lead risk assessment

2 September 2006, International Conference on Environmental Epidemiology & Exposure (ISEE/ISEA), Paris
ECNIS pre-conference WORKSHOP "Biomarkers for the study of environmental cancer: the ECNIS EU Network of Excellence"
Paolo Vineis and Peter Farmer - Introduction to ECNIS and its goals
Peter Farmer - Technological advancements in biomarkers of exposure and early response
David Phillips – High-throughput techniques for the measurement of DNA adducts
Roger Godschalk - Genetic susceptibility, phase I enzymes
Ari Hirvonen - Genetic susceptibility, phase II enzymes
Micheline Kirsch-Volders - Genetic susceptibility, DNA repair enzymes
Paul Brennan - Mendelian Randomization in epidemiology
Paolo Vineis – Validation of new biomarkers and the creation of a European database of biomarkers for epidemological research
Paolo Boffetta – The integration of biomarkers into multicentre studies on cancer and the environment
Roel Vermeulen – Perspectives: developing new high-throughput technologies for proteomics and metabonomics
http://www.paris2006.afsse.fr/

ECNIS members presentations during the ISEE/ISEA conference
- "Dietary exposure to PAHs and its assessment" - D.H. Phillips
- "ECNIS (Environmental Cancer Risk, Nutrition and Individual Susceptibility) – on the road to research excellence and integration" – K.Rydzynski
- "Epidemiology of Dietary Exposure to Polycyclic Aromatic Hydrocarbons (PAH) and Cancer Risk" – A Agudo
- "Technological advances in biomarkers of exposure and early effects" –Peter Farmer

29-30 September 2006, Heidelberg, Germany
Biomarker of Exposure and Cancer Risk: DNA Damage and DNA Adduct Detection
ECNIS-sponsored Workshop on Biomarker of Exposure and Cancer Risk:
DNA Damage and DNA Adduct Detection
Chairs: Volker Arlt
Prof. Dr. Otmar Wiestler, Chairman and Scientific Director of the German Cancer Research Center
Session I
Chair: Helmut Bartsch (German Cancer Research Center, Germany)
Keynote Lecture - Frederick Beland (National Center for Toxicological Research, USA):
Acrylamide: adducts, mutations, and cancer
Arthur Grollman (State University of New York, USA): Role of aristolochic acid in the etiology of endemic nephropathy
Session II

Chair: Peter Farmer (Biocentre, University of Leicester, UK)
David Phillips (Institute of Cancer Research, UK): Elucidating pathways of metabolic activation of carcinogens by quantifying and characterising their DNA adducts
Bernadette Schoket (National Institute of Environmental Health, Hungary): Immunoassays for the determination of PAH-DNA adducts
Karen Brown (University Leicester, UK): Accelerator mass spectrometry for DNA adduct detection
Lennart Möller (Karolinska Institute, Sweden): DNA-adduct analyses of human tissues by the ^{32}P-HPLC method (O6)
Poster Presentation: Session 1
Poster Presentation: Session 2
Session III
Chair: David Phillips (Institute of Cancer Research, UK)
Peter Farmer (Biocentre Leicester, UK): Alternative approaches to ^{32}P-postlabelling for detection of low levels of DNA adducts (O7)
Peter Farmer (Biocentre Leicester, UK): Alternative approaches to 32P-postlabelling for detection of low levels of DNA adducts
Jagadeesan Nair (German Cancer Research Center, Germany): Novel ^{32}P-postlabelling method for the determination of adducted deoxynucleosides in human body fluids
Oliver Schmitz (University Wuppertal, Germany): Determination of the DNA methylation level with capillary electrophoresis and laser-induced fluorescence
Session IV
Chair: Frederik-Jan van Schooten (University of Maastricht, The Netherlands)
Matilde Marques (Technical University of Lisbon, Portugal): Tamoxifen and tamoxifen analogues: activation to DNA adducts in vitro and in vivo
Volker Manfred Arlt (Institute of Cancer Research, UK): The potential use of DNA adducts formed by the carcinogenic air pollutant 3-nitrobenzanthrone in human biomonitoring
Marie Stiborova (Charles University Prague, Czech Republik): Cytochrome P450- and peroxidase-mediated formation of covalent DNA adducts by an anticancer drug ellipticine - a novel mechanism of ellipticine action
Heinz Schmeiser (German Cancer Research Center, Germany): Molecular basis of Aristolochia carcinogenicity
Symposium Prof. Manfred Wiessler (65th birthday)
Chair: Heinz Schmeiser & Eva Frei (German Cancer Research Center, Germany)
Otmar Wiestler (German Cancer Research Center, Germany): Welcome
Gerd Eisenbrand (University Kaiserslautern, Germany): Highlights of the scientific career of Prof. Manfred Wiessler
Christopher Michejda (National Cancer Institute at Frederick, USA): Replication control in tumor cells as a target for DNA-interacting anti-tumor agents
Session V
Chair: Bernadette Schoket (National Institute of Environmental Health,Hungary)
Panagiotis Georgiadis (National Hellenic Research Foundation, Greece): Progress towards the development of high-throughput immunochemical assays for DNA damage and repair (O15)
Dan Segerbäck (Karolinska Institute, Sweden): ^{32}P-Postlabelling analysis of UV-induced pyrimidine dimers from human skin and urine (O16)
Hansruedi Glatt (German Institute of Human Nutrition, Germany): Formation of DNA adducts in humans and laboratory animals by phytochemicals from common vegetables and fruits (O17)

Session VI
Chair: Soterios Kyrtopoulos (National Hellenic Research Foundation, Greece)
Monica Hollstein (German Cancer Research Center, Germany): In vitro cell immortalization selects for p53 gene mutations found in human cancers (O18)
Albrecht Seidel (Biochemical Institute for Environmental Carcinogens, Germany): Determination of urinary PAH metabolites as a non-invasive human biomonitoring method (O19)
Jan Topinka (Institute of Experimental Medicine AS, Czech Republic): Use of DNA adduct analysis to study mechanism of drug genotoxicity - example cyproterone acetate (CPA) (O20)
Erwin Eder (University of Würzburg, Germany): Early markers in the development of colorectal tumours in the rat: DNA adducts compared with isoprostanes, histological and morphological alterations in the early stage (O21)
Session VII
Chair: Oliver Schmitz (University of Wuppertal, Germany)
Roger Godschalk (University of Maastricht, The Netherlands): The use of DNA adducts in surrogate tissues: pitfalls and opportunities (O22)
Marco Peluso (Tuscany Cancer Institute, Italy): DNA adducts and lung cancer risk in a case-control study nested in the EPIC investigation (O23)
Elmar Richter (University of Munich, Germany): Sources of adducts releasing 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB) from DNA and haemoglobin in humans (O24)
Wolfgang Pfau (GAB-Consulting, Germany): Dietary DNA adducts: heterocyclic amines and pesticides

Werner Lutz (University of Würzburg, Germany): Correlation of DNA adducts with other endpoints of genotoxicity in mouse lymphoma cells treated with methyl methanesulfonate (O#26)
http://www.ecnis.org/images/stories/ecnis/documents/ecnis_gum_dkfz_workshop_2nd.pdf

9-10 November 2006, Venice, Italy
HuGENet Workshop on Assessment of Cumulative Evidence on Genetic Associations
Agenda
November 9, 2006

- Setting the stage: what we know and what others have done -Moderator: Julian Little
- Welcome, introductions and objectives of meeting: Paolo Boffetta and Paolo Vineis
- HuGENet: Vision for Network of Networks: Muin Khoury
- What others have done: Julian Little
- Developing and Updating Cumulative Evidence on Genetic Associations: Experiencees to date -Moderator: Muin Khoury
- Options for developing ongoing assessment of cumulative evidence - John. Ioannidis
- Osteoporosis network knowledge base and field synopses -Andre Uitterlinden
- Preterm delivery network knowledge base and field synopses - Siohban Dolan
- Childhood leukemia network knowledge base and field synopsis - Anand Chokkalingam
- Type 2 diabetes field synopsis -Mark McCarthy
- General discussion and lessons learned
- Linking human genome epidemiology with biological plausibility -Co-moderators: André Uitterlinden & Tom O'Brien

- Introduction and Overview of Session – Tom O'Brien Assessment of Biological Plausibility in Infectious Disease: CCR5, HIV and West Nile Virus – David McDermott
- Assessment of Biological Plausibility in Pharmacogenetic Studies: CYP 450 and Drug Metabolism - Magnus Ingelman-Sundberg
- Assessment of Biological Plausibility in Chronic Disease: Osteoporosis - André Uitterlinden
- Assessment of Biological Plausibility in Chronic Disease: Cancer-Paolo Boffetta
- Discussion. How can we assess the biological plausibility of findings from studies of genetic epidemiology? – Moderators: André Uitterlinden & Tom O'Brien
- Framework for causal inference in human genome epidemiology -co-moderators: Paolo Boffetta and Paolo Vineis
- Causal assessment in epidemiology – P Vineis
- Specificities of causal reasoning in genetics – G Page
- Discussion

November 10, 2006

- Framework for causal inference in human genome epidemiology -co-moderators: Paolo Boffetta and Paolo Vineis
- Statistical modeling and causal inferences in genetics - D Balding
- Causal inferences in whole genome scans – D Clayton
- Discussion

Luxembourg, 29 November 2006

ECNIS Workshop on "Biomarkers and their potential in Human Biomonitoring and Environmental Health Surveillance"

Luxembourg, 29 November 2006

PROGRAMME

Introduction to the Workshop (Soterios A. Kyrtopoulos, National Hellenic Research Foundation, Athens, Greece; ECNIS)

The ECNIS NoE and biomarker-related research in Europe (Konrad Rydzynski, Nofer Institute of Occupational Medicine, Lodz, Poland; ECNIS co-ordinator)

Human biomonitoring: policy needs and knowledge gaps (Birgit Van Tongelen, European Commission, DG Environment)

Biomarkers of environmental health: potential and limitations (Soterios A. Kyrtopoulos, National Hellenic Research Foundation, Athens, Greece; ECNIS)

Biomonitoring in the workplace: experience and lessons for biomonitoring of environmental exposure (Micheline Kirsch-Volders, Free University of Brussels, Belgium; ECNIS)

Recent scientific and technological developments and their impact on biomarkers of environmental health (Jos Kleinjans, University of Maastricht; ECNIS, and co-ordinator of NewGeneris)

The use of human biomarkers in risk assessment (Hans Kromhout, Institute of Risk Assessment Sciencies, University of Utrecht; ECNIS)

Scientific basis for the selection of pollutants and target populations in biomonitoring for environmental health surveillance (Lisbeth Knudsen, University of Copenhagen, Denmark; ECNIS)

Cancer research funding - from FP6 to FP7 (Olaf Kelm, European Commission, DG Research)

Round Table discussion on needs and prospects in the development of activities on human biomonitoring and environmental health risk assessment; short contributions from invited speakers and discussion with audience. Chairman: Konrad Rydzynski, ECNIS co-ordinatorTuomo Karjalainen, European Commission, DG Research; Ludwine Casteleyn, University of Leuven; SCALE Implemenation

Group on Human Biomonitoring, and ECNIS; Reinhard Joas, ESBIO co-ordinator; Paolo Boffetta, International Agency for Research on Cancer, Lyon, ECNIS

2nd Forum of Young Hygienist 2, 1-3 June 2006, Szeged, Hungary;Fiatal Higiénikusok II. Fóruma

- Környezeti PAH expozíció összehasonlítása felnott és gyermek populációban 1-hidroxipirén szintek meghatározásával – irodalmi adatok összehasonlító elemzése (Comparison of environmental PAH exposure in adult and children populations by determination of 1.hydroxypyrene levels - comparative analysis of literature data). - Kovács K, Gyorffy E, Anna L, Schoket B:

- Genotoxikus expozíció biomarkerei közötti korreláció célszövetben és helyettesíto szövetben – irodalmi adatok és saját kutatási eredményeink tükrében (Correlation among biomarkers of genotoxic exposure in target and surrogate tissues - in literature data and own research results) - Gyorffy E, Kovács K, Anna L, Schoket B:
- A p53 mutáció és polimorfizmus összefüggései a tüdorákban (Relationships between p53 mutations and polimorphisms in lung cancer) Anna L, Gyorffy E, Gyori Z, Segesdi J, Minárovits J, Soltész I, Kostic S, Csekeo A, Holmila R, Husgafvel-Pursiainen K, Schoket B:

Mini-symposium at the Veterinary Research Institute, June 2006 Brno, Czech Republic

- Deregulation of contact-inhibition by the aryl hydrocarbon receptor. - C. Dietrich

University of Wuppertal, Department of Chemistry, Bergische Universität Wuppertal, Wuppertal, Germany, June 29, 2006

- "Biomonitoring der inneren Belastung der Allgemeinbevölkerung mit polycyclischen aromatischen Kohlenwasserstoffen und aromatischen Aminen als Kontaminanten von Lebensmitteln"– Albrecht Seidel

Conference (ICCA)Minneapolis, July 26-27th 2006

- "Biomonitoring data:Gaps and needs" -Peter Farmer

Symposium on molecular and systemic toxicology, July 2006, Basel, Switzerland

- Deregulation of contact-inhibition by the aryl hydrocarbon receptor. F. Oesch

8th International Symposium on Selenium in Biology and Metabolism, Madison, WI, July 2006.

- Separation of selenium, zinc and copper compounds in bovine whey using size exclusion chromatography linked to inductively coupled plasma mass spectrometry. Hoac T, Lundh T, Purup S, Önning G, Sejrsen K, Åkesson B.
- Effect of selenium supplement on the selenium content and the distribution of trace elements in bovine milk, whey and plasma. Hoac T, Stagsted J, Lundh T, Nielsen JN, Åkesson B.
- Occurrence of selenoprotein enzymatic activities and mRNA in bovine mammary tissue. Bruzelius K, Hoac T, Sundler R, Önning G, Åkesson B.
- Proteome analysis of the biosynthesis of selenoproteins in cultured bovine mammary cells. Bruzelius K, Purup S, James P, Sejrsen K, Önning G, Åkesson B.

International Research Conference on Food, Nutrition and Cancer. 13-14 July 2006 Washington, USA

§ Diet, HPV and Cervical Cancer - Carlos A.González

6th International Symposium on Microsomes ad Drug Oxidation, 3-7 September 2006, Budapest, Hungary

§ Relationship between single and combined CYP genetic polymorphisms and smoking-related DNA adducts in human bronchial tissues. - E. Gyorffy, S. T. Saarikoski, L. Anna, R. Holmila, Z. Gyori, J. Segesdi, J. Minárovits, S. Soltész, S. Kostic, A. Csekeo, K. Husgafvel-Pursiainen, B. Schoket:

Molecular Research in Environmental Medicine, 2nd International Conference, 8th Sept. 2006 Paris

§ Genotyping, repair phenotyping and genetic biomarkers to assess cancer risk in occupational settings" - Micheline Kirsch Volders and Ilse Decordier

3-5 October 2006, Siófok, Hungary Magyar Higiénikusok Társasága, Siófok (Annual Meeting of the Hungarian Hygienists' Society)

§ Környezeti PAH expozíció összehasonlítása felnott és gyermek populációban 1-hidroxipirén szintek meghatározásával – irodalmi adatok összehasonlító elemzése (Comparison of environmental PAH exposure in adult and children populations by determination of 1-hydroxypyrene levels - comparative analysis of literature data). Kovács K, Gyorffy E, Anna L, Schoket B

§ Genotoxikus expozíció biomarkerei közötti korreláció célszövetben és helyettesíto szövetben – irodalmi adatok és saját kutatási eredményeink tükrében (Correlation among biomarkers of genotoxic exposure in target and surrogate tissues - in literature data and own research results) Gyorffy E, Kovács K, Anna L, Schoket B

National Congress, October 2006, Logroño,Spain

§ Nutrition and Cancer:Challenge for the Epidemiology - Carlos A. González

Fifth Annual Conference on Frontiers in Cancer Prevention Research. Boston (USA), 12-15, October 2006.

§ "Toenails: an easily accessible and long-term stable source of DNA for genetic analyses in large-scale epidemiological studies." van Breda SGJ, Hogervorst JG, Schouten LJ, Knaapen AM, van Delft JHM, Goldbohm RA, van den Brandt PA, van Schooten FJ.

INES: Institutionalisation of Ethics in Science & Technology Policy
Funded by the European Union under Framework 6, Final Report Presentation and Dissemination Conference, October 26-27 2006 Stanhope Hotel, Brussels

§ "Towards consistent social, ethical and legal approaches in the use of human biomarkers in environmental health", by Ludwine Casteleyn

International Symposium on Recent Advances in Endemic Nephropathy, Zagreb, Croatia, 20-22 October, 2006.

- Aristolochic acid mutagenesis; a molecular clue to the etiology of Balkan endemic nephropathy-associated urothelial cancer? – David Phillips

Section on Xenobiotic Metabolism of the German Society of Pharmacology and Toxicology meeting, Würzburg, October, 2006

§ Direct and indirect regulation of xenobiotic metabolism by transcription factors. - F. Oesch

Microsomes and Drug Oxidations Congress, September, 2006, Budapest

§ Predictive toxicology of AhR activators: Cell type-specific divergent signalling. - F. Oesch

Conference (NCRI))Birmingham, October 11th, 2006

§ The potential for dietary agents for cancer prevention and treatment – Peter Farmer

Conference: Get ready for EC 7th Framework Programme, Riga, Latvia 19 October 2006

§ Experience from coordinating ECNIS Network of Excellence – K.Rydzynski

6th International Congress of the Turkish Society of Toxicology, 2-5th November 2006, Antalya, Turkey

§ "Individual susceptibility to oxidative damage" - by Micheline Kirsch Volders, Peter Aka, Muriel Emmery and Raluca Mateuca.

AOAC, International Workshop 'Foods to Dye for –Contaminants-sampling, analysis, legal limits' Cyprus, November 6, 2006

§ "Analysis of PAH's in food" Limassol,– Albrecht Seidel

BELTOX/BEEMS joint meeting, 1st December 06 Leuven

§ "The influence of xenobiotic metabolism and DNA repair genetic polymorphisms on micronucleus frequencies in human lymphocytes in vivo": Raluca Mateuca, Mathieu Roelants, Annie Tremp, Stefano Bonassi, Michael Fenech and Micheline Kirsch Volders.

"Post-Academishe vorming in de arbeidsgezondheidskunde en bedrijfsgezondheidszorg" 6th December 2006 Leuven

§ "The relationship between mutagenicity, cytogenetic effects and cancer" - Micheline Kirsch Volders and Noomi Lombaert.

Stakeholder Workshop on Human Biomonitoring (Data Interpretation and Ethics), December 6-7 2006, Brussels, Organized by DG Environment, in close cooperation with ECETOC and the Health & Environment Alliance

- "Ethical issues associated with Human Biomonitoring studies illustrated by (hypothetical) case studies"- Birgit Dumez

Karolinska Institute, Department of Biosciences amd Nutrition, Stockholm, Sweden, 4. December, 2006. (invitation by Prof. L. Möller)

- Aristolochic acid: a potent human carcinogen found in traditional dietary herbal remedies.- David Phillips

Friedrich-Schiller University Jena, Department of Nutritional Toxicology, Jena, Germany, 16. January, 2007. (invitation by Prof. B.L. Pool-Zobel)

- Aristolochic acid: a potent human carcinogen found in traditional herbal remedies.- David Phillips

Institute of Pharmacology, University of Mainz , January 2007

§ The aryl hydrocarbon receptor: identification of a novel signaling pathway - F. Oesch

Conference (AACR and ACS)San Diego February 4-7th, 2007

§ ”Selective measurements of DNA adducts and their role in carcinogenesis” - Peter Farmer

ESBIO workshop on ethics and communication, Copenhagen 11-13 March, 2007

§ “Research on ethics in ECNIS and NewGeneris: A bottom up approach” - Birgit Dumez

48th Spring Meeting of the German Society for Pharmacology and Toxicology, 13.-15. March, 2007, Mainz, Germany:

§ Identification of JunD interaction partner in regulating AhR-dependent Cyclin A expression. D. Faust. C. Weiss, I. Schreck, F. Oesch, C. Dietrich
§ Mechanisms of BPDE induced activation of stress activated protein kinases in human cells - Schreck, F. Oesch, C. Weiss, C.
§ AhR signalling is not induced by polybrominated diphenyl ether (BDE47) in rat hepatoma cells - C. Weiss
§ Direct control of the mammalian circadian clock genes Per1 and Per2 by dioxin, AHR and ARNT - B. Oesch-Bartlomowicz , H. Zatonski E. Reszka, W.Wasowicz, F. Oesch
§ Significance of human ARNT polymorphisms in environmental carcinogenesis due to changes in some carcinogen metabolizing enzymes and circadian rhythms - E. Reszka, H. Zatonski, W.Wasowicz, F. Oesch, B. Oesch-Bartlomowicz
§ Exposure to benzo[a]pyrene in the hepatic cytochrome P450 oxidoreductase null mouse: detoxification by hepatic cytochrome P450 is more important than metabolic activation.- David Phillips

ECETOC Workshop on the Refinement of Mutagenicity/Genotoxicity Testing, Malta, April, 2007

§ Metabolism and genetic susceptibility in in vitro testing for mutagenicity/genotoxicity. - F. Oesch

Annual Meeting of the American Association for Cancer Research, Los Angeles, April 2007.

§ “Activated neutrophils inhibit nucleotide excision repair in human pulmonary epithelial cells: role of myeloperoxidase.” Güngör N, Godschalk RWL, Van Schooten FJ, Knaapen AM

Porto Cancer Meeting XVI Edition, 20-21 April 2007 Oporto, Portugal
Main finding in the EPIC Study Carlos A. González

17 April 2007 Insitute Seminar

§ O4-Etiltimidin DNS adduktok keletkezése tüdoben dohányzás hatására - beszámoló a heidelbergi ECNIS munkaprogramról (Formation of O4-Ethilthymidine DNA adducts in lung due to smoking - Report on the ECNIS fellowship project in Heidelberg – Anna L, Kovács K, Gyorffy E, Schoket B

First Annual Meeting of EU Integrated Project PHIME (www.PHIME.org), April 26-27, 2007, Portoroz, Slovenia.

§ Selection of most influential genetic markers among a large number of candidates based on effect estimation rather than hypothesis testing. (Oral) - Strömberg U.

JRC Institute for Reference Materials and Measurements (IRMM) - Geel, Belgium, May 8, 2007

§ "Toxicological Assessment and Profile Analysis of PAH Mixtures Including the EFSA Priority Compounds"– Albrecht Seidel

Scientific Symposium EnTox 2007 Dortmund, Germany, May 11, 2007

§ "New Biomarkers of Occupational Exposure to Polycyclic Aromatic Hydrocarbons"– Albrecht Seidel

The 5th International Conference on Environmental Mutagens in Human Populations (ICEMHP) Antalya, Turkey, May 21, 2007

§ "Determination of urinary chemical metabolites for assessment of exposure of the general population to environmental toxic PAH" – Albrecht Seidel

The relationship between vitamin D and cancer. Montecatini, Italy, 2 September 2009, A joint ECNIS-NuGO Symposium

Integration of molecular epidemiology into cancer risk assessment of benzene. Taipei, Taiwan, 23 April 2010. During the Epidemiology in Occupational Health conference held from 21-25 April in Taipei, Taiwan

Other

June 2005	Flyer	General public	Greece	Production of flyer about our group´s research, in which ECNIS is highlighted; distributed at science forum and related occassions
Oct./Nov. 2005	Direct correspondence and e-mailing	European level decision makers / industry / consumer organisations	EU	Correspondence to introduce ECNIS and seek further contact to plan activities related to dissemination
November 2005	Meetings	EU decision makers / European industry (CEFIC)	Europe	Meetings of ECNIS representatives with stakeholders to discuss possible collaboration related to dissemination
November 2005	Conference	Decision makers, health professionals, NGOs	Europe	Participation of ECNIS Science Communication Officer in CER (Communicating European Research) 2005
January 2006	Press release(press/radio /TV)	General public	Greece	ECNIS Research-planning workshops
January 2006	Media briefing	General public	Greece	ECNIS Research-planning

		(newspaper interviews)		workshops
April 2006	Newsletter	All	Europe	ECNIS Newsletter no. 1; No. 2 planned for 07/06, other issues to follow twice per year
April 2006	Conference	Decision makers, NGOs	Poland	Conference " Poland in the EU Framework Programs" Meeting of ECNIS representative with stakeholders
Spring 2006	Media	General public	Sweeden	Press interview: Dagens nyheter(largest morning paper in Sweden)
Luxembourg, 29/11/2006	Meetings	Policy makers; members of the SCALE Consultative Forum	Belgium	Conference: Stakeholder Workshop: "Biomarkers and their potential in Human Biomonitoring and Environmental Health Surveillance
December 19 2006	Meetings	Flemish Parliament	Belgium	Presentation on Human biomonitoring and ethics
Brussels, 29/1/2007	Media	General public	Belgium	Presentation of ECNIS in DVD prepared by DG Research on Food-related research projects
May 07	Media	General public	Europe	Flyers: 2nd ECNIS brochure
2006/2007	Newsletters (3 issues)	All	Europe	
Fall, 2007	Newsletter	stakeholders/decisionmakers	Sweden	National newsletter "Biosci News" from KI (fall 2007) to stakeholders/decisionmakers in Sweden, articles
November 2007	Meetings	EU decision makers – EU Networks representatives	Europe - Brussels	Open Forum: Future of the European Networks of Excellence
January, 2008	Newsletter	General public	Europe	Presentation of ECNIS in "Parliament Magazine" issue 260, 28.01.2008
March, 2008	Conference	European Parliament	Europe - Brussels	Presentation by L. Casteleyn 'A coordinated approach to HBM' Public Health and Food Safety Committee and Economic and Scientific Policy Department of DG IPO
March, 2008	Press release(press)	General public	Barcelona	ECNIS Annual Meeting In Dario Medico, 10 March, 2008
April, 2008	Media	General public (TV, channel 4)	Sweden	Informal contacts with national television
April, 2008	National paper	General public	Sweden	National paper, "Dagens Medicin", article
November, 2007; May 2008	Newsletter	All	Europe	ECNIS Newsletter no. 5, 6

Participation in the Conferences

ICR

37th Annual Meeting of the European Environmental Mutagen Society (EEMS), Basel, Switzerland, 9-13 September 2007. Arlt VM. The hepatic cytochrome P450 reductase null mouse as a tool to study carcinogen metabolism.Symposium chair (oral presentation)

2nd Esophageal and Cardiac Cancer Summit, Beijing, China, 18-20 October 2007. Phillips DH. PAHs carcionogenesis, exposure and biomonitoring. (oral presentation)

Scientific Meeting on Balkan Endemic Nephropathy and Associated Urothelial Cancer, Belgrade, Serbia, 9-10 November 2007. Arlt VM. Aristolochic acid mutagenesis: new insights into the aetiology and pathogenesis of Balkan endemic nephropathy-associated urothelial tumours. (oral presentation)

Scientific Meeting on Balkan Endemic Nephropathy and Associated Urothelial Cancer, Belgrade, Serbia, 9-10 November 2007. Phillips DH. Genetic toxicology of candidate aetiological agents for BEN and associated urothelial cancer. (oral presentation)

CRUK Strategic Workshop on Predisposition/Screening/Diagnostic Biomarkers, London, UK, 9 January 2008. Phillips DH. Biomarkers of exposure, effect and cancer risk. (oral presentation)

University of Lancaster, Department of Biological Sciences, Lancaster, UK, 9 May 2007.Arlt VM. DNA adducts as markers of carcinogen exposure and cancer risk. (Invited Seminar)

Faculty of Medicine, Campus Erasme, Universite Libre de Bruxelles, Brussels, Belgium, 14 May 2007. Arlt VM. Aristolochic acid nephropathy and urothelial cancer: DNA adducts as markers of carcinogen exposure and cancer risk. (Invited Seminar)

University of Leicester, Cancer Biomarkers and Prevention Group, Leicester, UK, 27 June 2007.Arlt VM. Elucidating pathways of metabolic activation of carcinogens by quantifying and characterising their DNA adducts. ECNIS Videolink (Invited Seminar)

University of Leeds, Institute of Genetics, Health and Therapeutics, Leeds, UK, 30 July 2007. Arlt VM. TP53 mutations in human cancer: new insights into the aetiology and pathogenesis of Balkan endemic nephropathy-associated urothelial tumours. (Invited Seminar)

Biomedical Research Center, Cancer Research UK Molecular Pharmacology Unit, Dundee, UK, 12. February, 2008.Arlt VM. Metabolic activation of benzo(a)pyrene in vitro by hepatic cytochrome P450 contrasts with detoxification in vivo: experiments with the hepatic cytochrome P450 reductase null mice. (Invited Seminar)

Biomedical Research Center, Cancer Research UK Molecular Pharmacology Unit, Dundee, UK, 12. February, 2008. Phillips DH. Use of transgenic mouse models to understand the basis of carcinogen organotropism – speculations. (Invited Seminar)

University of Surrey, School of Biomedical and Molecular Sciences, Guildford, UK, 2 April 2008. (invitation by Dr. S. Price)Arlt VM. Monitoring for DNA adducts in humans. (Invited Seminar)

Nottingham Trent University, School of Science and Technology, Nottingham, UK, 23 April 2008. Arlt VM. 3-Nitrobenzanthrone, a potential human cancer hazard in diesel exhaust and urban air pollution. (Invited Seminar)

Institute of Cancer Research, Section of Molecular Carcinogenesis, Sutton, UK, 19 April 2007.
Arlt VM. Exposure to benzo[a]pyrene in the hepatic cytochrome P450 oxidoreductase null mouse: detoxification by hepatic cytochrome P450 is more important than metabolic activation. (Internal Seminar)

Institute of Cancer Research, Section of Molecular Carcinogenesis, Sutton, UK, 10 April 2008.
Arlt VM. Gene expression profiles modulated by the human carcinogen aristolochic acid in human cancer cells and their dependence on TP53. (Internal Seminar)

5th International Conference on Environmental Mutagens in Human Populations, Tekirova, Antalya, Turkey, 20-24 May 2007. Arlt VM, Lord GM, Nortier JL, Simoes ML, Phillips DH, Hollstein M, Schmeiser HH. Aristolochic acid mutagenesis: molecular clues to the aetiology of Balkan endemic nephropathy-associated urothelial cancer. (poster)

5th International Conference on Environmental Mutagens in Human Populations, Tekirova, Antalya, Turkey, 20-24 May 2007. Arlt VM, Glatt H, Gamboa da Costa G, Takamura-Enya T, Schmeiser HH, Phillips DH. DNA adducts formed by the air pollutants 2- and 3-nitrobenzanthrone as a means to assess their carcinogenic risk to humans. (poster)

30th Annual Meeting of the United Kingdom Environmental Mutagen Society (UKEMS), Cardiff, UK, 1-4 July 2007. Zuo J, Arlt VM, Brewer D, Fenwick K, Mackay A, Tamber N, Ashworth A, Cooper C, Phillips DH. Gene expression profiles in target and non-target organs. (poster)

30th Annual Meeting of the United Kingdom Environmental Mutagen Society (UKEMS), Cardiff, UK, 1-4 July 2007. Simoes ML, Hockley SL, Gamboa da Costa G, Schwerdtle T, Phillips DH, Arlt VM. The human carcinogen aristolochic acid exerts expression profiles in human cancer cells that are dependent or independent of TP53. (poster)

30th Annual Meeting of the United Kingdom Environmental Mutagen Society (UKEMS), Cardiff, UK, 1-4 July 2007. Arlt VM, Stiborova M, Henderson CJ, Thiemann M, Frei E, Aimova D, Singh R, Gamboa da Costa G, Schmitz O, Farmer PB, Wolf CR, Phillips DH. Exposure to benzo[a]pyrene in the hepatic cytochrome P450 oxidoreductase null mouse: detoxification by hepatic cytochrome P450 is more important than metabolic activation. (poster)

30th Annual Meeting of the United Kingdom Environmental Mutagen Society (UKEMS), Cardiff, UK, 1-4 July 2007. Arlt VM, Glatt H, Gamboa da Costa G, Reynisson J, Takamura-Enya T, Phillips DH. Mutagenicity and DNA adduct formation by the urban air pollutant 2-nitrobenzanthrone. (poster)

37th Annual Meeting of the European Environmental Mutagen Society (EEMS), Basel, Switzerland, 9-13 September 2007. Zuo, J, Arlt VM, Brewer D, Cooper C, Phillips DH. Gene expression profiles in benzo(a)pyrene-treated mouse target and non-target organs. (poster)

37th Annual Meeting of the European Environmental Mutagen Society (EEMS), Basel, Switzerland, 9-13 September 2007. Simoes ML, Hockley SL, Gamboa da Costa G, Schwerdtle T, Phillips DH, Arlt VM. The human carcinogen aristolochic acid exerts expression profiles in human cancer cells that are dependent or independent of TP53. (poster)

6th Annual American Association of Cancer Research (AACR) International Conference Frontiers in Cancer Prevention Research, Philadelphia, USA, 5-8 December 2007. Phillips DH, Stiborova M, Henderson CJ, Thiemann M, Frei E, Aimova D, Singh R, Gamboa da Costa G, Schmitz O, Farmer PB, Wolf CR, Arlt VM. Metabolic activation of benzo[a]pyrene in vitro by hepatic cytochrome P450 contrasts with detoxification in vivo: experiments with the cytochrome P450 reductase null mice. (poster)

47th Annual Meeting of the Society of Toxicology (SOT), Seattle, USA, 16-20 March 2008. Gamboa da Costa G, Singh, R Arlt VM, Mirza A, Richards M, Takamura-Enya T, Schmeiser HH, Farmer PB, Phillips DH. Quantification of 3-nitrobenzanthrone DNA adducts using on-line sample preparation and HPLC-electrospray tandem mass spectrometry (poster)

ULEIC

Use of biomarkers to identify health risk from exposure to hazardous environmental pollutants. Role of mass spectrometry in assessing biologically effective doses of genotoxic agents.P B Farmer International Conference on Environmental Mutagens in Human Populations, May 20-24, 2007, Antalya, Turkey (oral presentation)

Biomarkers of exposure and effect for environmental carcinogens, and their applicability to human molecular epidemiological studies.P B Farmer US EPA Public Health Applications of Human Biomonitoring, September 24-25, 2007, Research Triangle Park, NC, USA. (oral presentation)

Mass spectral approaches for determining carcinogen-induced DNA damage.P B Farmer Royal Society of Chemistry, Analytical Division and Chemical Biology interface forum, DNA Damage: Tools and Analytical Techniques, March 28 2008, Dublin, Ireland (oral presentation)

NIEH

Switzerland, Basel; 2007. September 9-13; Anna L., Kovács K., Gyorffy E., Schoket B., Nair J. : Smoking related O^4-ethylthymidine DNA adducts in human lung tissues (oral presentation)

Schoket B.: Correlations among DNA adduct end-points in human biomonitoring studies (oral presentation)

2007 May 22 Anna Lívia et al: "O4-etiltimidin DNS adduktok keletkezése tüdoben dohányzás hatására" (in Hungarian) (oral presentation)

Kovács Katalin et al: "Környezeti policiklusos aromás szénhidrogén (PAH) expozíció biomonitorozása exponált populációkban" (in Hungarian) (oral presentation)

2007 September 25 Anna Lívia et al: "O4-etiltimidin DNS adduktok keletkezése tüdoben dohányzás hatására" (in Hungarian) (oral presentation)

Kovács Katalin et al: "Környezeti policiklusos aromás szénhidrogén (PAH) expozíció biomonitorozása exponált populációkban" (in Hungarian) (oral presentation)

2008 February 19 Schoket B.: 2007 Annual report on our ECNIS and NewGeneris activities(oral presentation)

KUL
ESBIO workshop on ethics and communication, Copenhagen 11-13 March 2007 “Research on ethics in ECNIS and NewGeneris: A bottom up approach - Birgit Dumez/Ludwine Casteleyn, University of Leuven (oral presentation)

Belgian PHGEN task force meeting of June 25 2007 Integration of genome-based knowledge and technologies into Occupational health practices, K Van Damme (oral presentation)

Workshop Ethical Issues raised by Personalized Nutrition, Lund University, 17-18 August 2007 (Ludwine Casteleyn) (oral presentation)

Green Week 2007, Health Sessions, 12 June 2007, Brussels (Ludwine Casteleyn) (oral presentation)

Belgian PHGen meeting June 2007 “Integration of genome-based knowledge and technologies into Environmental health practices in Belgium” L Casteleyn(oral presentation)

EU Environment and Health Action Plan: Mid-term review 2004-2010” at European Parliament, Brussels; 6 March Ludwine Casteleyn,) (oral presentation)

ULUND
The seventh international symposium on biological monitoring in occupational and environmental health, Sept 10-12 2007 Beijing, China. Bo AG Jönsson and Christian H Lindh. A method for determination of persistent organochlorine pollutant (POP) exposures from small-volume biobanked serum samples.

Karolinska Institute, Huddinge, February 2008 Gunilla Önning. Nutrigenomics. Gothenburg University, April 2008 Lecture at Dept of Clinical Nutrition,. Gunilla Önning. Nutrigenomics.
Nordic Conference for Dieticians, Uppsala, April 2008.Gunilla Önning. Nutrigenomics.
Universidad Mayor San Simon, Cochabamba, Bolivia, March 2008.B. Åkesson. Nutrition and Public Health.

Lund University, May 2007 and December 2007.B. Åkesson. Interaction of food and genes. Symposium DFG Priority Programme 1087 Selenoproteins, Berlin, June 29-30 2007.B. Åkesson. Selenoproteins and other selenocompounds in mammary tissue and milk.

Epi-Tok meeting at Debowa Gora, Poland, April 22, 2008.B. Åkesson. Selenoproteins and other selenocompounds in mammary tissue and milk.

JOGU

37th annual meeting of the EEMS, Basel Sept. 2007 Deregulation of cell cycle control by the aryl hydrocarbon receptor. C. Dietrich, D. Faust, F. Oesch, C. Weiss (poster)

II Polish Congress of Genetics, Warsaw, Poland Sept. 2007 Functional relevance of hARNT genetic polymorphism analysed in vitro. E. Reszka, B. Oesch F.Oesch, H. Zatonski W.Wasowicz (poster)

49th Spring Meeting of the German Society for Pharmacology and Toxicology, 11.-13. March, 2008, Mainz, Germany March 2008

– Protection by indolo[3,2-b]carbazole against DNA-damage by benzo[a]pyrene and hydrogen peroxide in Caco2-cells. D. Faust, F. Oesch, C. Dietrich (poster)

– Role of stress-activated-protein-kinases p38 and JNK in benzo[a]pyrene-7,8- dihydrodiol-9,10-epoxide (BPDE) induced cytotoxicity. N. Grico F. Oesch, C. Weiss (poster)

CASCADE summer school on endocrinology, Bregenz, Austria July2007, C. Weiss (oral presentation)

Institut für umweltmedizinische Forschung der Heinrich-Heine-Universität January 2008
Identification of a novel AhR-dependent signalling pathway in rat oval cells. C. Dietrich

Heinrich-Heine-Universität, Düsseldorf April 2008, The aryl hydrocarbon receptor: mediator of toxicity and protection? Symposium „Nutrition and Health: intestinal effects of food constituents“, C. Dietrich (oral presentation)

Nofer Institute of Occupational Medicine, Lodz, Poland April2008, “Ah-receptor: from diverging signalling to circadian rhythm” B. Oesch (oral presentation)

DKFZ

European Congress of Epidemiology in Cork / Ireland, 12 – 14 September 2007 [Nimptsch K, Rohrmann S, Linseisen J. Dietary intake of vitamin K and risk of prostate cancer in EPIC-Heidelberg. oral presentation]

6th Annual International Conference, Frontiers in Cancer Prevention Research, Philadelphia, PA, December 5-8, 2007. Rohrmann S, Hermann S, Linseisen J. The association of dietary intake of heterocyclic aromatic amines and colorectal adenomas is modified by the intake of flavonols – Results from the EPIC-Heidelberg cohort [Poster]

ISI

American Association For Cancer Research Annual Meeting, 12-16 APRIL 2008
VALIDATION OF LYMPHOBLASTOID CELL LINES FOR THE IDENTIFICATION OF AT RISK DNA REPAIR GENOTYPES. Allione A, Giachino C, Zijno A, Porcedda P, Guarrera S, Polidoro S, Di Gregorio A, Vineis P, Saini F, Marcon F, Garofano B, Simonelli V, Barone F, Minoprio A, Narciso N, Loft S, Moller P, Vogel U, Piro S, Munnia A, Peluso M, D’Errico M, Mazzei F, Dogliotti E, Matullo G. (poster)

IMPROVEMENT OF FGFR3 MUTATION DETECTION SENSITIVITY IN ESFOLIATED CELLS FROM BLADDER CANCER PATIENTS.Silvia Polidoro, Alessandra Di Gregorio, Simonetta Guarrera, Alessandra Allione, Carlotta Sacerdote, Paolo Vineis, Giuseppe Matullo. (poster)

NIOM

II Polish Congress of Genetics, Warsaw, Poland Sept. 2007 Jablonska E., Gromadzinska J., Reszka E., Wasowicz W. Genetic polymorphism of 15 kDa selenoprotein and lung cancer risk. (poster).-

48th Spring Meeting Deutsche Gesellschaft für Experimentelle und Klinische Pharmakologie und Toxikologie Mainz, March 13-15, 2007.

– Oesch-Bartlomowicz, H. Zatonski, E. Reszka, W. Wasowicz, G.T.J. van der Horst, F. Oesch. Direct control of the mammalian circadian clock genes Per1 and Per2 by dioxin, AHR and ARNT Naunyn-Schmiedeberg's Archives of Pharmacology 375, Supplement 1, p. 89, 2007(poster).

– E. Reszka, H. Zatonski, W. Wasowicz, F. Oesch, B. Oesch-Bartlomowicz. Significance of human ARNT polymorphisms in environmental carcinogenesis due to changes in some carcinogen metabolizing enzymes and circadian rhythms. Naunyn-Schmiedeberg's Archives of Pharmacology 375, Supplement 1, p. 100, 2007 (poster).

V Zjazd Polskiego Towarzystwa Genetyki Czlowieka. Warszawa, 18-20 wrzesnia 2007.Reszka E., Oesch B., Oesch F., Zatonski H., Wasowicz W. Functional relevance of hARNT genetic polymorphism analysed in vitro. II Polski Kongres Genetyki. XVI Zjazd Polskiego Towarzystwa Genetycznego, Streszczenia, str. 200. (poster).

19th International Conference on Epidemiology in Occupational Health, Banff, Alberta, Canada, 9-12, 2007Beata Peplonska, Urszula Wilczynska, Wojciech Sobala, Neonila Szeszenia-Dabrowska,Risk of death from cancer in the rubber tire manufacture workers – follow up. (poster)

International Workshop on Air Pollution and Human Reproduction. 9-11.05. 2007, Monachium, W. Hanke, K. Polanska, From smoking pipes to smoking women: Tobacco smoke and IUGR.(oral)

Symposium “Endocrinology of Reproduction” 5-7. 09.2007. Mikolajki, W. Hanke, J. Jurewicz, K. Polanska. “Environmental exposure and the risk of poor pregnancy outcomes - epidemiological study results” (oral)

Rural Environmental Health. 16-20.06.2007, Trnava,

1. K. Polanska. “Scale of the foetus, infant and child exposure to environmental tobacco smoke” (oral)
2. K. Polanska. “Measurement of tobacco use, cessation and environmental exposure” (oral)

KSOHIA Conference- Children and environment. 9-11.11.2007 Modra-Harmonia Slovak Republic

- Polanska K. ETS exposure and childhood cancer – overview of current epidemiological evidence (poster)
- Jurewicz J, Hanke W.: Exposure to pesticides and childhood cancer – overview of current epidemiological evidence – (poster)
- Jurewicz J, Hanke W.: Exposure to pesticides of families working in agriculture and their children (poster)

VIII Polish Conference „Tobacco or Health". 15-16.11.2007, Poznan, Polanska K., Hanke W., Sobala W., Jurewicz J. Exposure to tobacco smoke of pregnant women - results of prospective study in Lodz region"(oral)

4 th International Conference on children's health and the environment; 10-12.07.2007, Viena.

- § J. Jurewicz, W. Hanke Biological monitoring of exposure to pesticides of members of families working in agriculture and their children-preliminary results (poster)
- § J. Jurewicz, W. Hanke, M. Radwan Exposure to environmental hazards and the risk of male infertility- multicenter national study in Poland.(poster)

VUB

MN - NewGeneris-IMSTAR meeting on automated micronuclei scoring, Brussels, Belgium (15-16th May 2007) Raluca Mateuca and Micheline Kirsch-Volders. "The influence of genetic polymorphisms on micronucleus frequencies in human lymphocytes in vivo" (15th May 2007), MN- (oral presentation).

MN - NewGeneris-IMSTAR meeting on automated micronuclei scoring, Brussels, Belgium (15-16th May 2007) Ilse Decordier and Raluca Mateuca. Oral presentation entitled: "Mechanisms of MN induction and MN frequency as a predictive biomarker of cancer risk" (15th May 2007), (oral presentation).

Vth International Conference on Environmental Mutagens in Human Populations (Vth ICEMHP), Antalya, Turkey (20-24th May 2007) Ilse Decordier and Micheline Kirsch Volders. "A comparison of repair capacities in mothers and newborn daughters" (21st May 2007), (oral presentation prepared by Ilse Decordier).

UKEMS, Cardiff, UK (1st–4th July 2007) Micheline Kirsch Volders and Ilse Decordier. "Chromosome instability: from phenotype to genotype, and vice versa" (oral presentation).

EEMS (9th-13th September 2007), Basel, Switzerland Raluca Mateuca, Mathieu Roelants, Christian Carton and Micheline Kirsch-Volders. "Occupational exposure to arsenic compounds: genetic polymorphisms and induction of genotoxic effects" (poster).

EEMS (9th-13th September 2007), Basel, Switzerland Raluca Mateuca, Mathieu Roelants, Gwenaelle Iarmarcovai , Stefano Bonassi, Michael Fenech, Jean-Louis Bergé-Lefranc and Micheline Kirsch-Volders. "Influence of DNA repair gene polymorphisms on micronucleus frequencies in human lymphocytes in vivo", (poster).

Second NewGeneris Annual meeting (11th–14th February 2008), Athens, Greece Kim Vande Loock, Ilse Decordier, Roberta Ciardelli, Raluca Mateuca, Dominique Haumont, Micheline Kirsch-Volders. "An aphidicolin-blocked NER cell phenotype assay measuring DNA incision and repair capacity", (poster).

IRAS

Epidemiology in Occupational Health EPICOH 2007, Banff, Canada, 9-12/10 2007
Roel Vermeulen Advancing occupational exposure assessment for case-control studies; Experiences from two studies on benzene exposure.

Hans Kromhout Quantitative exposure assessment in community-based studies. Lessons learned from the ECRHS.
Roel Vermeulen Where do farmers get their pesticide exposure from? Application versus background exposures.

Daisy Boers Third follow-up of a Dutch cohort study on the effects of occupational exposure to phenoxy herbicides, chlorophenols and contaminants. (oral presentation)

Susan Peters PAH exposure, urinary mutagenicity and DNA adducts in rubber workers. (oral presentation)

Frank de Vocht Could the association between increased lung cancer risk and bitumen fume be ascribed to assumptions in the assessment of the exposure? (oral presentation)

Frank de Vocht Occupation and the risk of non-Hodgkin lymphoma. (oral presentation)

Occupational Hygiene 2007 Annual Conference of British Occupational Hygiene Society. April 2007. Glasgow. (oral presentation)

Roel Vermeulen Data driven exposure assessment; Examples from epidemiological studies on benzene. (oral presentation)
International Conference of Toxicogenomics held on Nov 1-3, 2007, Seoul, Korea
Roel Vermeulen Proteomics and the identification of new markers of exposure and disease Is it really going to happen? (oral presentation)

NHFR
MGMT Conference, Mainz, Germany, June 13 - 16, 2007; Souliotis VL, Fousteri MJ, Mullenders LHF, Episkopou HG, Kyrtopoulos SA, MGMT- and nucleotide excision-mediated DNA repair: similarities in the rate-dependence on chromatin structure. (poster)

KI
J Rafter presented ECNIS at two international meetings, American Institute for Cancer Research (AICR) Annual Research Conference on Food, Nutrition, Physical Activity and Cancer. 6-7 Nov, 2008 Washington, USA. Lectured on: Probiotics and Colon Cancer Prevention and Vitafoods International Nutraceuticals Conference 2009, 5-7 May, 2009, Geneva, Switzerland. Lectured on: Probiotics and Colon Cancer Prevention

H. Karlsson presented a poster with ECNIS data at the Nanotoxicology, 2nd International Conference, Sept 2008, Zurich, Switzerland

HL. Karlsson. Oral presentation at theNov2k 2008 Biosciences Symposium at Karolinska Institutet, Sweden, 24th October 2008. Title: Big risks with small particles?

T. Bergström, C. Johansson C and L. Möller: Antioxidants at Physiological Concentration Induce 8-oxo-7,8-dihydrog-2'-deoxyguanosine Formation With a Great Variety of Potency

Nov2k 2008 Biosciences Symposium at Karolinska Institutet, Sweden, 24th October 2008. ECNIS was presented.

H. L. Karlsson, P. Cronholm, J. Gustafsson, L. Möller: Copper oxide nanoparticles are highly toxic: A comparison between metal oxide and carbon nanotubes
Nov2k 2008 Biosciences Symposium at Karolinska Institutet, Sweden, 24th October 2008. ECNIS was presented.

H. L. Karlsson, J. Gustafsson, P. Cronholm, L. Möller: The importance of size for the toxicity of metal oxide particles - a comparison between nano- and micrometer particles
Nov2k 2008 Biosciences Symposium at Karolinska Institutet, Sweden, 24th October 2008. ECNIS was presented.

HL. Karlsson. Oral presentation at the NanoNet meeting at Karolinska Institutet, Sweden, May 27th 2008. Title: Particularly harmful particles? – Studies on the toxicity of micro- and nanoparticles

LEICESTER
Biomarker assay validation in the EC programmes ECNIS and NEWGENERIS, P B Farmer, Second Copenhagen Workshop on DNA oxidation. January 29 - 30, 2009. Oral. International.

New approaches for measuring DNA adducts as biomarkers of exposure to environmental carcinogens, P B Farmer National Cancer Center Research Institute, Tokyo, Japan, December 9, 2008. Oral. International

New approaches for measuring DNA adducts as biomarkers of exposure to environmental carcinogens, P B Farmer. Division of Pharmaceutical Sciences, Okayama University, Japan, December 8, 2008. Oral. International.

Genotoxicity of environmental air pollutants, P B Farmer. Japanese Environmental Mutagen Society, Okinawa, December 4-6, 2008. Oral. International.

Biomarkers and Epidemiology: E.C. biomonitoring projects and the ECNIS Network of Excellence, P B Farmer. Imperial College London, UK, May 27, 2008. Oral. National.

Mass spectral approaches for determining carcinogen-induced DNA damage, P B Farmer, Royal Society of Chemistry, Oxidative DNA Damage workshop, Dublin City University, Ireland, March 28, 2008. Oral. International

ICR
V. Arlt: 24th Annual Meeting of the German Environmental Mutagen Society (GUM), Vienna, Austria, 17-22 February 2009; Title: “TP53-dependent DNA adduct formation of different environmental carcinogens in cell lines differering in TP53 status”.

V. Arlt: German Cancer Research Center, Division of Molecular Toxicology, Heidelberg, Germany, 2 July 2008; invitation by Dr. H.H. Schmeiser; Title: “Gene expression profiles modulated by the human carcinogen aristolochic acid I in human cancer cells and their dependence on TP53”.

V. Arlt: German Cancer Research Center, Research Group Genetic Alterations in Carcinogenesis, Heidelberg, Germany, 28 April 2009; invitation by Dr. H.H. Schmeiser; Title: “TP53-dependent DNA adduct formation of different environmental carcinogens in cell lines differering in TP53 status”.

V. Arlt: Friedrich-Schiller-University Jena, Institute for Nutrition, Jena, Germany, 7 May 2009; invitation by Prof. Dr. Lehmann; Title: “DNA adducts as biomarkers of exposure and marker of cancer risk”.

V. Arlt: 31st Annual Meeting of the United Kingdom Environmental Mutagen Society (UKEMS), Newcastle, UK, 15-18 June 2008.
Arlt VM, Stiborova M, Vaclav M, Gamboa da Costa G, Phillips DH, Reynisson J (2008) Mutagenic potential of nitrenium ions of nitrobenzanthrones: correlation between theory and experiment. Poster

D. Phillips: ICR Seminar 8 May 2008; Title: “Oesophageal cancer: environmental causes”

ICL

§ NeuroEPIC: Principles, study design, and an example of cigarette smoking associated with Amyotrophic Lateral Sclerosis incid, V Gallo, The 4th Conference of Epidemiological Longitudinal Studies in Europe (CELSE) Bergen, Norway, November 12-14, 2008 (oral, international)
§ Existing cohorts and biobanks, P Vineis, Biomarkers of environmental carcinogenesis - moving on to population studies, London, December 2007 (oral, international)
§ The STROBE-ME (ME = Molecular Epidemiology) guidelines, P Vineis, The workshop ‘Strengthening of scientific reporting’, March 19th 2009, in Lund.

NHRF

SA Kyrtopoulos, "Environment and Health Research", invited lecture at national event "Contribution of national research centres to technological development and innovation", Athens, 1 April 2009

- SA Kyrtopoulos, "Contribution of molecular biology to environmental health research", invited lecture at the workshop on "Molecular biology and society: challenges and prospects" organised by the Greek Society for Molecular Biology and Biotechnology, Athens, 28/11/2008

- P Georgiadis, oral presentation on"Advances in high-sensitivity, high-throughput immunological technologies for use in molecular epidemiology" at EEMS, Croatia, Sept. 2008

- H Episkopou, oral presentation on "Close association between transcriptional activity, local chromatin structure and the efficiencies of both sub-pathways of nucleotide excision repair of melphalan-induced N-alkylpurines" at EEMS, Sept. 2008

- SA Kyrtopoulos, "Contribution of molecular biology to environmental health research", invited lecture at the workshop on "Molecular biology and society: challenges and prospects" organised by the Greek Society for Molecular Biology and Biotechnology, Athens, 28/11/2008

- SA Kyrtopoulos, "Environment and Health Research", invited lecture at national event "Contribution of national research centres to technological development and innovation", Athens, 1 April 2009

Posters:
H Episkopou, SA Kyrtopoulos, P Sfikakis, M. Demopoulos and V.L. Souliotis Association between NER efficiency, transcriptional activity and chromatin structure in different genomic regions; EEMS, Croatia, Sept. 2008
H Episkopou, SA Kyrtopoulos, P Sfikakis, MA Dimopoulos, VL Souliotis, Development and validation of a multiplex, long quantitative PCR-based method to measure DNA adducts induced by chemotherapeutic agents in specific sequences, with clinical application potential; EEMS, Croatia, Sept. 2008
VL Souliotis, D Stellas, M Bekyrou, SA Kyrtopoulos, Discovering the molecular components of the B[a]P-induced S-phase arrest; EEMS, Croatia, Sept. 2008
VL Souliotis, PP Sfikakis, MA Dimopoulos, H Episkopou, SA Kyrtopoulos, New biological markers predicting clinical response to therapeutic treatment with melphalan in multiple myeloma; EEMS, Croatia, Sept. 2008

NIEH
L. Anna, K. Kovács, B. Schoket: Impact of the DNA isolation method on the measurement of bulky DNA adduct levels by ^{32}P-postlabelling.
38th Annual Meeting of the European Environmental Mutagen Society, Cavtat, September 20-25, 2008

K. Kovács, J. Evans, L. Anna, B. Schoket, D.H. Phillips: Mini-trial on methodology standardisation of TLC-^{32}P-postlabelling – Phase I.
38th Annual Meeting of the European Environmental Mutagen Society, Cavtat, September 20-25, 2008

K. Kovács, L. Anna, B. Schoket: Increase of through-put of ^{32}P-postlabelling for PAH-type bulky DNA adducts
NewGeneris 3rd Annual Meeting, Stockholm, February 2-5, 2009

Kovács K., Anna L., Schoket B.: A biológiai minták kezelésének jelentosége a molekuláris epidemiológiai vizsgálatokban. Fiatal Higiénikusok Fóruma IV., Gyor, 2008. május 29 – 31. (The importance of the processing of biological samples in molecular epidemiological investigations, 4th Forum of Young Hygienists, Gyor, Hungary, 2008 May 29-31).

Anna L., Kovács K., Schoket B., Rudnai P.: Our achievements in the ECNIS and NewGeneris EU projects in 2008 – Annual meeting at NIEH, Budapest, 2009. February 19.

ULUND
Lecture B. Åkesson, Eurobiotech, Krakow, October 2008
"Diet-responsive monogenic disorders - what can we learn from these old diseases in the genomic age?"

C. Lecture B. Åkesson, TEMA-13, Pucon, Chile, November 2008
"Selenium in milk – selenium speciation and health effects"

D. National: Gunilla Önning: Lecture on "Nutrigenomics" at the Department of Medical Nutrition, Karolinska Institute, February 2009

E. Participation with poster at NuGO week Potsdam, September 2008, Gloria Rodrigo.
"Antiproliferative activity on human colon cancer cells treated in vitro with extracts from Bolivian foods and other plants"

F. Participation with poster at NuGO week Potsdam, September 2008, M. Ulmius.
"Glucose and insulin responses after different dietary fiber rich meals"

G. Participation with poster at NuGO week Potsdam, September 2008, Gunilla Önning.
"Selenium in milk – selenium speciation and health effects"

H. Participation with poster at NuGO week Potsdam, September 2008, Mauricio Peñarrieta.
"Spectrophotometric methods and reversed-phase high performance liquid chromatography for the separation of phenolic compounds from foods"

I. Poster at Nordic Nutrition Conference, June 2008 Matilda Ulmius, Anna Johansson and Gunilla Önning.
"Glucose and insulin responses after different dietary fiber rich meals"
J. National: Poster at Livsmedelsforskardagarna, November 2008. Matilda Ulmius, Anna Johansson and Gunilla Önning.
Glucose and insulin responses after different dietary fiber rich meals.
K. Poster at Mass Spectrometry Metabolomics Workshop Copenhagen Feb 24-27 2009: Anna Johansson, Matilda Ulmius, Thaer Barri, Lars O. Dragsted and Gunilla Önning "LC-MS analysis of human urine and plasma metabolome from a high dietary fiber cross-over intervention"

Early Cancer Detection: Environment, Biomarkers and Mechanisms. Squillace, Catanzaro, Italy. 14-17 May 2010

Food for the 21st century: how EU research impacts on Food quality and Safety. Brussels, Belgium. 7-8 July 2010

Cohorts and Consortia. From Biotechnology to Populations. Banff, Alberta, Canada. 17-19 June 2009