ecnis news

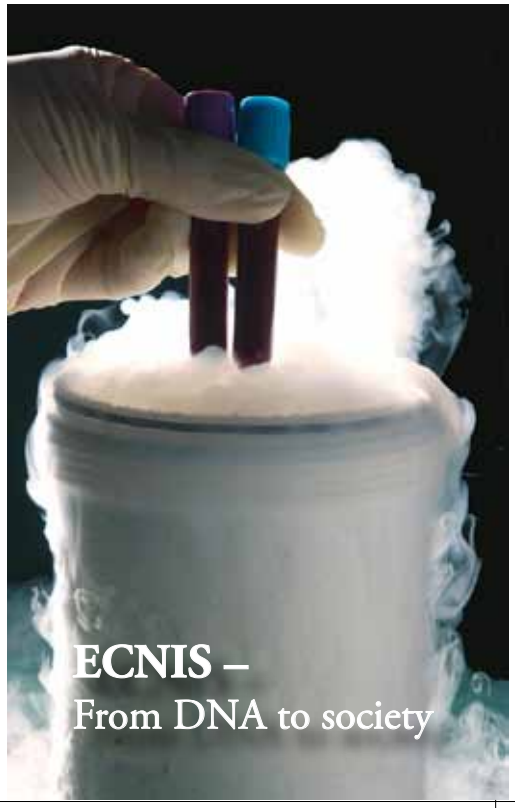
ENVIRONMENTAL CANCER RISK, NUTRITION AND INDIVIDUAL SUSCEPTIBILITY
EU Network of Excellence

2009 No.1 (8)

• Cereals & cancer

Cereals represent a large group of food products that have different effects on the metabolism, inflammation and cancer. Is it really the case that rye bread can affect prostate cancer?

Page 11



• ECNIS Meeting

The ECNIS Network had its yearly meeting in March. This time the meeting was held in two cities. The first day was in Brussels followed by two days in Leuven. The days were filled with parallel sessions on many subjects.

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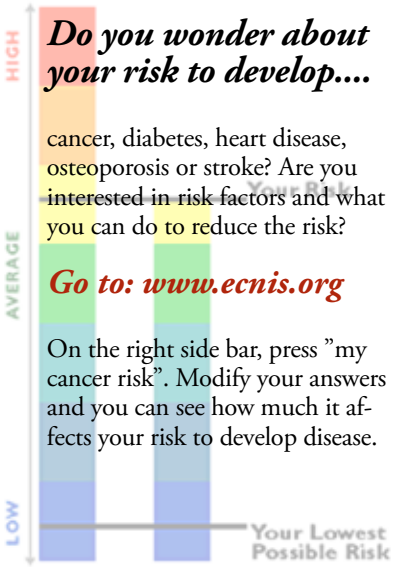
• Cancer risk?



Do you wonder about your risk to develop....

cancer, diabetes, heart disease, osteoporosis or stroke? Are you interested in risk factors and what you can do to reduce the risk?

Go to: www.ecnis.org

On the right side bar, press "my cancer risk". Modify your answers and you can see how much it affects your risk to develop disease.

• ECNIS Network

In this issue of the ECNIS newsletter there are two examples of activities in Poland and in Greece/Hungary, respectively. The Nicolaus Copernicus University, the ECNIS Partner 9, is presented and a student exchange from Budapest to Athens is reported.

Pages 6 and 7

• Breast cancer

Breast cancer is a very common form of cancer. What are the risk factors and can they be modified or reduced? Is daylight a problem or a solution to a part of this problem? Are European countries different in risk and are there special occupations that could be a risk factor?

Pages 3 and 13

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Sixth Framework Programme
FOOD-CT-2005-513943 ECNIS

The ECNIS Network of Excellence

• The EU Commission

The yearly meeting of the ECNIS Network of Excellence was held in two cities, Brussels and Leuven. The purpose of the first day in Brussels was to connect to the EU Commission. One session involved information and discussion regarding the future plans for "The Commission Scientific Committees" and the data generated within ECNIS.

• Brainstorm?

Brainstorm is a good illustration of a scientific meeting that cover 25 partners in 13 European countries. In front of the building in Brussels where the ECNIS meeting was held this actually took place in front of our eyes. It was stormy and raining, and in the midst, on top of a building, a huge brain was hanging in the storm. "Brainstorm" can obviously be shown in different ways.

• Hotel...

The days in Leuven was in the Old Town with buildings being up to 500 years old, some even older. This part of Leuven was filled with students in all directions. An illustration of the academic influence in Leuven was a hotel we passed on our walk to the conference site. The "Hotel Professor". An unusual name of a hotel, but very up to date. This is the type of place where we see one another. Where we sit late in the evenings discussing research data, upcoming meetings and scientific articles. Professors and students from all over Europe. This is another example of brainstorm. If there are a couple of professors staying at a hotel, there will be scientific discussions..., it is not an "if" it is just a matter of "where".

• The bell

A bell is used to get attention. This bell was on the roof, at a corner of a cathedral in Leuven. This illustrates an issue that is brought up in this newsletter. Scientists talk a lot, many discussions, scientific articles etc. But now and then there is a reason to ring the bell. One such "bell" is the discussion and data that indicate a connection between working nightshift and an increased risk for breast cancer. Nightshift does not always indicate work at night time, it could be flight attendants that on intercontinental flights constantly affect their day and night rhythm.

In the best case the science is clear, bright and precious, as the gold plated statue. In some cases it takes a long time before the scientific statement has a "golden" character, and as with metal, this is a process before matters become clear.

Lennart Möller /editor

• The road

The road of science to reach the "light" over scientific issues. In a network like ECNIS one first have to find the people (scientists) and put them on the same road (program). This is a time consuming process. While on the road there is a need of fuel (funding), another time consuming process. Being on the road there is a need to know the direction (aim). Some say that the road is short (funding agencies) while we all know that science is a constantly ongoing process. It is to constantly be at the road, not only walk the road but actually build a road where man has not walked before.

To do this the scientist must have a mental picture regarding direction and cooperation. The best way to build a road is to give a team that has shown that they can do this (they are already doing it) building material. The scientist can build that road, but it can be very inefficient if the road builder have to run away and look for building material all the time.

This is the reason why the ECNIS Network of Excellence, that is out there building the road, need building material (continous funding), just because ECNIS have showed that it can be done, the team is there, they know the direction and they are eager to continue building. Therefore, to continue such a network is very cost-effective.

Is breast cancer related to night shift work?

• IARC evaluation

In October 2007, an IARC Working Group classified "shift work that involves circadian disruptions" as probably carcinogenic to humans (Group 2A). After evaluation of the data from experimental studies and from epidemiological research the Group concluded that there is a "sufficient evidence" in animals for the carcinogenicity of light during the biological night, but the evidence in humans was considered to be limited[1].

• Light at night and melatonin

The causal relation between light at night and cancer seems to be biologically plausible through melatonin deprivation and the number of the effects related to low melatonin level. Melatonin was shown to inhibit tumor growth, to scavenge reactive oxygen species, to increase activity of the NK cells and other cells of immune system, and also to inhibit cell cycle and division of cancer cells. Melatonin was also shown to be involved in regulation of the gonadal function, with higher estrogen production and release resulting from low melatonin. Light at night might deregulate circadian genes involved in cancer related pathways.

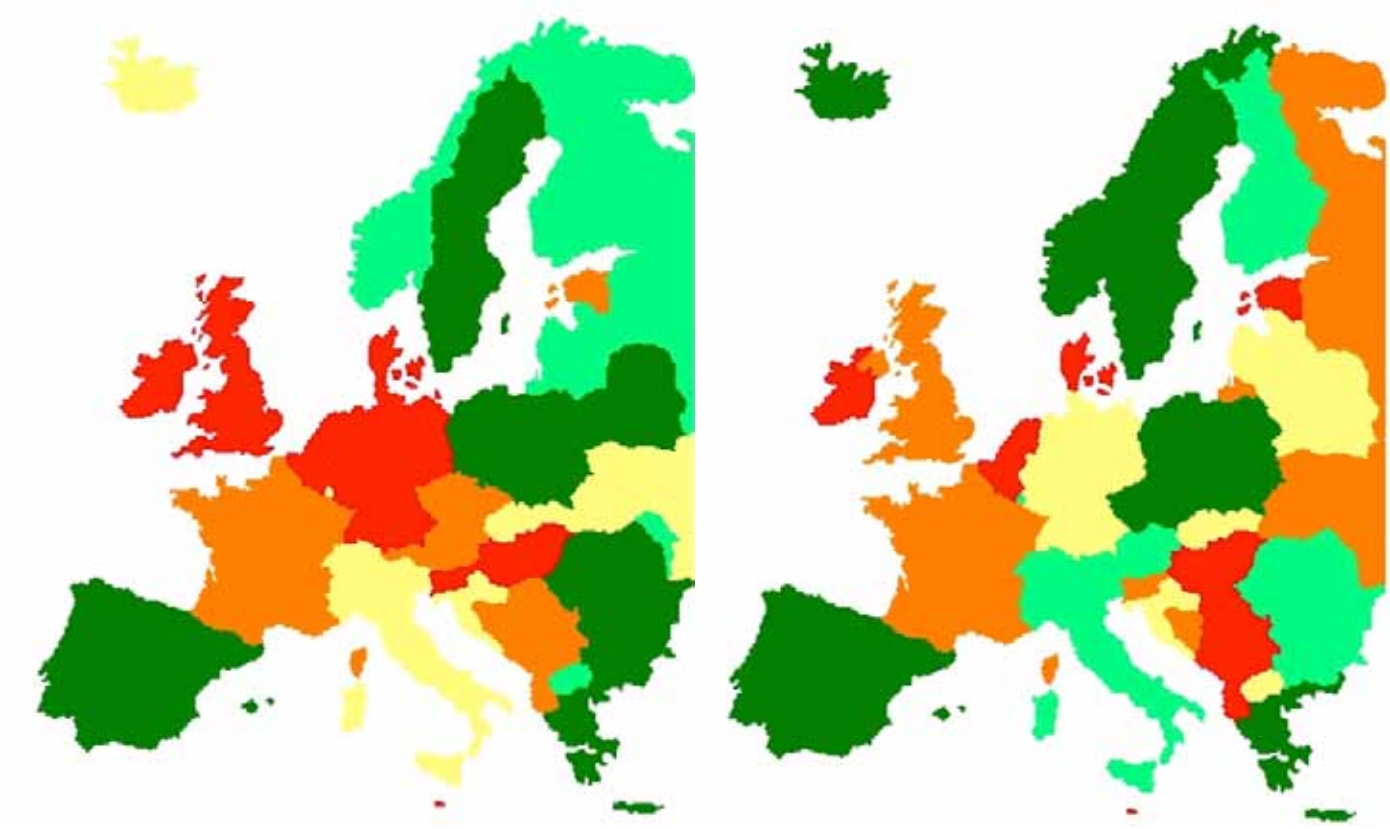
• Epidemiological evidence

Of the eight epidemiological studies, focusing on the association between night work and breast cancer risk, increase of risk was observed (up to OR = 2.2; 95% CI 1.1-4.5) in nurses in Norway with > 30 years of night shift work [2]. The dose (duration) response (statistically significant) trends have been also reported [3-6].

There have been, however, some limitations of these studies, like potential confounding by incomplete adjustments for known breast cancer risk factors [2, 3, 5-8], and in some relatively small numbers of cases reporting night work [3, 5, 7]. Besides each of these studies used different night shift-work definition, and in some, no direct information from individual subjects was available on either exposure or confounders [2, 3, 6, 8]. Recently published results of the data from the NHS nurses prospective cohort in the US showed that higher melatonin level was associated with lower breast cancer risk [9]. The increased risk for breast studies has been also found in female flight attendants, but beside exposure to light at night other exposures are of concern in this occupation like cosmic radiation, electromagnetic fields and some chemicals like fuel, jet engine exhausts and cabin air pollutants [10].

• Claims and compensations in Denmark

Simultaneously (2007) an evaluation of the epidemiological data was performed by Occupational Diseases Committee in Denmark. The Committee decided that breast cancer occurring in a woman after many years of night-shift work qualifies for recognition as an industrial injury. Practical consequences of this judgment have been already encountered. In 2008 almost forty breast cancer cases were compensated in Denmark (nurses, flight attendants). The cases had substantial 20-30 years period of night work at least one night shift per week, and had no underlying significant risk factors for breast cancer, like for example strong familial history of breast cancer. Following Danish precedent, first claim has been submitted to the court in Germany.



The breast cancer mortality in European women at all ages. The breast cancer mortality in European women at 0-64.

Green is a low risk and red indicate a high risk. Data are from IARC.

The night shift work is one of the most widespread occupational exposures in working populations of industrialized countries. Estimates show that about 20% of the working population in Europe and US engages in such work. On the other hand breast cancer is the most common cancer in women, with over one million incident cases diagnosed in the world each year. These two figures indicate that there might be a large number of potentially preventable breast cancer cases if the association between night work and breast cancer truly exist.

• Ongoing epidemiological studies

The premise is that in few years more decisive epidemiological data will become available. A number of studies and analyses are currently going on, including nested case-control studies in the cohorts of nurses (Denmark, Sweden), and newly initiated case-control studies, which address specifically questions on shift work (e.g. in Spain, Germany). Besides, cross-sectional studies in nurses (Poland, US, Canada) addressing various biomarkers (exposure, susceptibility, and potentially early-effects) are being carried out, and might add to our understanding of underlying mechanisms.

• IARC Workshop

The standard approach in exposure assessment seems to be a prerequisite for further analyses. To harmonize an on-going or future efforts a "IARC Workshop on Shift-work Exposure Assessment" was organized in April 2009, resulting in recommended set of questions on shift work and list of variables that should be addressed in order to obtain accurate and comparable measures of night shift work.

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• References

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2 Lie JA, Roessink J, Kjaerheim K. Breast cancer and night work among Norwegian nurses. *Cancer Causes Control 2006;17 (1):39-44.*

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4 Schernhammer ES, Laden F, Speizer FE, et al. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. *J Natl Cancer Inst 2001;93 (20):1563-8.*

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10 Ballard T, Lagorio S, De AG, et al. Cancer incidence and mortality among flight personnel: a meta-analysis. *Aviat Space Environ Med 2000;71 (3):216-24.*

ECNIS Reports

- **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
  ISBN 978-83-60818-14-5

- **State of the art of genotype vs. phenotype studies**

  Edited by
  Ari Hirvonen
  ISBN 978-83-60818-13-8

- **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
  ISBN 978-83-60818-06-0

- **Epidemiological concepts of validation of biomarkers for the identification/quantification of environmental carcinogenic exposures**

  Edited by
  Paolo Vineis, Valentina Gallo
  ISBN 978-83-60818-03-9

- **Dietary vitamins, polyphenols, selenium and probiotics: biomarkers of exposure and mechanism of anticarcino genic action**

  Edited by
  Björn Åkesson, Per Mercke
  ISBN 978-83-60818-02-2

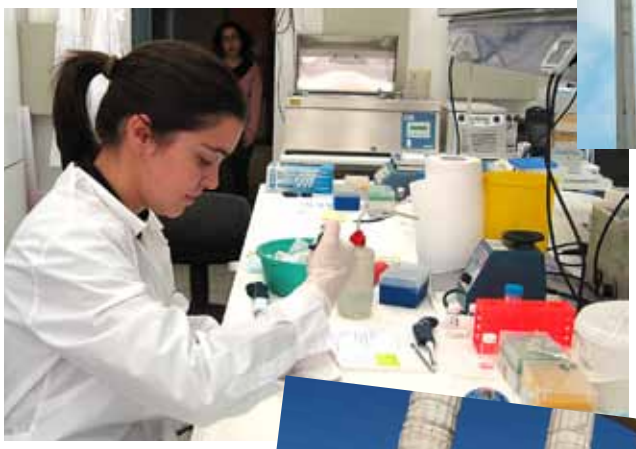
- **Biomarkers of carcinogen exposure and early effects**

  Edited by
  Peter B. Farmer, Jean M. Emeny
  IISBN 83-88261-78-9

In the cradle of the culture – ECNIS Exchange Fellowship in Athens

May I express my thanks to ECNIS for the award for a two-and-a-half month exchange fellowship (autumn, 2008) to Professor Soterios Kyrtopoulos's laboratory, NHRF, Athens within our WP6 activities. During the fellowship program I learnt a new PAH-DNA ELISA immunoassay technique which is closely linked to the DNA adduct research which is being carried out in my home laboratory at NIEH, Budapest during the past twenty years. My theoretical and practical knowledge has been further developed in the research and applications of DNA adduct biomarkers in human PAH exposure measurements. It was quick and easy to feel comfortable in the host laboratory because I had met several lab members at ECNIS conferences, workshops and courses before. Evi Makedonopoulou is one of my great friends who helped me with everything. I had a successful time and it was also excellent opportunity to meet and work with junior and senior colleagues in the ECNIS partner laboratory in a very friendly, joyful and supporting atmosphere.

Athens is a most beautiful and interesting city. It was the birthplace of many prominent philosophers, writers and politicians of the ancient world. Whenever I went up to the Acropolis the "genus loci" always touched me! During the weekends I discovered many museums of Athens and traveled to the famous cities and islands (Delphoi, Naphlio, Sounion, Aegina and Hydra islands). Those were amazing places! I have great memories from the everyday work in the lab and from Athens, a cradle of ancient human culture and the present exciting mixture of past and present.



Acknowledgement

I would like to thank my supervisors Drs. Soterios Kyrtopoulos and Panagiotis Georgiadis and his team in NHRF, Athens for the excellent research guidance, and the personal support. I gratefully acknowledge the financial support of ECNIS.

Katalin Kovács
NIEH, Budapest, Hungary

ECNIS Partner 9.

Department of Clinical Biochemistry, Collegium Medicum, Nicolaus Copernicus University

The Department of Clinical Biochemistry (DCB) was created in 1988 by Prof. Ryszard Olinski at The Ludwik Rydygier Medical Academy in Bydgoszcz, Poland. In 2004 The Medical Academy was merged with Nicolaus Copernicus University (NCU) located in Torun, 40 km from Bydgoszcz. Nowadays NCU is the biggest university in Northern Poland comprising 15 faculties and ca 40,000 students.

For over 20 years the research carried out at The Department of Clinical Biochemistry has been focused mainly on the involvement of oxidative damage to DNA, its repair, and efficiency of antioxidant systems in etiology of human diseases and ageing. Over the years DCB participated in 19 research grants financed by Polish Ministry of Science and Higher Education, two grants from Polish-American Maria Sklodowska-Curie Joint Fund II, and two grants (EUROFEDA and ESCODD) financed by 5th Framework Program of EU. All eleven members of The ECNIS Network of Excellence from Bydgoszcz have their appointments at DCB.

Particular group members explore currently the following research directions:

Karol Bialkowski
(Ph.D., D.Sc., Assoc. Prof.)
Antimutagenic MTH1 protein (8-oxo-dGTPase) biological role, regulation of its expression and enzymatic activity, involvement in carcinogenesis, potential application as a biomarker of carcinogenesis and oxidative stress.

Marek Foksinski
(Ph.D., Assist. Prof.)
Oxidative DNA damage and antioxidant status in patients undergoing chemotherapy and radiotherapy. DNA methylation and carcinogenesis. Single-stranded DNA fragments in urine and plasma as possible DNA repair products.

Daniel Gackowski
(Ph.D., Assist. Prof.)
The role of modified bases in DNA as biomarkers of cancer susceptibility and prognostic factor in anticancer therapy - in association with antioxidant status.

Rafal Rozalski
(Ph.D., Assist. Prof.)
Oxidatively modified nucleobases and nucleosides in biological fluids - sources, meaning, potential application in diagnostics of neoplastic and cardiovascular diseases.

Agnieszka Siomek
(Ph.D., Assist. Prof.)
Activity of NFκB signaling pathway, coeliac and cardiovascular disease, human ageing - their relationships with oxidatively modified DNA.

Tomasz Dziaman
(Ph.D., Assist. Prof.)
Potential links between the level of 8-oxo-2'-deoxyguanisine in DNA and BRCA1 deficiency in breast cancer patients and healthy individuals.

Jolanta Guz
(Ph.D., Assist. Prof.)
Global DNA methylation - biological role, involvement in carcinogenesis, links between DNA methylation and oxidative stress.

Prof. Ryszard Olinski
(Ph.D., D.Sc., Full Professor) as a Chief of DCB supervises and manages all aspects of scientific activities of the department.

Anna Szpila
(M.Sc. Res. Tech.)
Modulation of MTH1 protein expression and its 8-oxo-dGTPase activity in different stages of colon cancer development.

Ewelina Zarakowska
(M.Sc., Ph.D. student)
Chromatin condensation status versus susceptibility of DNA to oxidative damage – potential links to the development of infertility and cancer.

Bartlomiej Kalinowski
(M.Sc., Ph.D. student)
2'-Deoxyuridine in DNA as a potential source of mutations – elaborating a reliable method of its quantitative determination.

Workshop on Outcome of Type B projects:
Leuven, Belgium, March, 2009

Collaborative projects are a central part of the ECNIS enterprise and were the focus of a WP6 workshop, attended by over 70 delegates, held in the historic Faculty Club, Leuven, in conjunction with the 4th ECNIS Annual Meeting. A brief introduction to the work of WP6, given by Jean Emeny, University of Leicester, was followed by presentations on seven of the 24 collaborative projects funded to date.

Epidemiological studies have indicated a protective role of selenium against cancer but the optimal type and dose of selenium supplements have yet to be determined. Björn Åkesson, Lund University, described a short-term intervention trial in humans with selenium-enriched yeast and selenium-enriched milk. This revealed significant changes in gene expression in peripheral blood mononuclear cells (PBMCs) although these differed from those found in previous studies.

Alcohol drinking is associated with an increased risk of developing certain cancers. In a project to develop a biomarker of alcohol intake, presented by Dan Segerbäck, Karolinska Institutet, N2-ethylidenedeoxyguanosine showed promise. An intervention study in humans is planned to test the levels, stability and persistence of this marker in blood and buccal cells of volunteers after alcohol consumption.

There is growing evidence of an association between urinary 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) and various pathological disorders; however, discrepancies remain between the levels measured by ELISA and those determined by chromatographic techniques. Marcus Cooke, University of Leicester, reviewed progress by the European Standards Committee on Urinary (DNA) Lesion Analysis (ESCULA), which is addressing these discrepancies and attempting to clarify the source of 8-oxodG in urine. Data from a second round of inter-laboratory comparisons of chromatographic techniques and ELISA are being analysed and a third round is scheduled.

The first ECNIS Comet Assay Validation Group (ECVAG) trial to assess variation in measurement of DNA damage and repair activity between laboratories and the effectiveness of calibration of the assay indicated that laboratories are able to detect dose–response relationships in coded samples, but the measured level of DNA damage varies between laboratories. A second trial, described by Peter Møller, University of Copenhagen, aims to establish reference conditions for the assay, and to continue analysis of variation in DNA damage and development of a true internal standard.

A validation trial to test whether EBV-transformed lymphoblastoid cell lines are suitable surrogates of cryopreserved PBMCs for DNA repair genotype–phenotype correlation studies was described by Giuseppe Matullo, ISI Foundation, Turin. For the assays tested, the two cell types were found to differ, with the former showing greater inter-individual variability, making them inappropriate surrogates. An ECNIS-wide study is proposed that will look at DNA repair genotype–phenotype correlations in cryopreserved PBMCs so that functional SNPs/haplotypes can be identified.

Farhad Islami, IARC, Lyon, reported the results of a molecular epidemiological study to test the hypothesis that exposure to polycyclic aromatic hydrocarbons (PAHs) might have a major role in the increased incidence of oesophageal cancer in Golestan Province, northern Iran. Some differences were found in DNA adduct levels in certain subpopulations that were partly related to cooking methods. Further analyses will be undertaken to identify the source(s) of the PAHs and the relationships between different PAH-related biomarkers.

Since humans are exposed to mixtures, elucidating the pathways differentially induced by genotoxic versus nongenotoxic carcinogens will allow the potential cross-talk between these to be examined and thus the risk of such mixtures to be more reliably predicted. Franz Oesch, Johannes Gutenberg University, Mainz, described a project designed to study independently the two pathways triggered by a genotoxic tumour initiator and by a non-genotoxic tumour promoter, using the AhR ligand benzo[a] pyrene (BaP) as a prototype. The pathways triggered by BaP and/or its metabolites will be compared with the changes elicited by the non-genotoxic AhR ligand 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD) in a new study.

Jean Emeny
University of Leicester, UK

Workshop on prioritising, planning and implementing large-scale human studies:
Leuven, Belgium, March, 2009

An important part of the work of ECNIS is to ensure that future projects involving human subjects are effectively organised and make the best use of the Network's resources. In order to consider the issues involved in such studies, over 50 participants gathered in the splendid Willem Van Croy room of the Faculty Club in Leuven for a WP1 workshop on 'Prioritising, planning and implementing large-scale human studies', held in conjunction with the ECNIS 4th Annual Meeting.

The workshop began with a brief update of progress in the integrating activities of WP1 given by Peter Farmer, University of Leicester. Next, the concerted efforts to implement harmonised biomonitoring across Europe were described by Ovnair Sepai, UK Health Protection Agency. This harmonisation will improve quantification of exposure of the general European population to existing and emerging pollutants and determination of reference values for exposure and will allow the EU to ascertain exposure across boundaries. Additionally, better data comparability will allow evaluation of policy actions aimed at reducing exposure to potentially hazardous environmental stressors at a European level.

Given that to be useful an individual biobank needs to be "considerably larger than can realistically be afforded", one essential requirement is to ensure that biobanks are networked, have harmonised designs and can provide an effective platform for future information pooling. Using the Public Population Program in Genomics (P3G) as an example, Paul Burton, University of Leicester and P3G, University of Montreal, described the on-going development of information resources and tools to facilitate harmonisation.

An illustration of the value and difficulties of comparing and pooling data from several studies was presented by Emanuela Taioli, State University of New York, who described an exploration of the relationship between vitamin levels, DNA adducts and smoking in healthy subjects. The results reinforce the need for a diet rich in vitamin components for the general population as well as smokers.

The design of a prospective cancer study in which both peripheral blood and normal and tumour tissue were collected for analysis of gene expression (the transcriptome) was described by Eiliv Lund, University of Tromsø. This design could be thought of as an example of 'systems epidemiology', with potential for an improved understanding of causality.

Finally, a survey of prospective studies of cancer in low- and middle-income countries by Paolo Boffetta, IARC, showed how they present a unique opportunity to investigate the effects of changes in lifestyle on risk of cancer. Because of specific patterns of exposure, the study of interactions between carcinogens in such countries could provide important information for cancer research, e.g. the pattern of interaction between HBV infection, tobacco smoking and alcohol drinking. A study of the aetiology of oesophageal squamous cell carcinoma in Central Asia, a high-risk area, was described in detail.

During a lively Round Table discussion, it was suggested that it would be valuable to update the inventory of ECNIS resources, including data and samples, for potential harmonisation with other networks. The value of funding studies in the long term or whether new ones should be established was considered from the point of view of both scientists and funding bodies. Other issues debated were the best use of stored samples and the kinds of samples that should be collected in future studies.

Jean Emeny
University of Leicester, UK

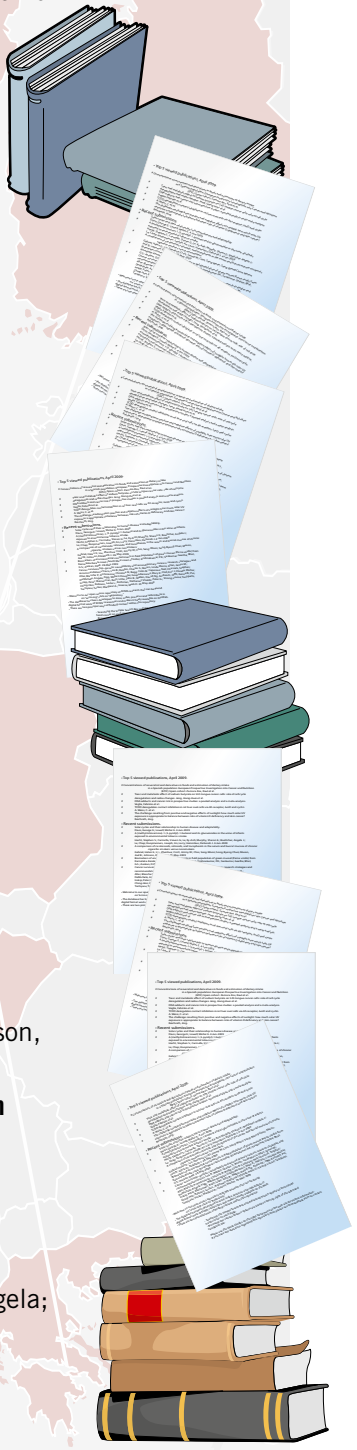
ECNIS Repository

- **Welcome to our open access repository of ECNIS research that can be found on "ecnis.org", click on "Repository"**
- **The database has been developed to store, index, preserve and redistribute in digital format work of ECNIS researchers and makes it freely available on the Web.**
- **There are two principal ways of finding content within this repository:**

  - ***Searching,*** the Simple Search Box and Advanced Search appear at the top left hand corner on each page.

  - ***Browsing,*** the various browse options are listed on the top right of the left-hand navigation bar.

  Please use the Quick Guides on the right hand menu at the web site for further information. If you have any questions regarding this repository then please use the Feedback form to contact the database administrator.



- **Top 5 viewed publications, April 2009:**

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. Zamora-Ros, Raul et al.

Toxic and metabolic effect of sodium butyrate on SAS tongue cancer cells: role of cell cycle deregulation and redox changes. Jeng, Jiiang-Huei et al.

DNA adducts and cancer risk in prospective studies: a pooled analysis and a meta-analysis. Veglia, Fabrizio et al.

TCDD deregulates contact inhibition in rat liver oval cells via Ah receptor, JunD and cyclin A. Weiss, C. et al.

The challenge resulting from positive and negative effects of sunlight: how much solar UV exposure is appropriate to balance between risks of vitamin D deficiency and skin cancer? Reichrath, Jörg.

- **Recent submissions:**

Solar cycles and their relationship to human disease and adaptability. Davis, George E.; Lowell, Walter E. 4-Jun-2009

4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides in the urine of infants exposed to environmental tobacco smoke. Hecht, Stephen S.; Carmella, Steven G.; Le, Ky-Anh; Murphy, Sharon E.; Boettcher, Angela J.; Le, Chap; Koopmeiners, Joseph; An, Larry; Hennrikus, Deborah J. 4-Jun-2009

A comparison of carotenoids, retinoids, and tocopherols in the serum and buccal mucosa of chronic cigarette smokers versus nonsmokers. Gabriel, Helen E.; Liu, Zhenhua; Crott, Jimmy W.; Choi, Sang-Woon; Song, Byeng Chun; Mason, Joel B.; Johnson, Elizabeth J. 28-May-2009

Biomarkers of environmental contaminants in field population of green mussel (Perna viridis) from Karnataka-Kerala coast (South West coast of India). Krishnakumar, P.K.; Sasikumar, Geetha; Bhat,G.S.; Asokan, D.P.K. 28-May-2009

Cancer survivorship--genetic susceptibility and second primary cancers: research strategies and recommendations. Travis, Lois B.; Rabkin, Charles S.; Brown, Linda Morris; Allan, James M.; Alter, Blanche P.; Ambrosone, Christine B.; Begg, Colin B.; Caporaso, Neil; Chanock, Stephen; DeMichele, Angela; Figg, William Douglas; Gospodarowicz, Mary K.; Hall, Eric J.; Hisada, Michie; Inskip, Peter; Kleinerman, Ruth; Little, John B.; Malkin, David; Ng, Andrea K.; Offit, Kenneth; Pui, Ching-Hon; Robison, Leslie L.; Rothman, Nathaniel; Shields, Peter G.; Strong, Louise; Taniguchi, Toshiyasu; Tucker, Margaret A.; Greene, Mark H. 25-May-2009

Workshop on the role of intake of cereal foods for the risk of cancer, Malmö, Sweden, April, 2009.

• Background

The workshop was organized by the ECNIS WP 9: "Mechanisms of modulation of cancer by dietary factors". Within ECNIS the role of the intake of food groups in relation to cancer risk has received only little attention and the present workshop was focused on the these links. Another link was made to the EU project Beta-Glucan focusing on the relation between oat products and blood lipid levels (coordinator Gunilla Önning). The aim was to bring together scientists for an interdisciplinary discussion on such aspects as epidemiological findings, the molecular mechanisms of action of compounds in cereals as well as public health perspectives. The meeting was also linked to the Nordic CoE SYSDIET. It was chaired by Gunilla Önning and Jakob Linseisen, and 40 persons from eight countries took part.

In her *Introduction on cereals and health*, ***Gunilla Önning*** /Lund, reviewed the beneficial health effects of cereals, especially of whole grain cereals. Clinical trials of cereal intake have shown changes in the metabolism of lipids and glucose, inflammation and other biomarkers. In the WCR Fund/AICR monograph an increased consumption of unprocessed cereals rich in dietary fiber was proposed to decrease the risk of cancer.

The speakers were from left to right Rikard Öste, Kaisa Poutanen, Jakob Linseisen (also co-chair), Rikke Egeberg, Leif Holmgren, Theo de Kok, Emily Sonestedt, Martine Laville, Gunilla Önning (also chair).

• Epidemiological studies

Jakob Linseisen, Heidelberg/Munich, *Cereals, dietary fiber and cancer risk* assessed the epidemiological evidence. He stated that there is a moderately large amount of data on the possible association between dietary fiber and the risk for colorectal cancer; however, the results have varied and no firm conclusion can be drawn. Studies focusing on specific types of cereals are hardly available. Applying new and validated biomarkers for fiber intake may stimulate research in this field. However, intervention studies with increasing fiber intake in high-risk populations were largely negative so far.

Rikke Egeberg , Copenhagen, discussed her results on the *Intake of whole grain products and risk of breast, colorectal and prostate cancer in the Danish EPIC cohort.* A higher intake of whole grain products was associated with a lower risk of colon and rectal cancer, however only consistently in men. Furthermore, a higher intake of rye bread was associated with a lower risk of prostate cancer. However, a higher whole grain product intake did not seem to be associated with a lower risk of breast cancer.

Emily Sonestedt, Malmö Diet and Cancer study) presented her work on Plant foods, plasma enterolactone and breast cancer – with a focus on estrogen receptor status and genetic variation. She concluded that a high-fiber diet including high-fiber bread, fruit, berries and vegetables will likely reduce the risk of breast cancer in middle aged and older women. High enterolactone concentrations were associated with decreased breast cancer risk and the protective effect of a high-fiber diet might be due to its content of lignans. The reduced breast cancer risk with high enterolactone concentrations was only observed for ERα-positive and ERβ-negative tumors.

• Cereal food functionality and health effects

Kaisa Poutanen, Helsinki and Kuopio, gave a broad overview on *Physiological functionality and health effects of rye products.* Rye whole grain flour delivers in addition to fiber a wide range of phytochemicals, minerals and vitamins. Recently the knowledge about the bioavailability, bioconversions and metabolism of phenolic compounds in rye has increased substantially. Postprandially rye bread produces a lower insulin response, but not that of glucose, as compared to white wheat bread. A daily intake of rye bread for 8-12 weeks resulted in improved glucose homeostasis as measured by glucose tolerance tests, and also down-regulated the expression of genes linked to insulin signaling and apoptosis in adipose tissue. She concluded that using these results the health potential of rye foods can be further exploited.

Martine Laville, Lyon, reported on her studies of *The effect of beta-glucan on glucose metabolism.* The aim of the Beta-Glucan project was to find an efficient dietary fiber to be proposed in a lunch. The addition of 5g beta-glucan to 75 g of polenta delayed the absorption of 13C-glucose with additional changes in glucose kinetics. In a randomized trial done in Lund and Lyon a soup containing added beta-glucan decreased triglyceride levels but had no effect on cholesterol profile, HbA1c and fasting glucose in type 2 diabetic subjects with normal cholesterol levels.

In the next presentation by ***Leif Holmgren,*** Umeå, *Impact of energy and rye bran intake on incidence and mortality of prostate cancer: can tumor progression be inhibited by changes in life style?,* the metabolic and hormonal factors acting on tumor initiation and progression were reviewed. In animal models inhibited tumor growth and increases in tumor apoptotic index were associated with the intake of rye bran, soy protein and lignans. In a randomized intervention in prostate cancer an increased apoptotic index was observed in subjects given rye bran for 3 weeks. These examples indicate that changes in life style including diet may even reduce the burden for the health care system of complications of prostate cancer.

• Genomics markers

Theo de Kok, Maastricht, discussed the *Development and application of genomics markers in dietary intervention studies.* The evidence for a preventive action of food-born phytochemicals from mechanistic studies is becoming stronger, whereas some recent prospective studies are less convincing. This discrepancy may be overcome by introducing molecular markers in future epidemiological studies, taking modulation of molecular processes and genetic variability into account. The findings shown demonstrated that the use of genomics techniques may be a promising approach to establish mechanistic pathways.

• New cereal foods

In the lecture *Development of health-promoting liquid oat products*, ***Rickard Öste,*** Lund, reviewed the development of new cereal foods. 'Oat milk', used as a base for making different milk-free dairy products, is manufactured from pure oats and water without the use of emulsifiers and stabilizers. The nutritional quality of oat milk and related products such as yoghurts, creams and ice creams were discussed e.g. the serum-cholesterol-lowering property. Further efforts are made to find new oat varieties.

• Panel discussion

Many ideas were brought up regarding methodology and focus of future studies. Jakob Linseisen stressed the need to decrease misclassification in epidemiological studies. The possible common mechanisms in different diseases were briefly discussed, and maybe the use of nutritional genomics may resolve some questions in this field. Regarding public health aspects Elisabet Wirfält (Malmö) pointed out the increasing focus on meal patterns in addition to the intake of nutrients.

The abstracts are available on the ECNIS web site (ecnis.org)

Matilda Ulmius, Gunilla Önning

Circadian rhythms and chemical carcinogenesis: potential link

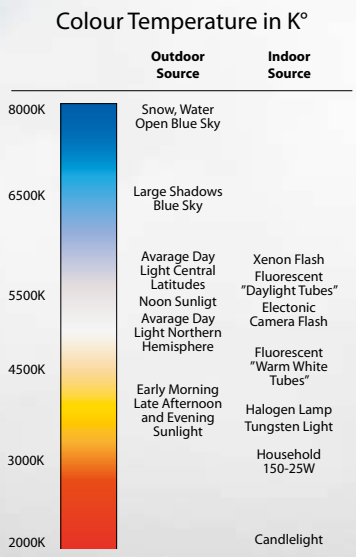
Recent information provided by a Workpackage 10 ("Mechanisms") ECNIS Workshop at the occasion of the European Environmental Mutagenesis Congress in Cavtat, Croatia

There is growing interest in the possibility that disruption of normal circadian rhythm may increase the risk of cancer development. Nightshift work may exhibit altered night time melatonin levels and reproductive hormone profiles that could increase the risk of hormone-related diseases, including breast cancer and colorectal cancer.

At the occasion of the European Environmental Mutagenesis Congress on September 21-25, 2008, in beautiful Cavtat, Croatia, the Jogu Mainz team of Workpackage 10 "Mechanisms" organized a Workshop on this timely topic. The organizers were Barbara Oesch, Cornelia Dietrich, Carsten Weiss and Franz Oesch, Barbara Oesch being the main organizer. The goal of the Workshop was to provide information about factors that can disrupt circadian rhythm and alter normal nocturnal production of melatonin and reproductive hormones of relevance to cancer etiology, especially breast cancer. Moreover, the proposed workshop should elucidate whether polymorphisms of the genes thought to regulate the human circadian clock are associated with the ability to adapt to night shift work. The workshop brought together experts on the field of the impact of circadian rhythms on experimental mutagenesis and carcinogenesis, the impact of disturbance of the normal human circadian rhythms by nightshift work, by dim indoor light in the daytime and by light sources of varying wavelengths and intensities during the nighttime.

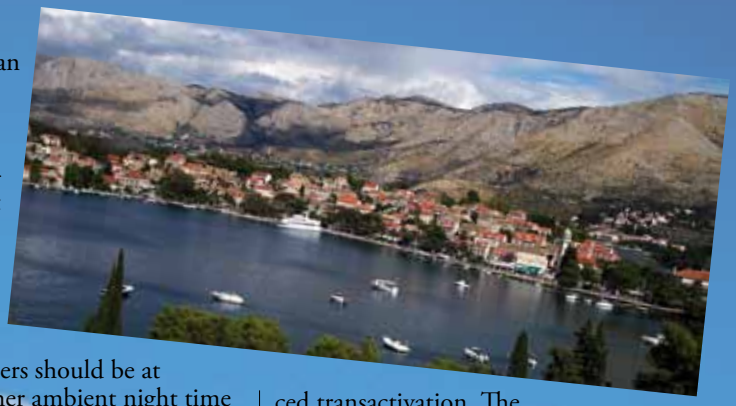
Gijsbertus van der Horst from the Department of Genetics, Erasmus University Rotterdam, in accordance with the interests of the participants in the European Environmental Mutagenesis Congress presented timely information on the impact of the circadian clock on in vitro genotoxicity risk assessment assays. His lecture being the first of the Workshop he started with a didactical overview on the current status of knowledge on the mechanisms of the control of circadian rhythms. Like most organisms, mammals are equipped with an internal clock that drives 24 hour rhythms in physiology and metabolism. Cells contain a molecular oscillator, made up of a set of clock genes that regulate their own expression as well as that of clock controlled output genes with an approximate 24-hour periodicity. The mammalian circadian system consists of a light-entrainable master clock in the suprachiasmatic nucleus (SCN) in the hypothalamus, and light-irresponsive oscillators in the cells of virtually all peripheral tissues. SCN-mediated synchronization of cellular oscillators is required to maintain a coherent output rhythm in peripheral tissues. Interestingly DNA damaging agents can synchronize the circadian clock, and as a consequence clock-controlled output genes.

Thus transcriptional changes upon exposure to genotoxic agents, are not limited to the DNA damage response. Energy metabolism (producing reactive radicals) and xenobiotic metabolism are prominently controlled by the circadian clock, implying that the sensitivity of tissues to geno- and cytotoxic agent induced toxicity may well depend on the phase of the circadian clock (chronotoxicity).



Francis Levi, from the University Paris Sud and from the Hospital Paul Brousse, Villejuif, presented recent data on the relevance of circadian disruption for cancer processes. The circadian timing system can be disrupted through alterations in environmental cycles (jet lag, light during night), clock gene mutations or toxic agents. Such disruption accelerates cancer processes, ranging from initiation to promotion and progression. Mechanisms involve genetic instability and decreased apoptosis. Epidemiological data support an increased risk of breast, colon and prostate cancers in workers exposed to iterative changes in occupational schedules. The experimental, mechanistic and epidemiological data led the WHO International Agency for Research on Cancer to warn that shift work that causes circadian disruption is a likely cause of cancer (risk level 2A). The rest-activity rhythm monitored in metastatic cancer patients showed a dichotomy index (one of the most robust rest-activity rhythm parameters) which indicated the relevance of the circadian timing system for treatment tolerability, tumor response and survival. Furthermore poor expression of the clock protein PER2 in colorectal cancer represents an independent predictor of survival, supporting the inhibitory role of the circadian clock on malignant progression

Richard Stevens from the University of Connecticut Health Center, Farmington, USA, presented recent results on breast cancer and circadian disruption from electric lighting. Risk of breast cancer is much higher in industrialized than in developing countries. The prime suspect, differences in diet, has not been supported by large cohort studies. But on the other hand it has become clear that light during the night of sufficient intensity can lower circulating melatonin levels, and melatonin has a clear effect on chemically induced mammary tumors in rodents, and on the growth of human breast cancer xenografts in nude rats. Predictions following these observations would be that night shift working women should be at higher risk for developing breast cancer, blind women and long sleepers should be at lower risk, and higher ambient night time light intensity should be associated with higher risk. Positive evidence is accumulating on each of these predictions.



Finally Marina Antoch from the Department of Molecular and Cellular Biology, Roswell Park Cancer Institute, Buffalo, USA reported on pharmacological modulators of the circadian clock as potential therapeutic drugs. A broad range of pathological conditions, such as cancer, cardiovascular disease, bronchial asthma and acute pain, display a strong circadian component in manifestation of the disease or in the response to treatment. Presently there are no drugs that modulate the molecular clock. Marina Antoch has developed two readout systems for monitoring the activity of the CLOCK/BMAL1 transcriptional complex. One of them is based on a cell line over expressing CLOCK, BMAL1 and the luciferase reporter under the control of the Period promoter. This cell line, which is characterized by a high level of luciferase expression, was used to screen for chemical compounds that repress CLOCK/BMAL1–induced transactivation. The second system is based on a cell line over expressing Per1-luciferase reporter and CLOCK and BMAL1 in combination with their transcriptional inhibitor, CRYPTOCHROME (CRY). This cell line, which has low levels of the luciferase signal, was used to screen for compounds that restore CRY1-repressed CLOCK/BMAL1-dependent transactivation. Both screens identified compounds that either up-regulate or down-regulate CLOCK/BMAL1-dependent transactivation. After experimental validation of these "primary hits" it is expected to obtain compounds that can be used as tools for studies of the CLOCK/BMAL1-dependent transcriptional activation and may be used as prototypes for developing clinical drugs to be used as modulators of stress response, metabolic and age-related disorders.

Barbara Oesch
University of Mainz, Germany

In the lively final discussion current gaps and needs for future research were defined. Thus in in vitro and in vivo mutagenicity/carcinogenicity experiments the time of initiation of the monitored process by addition of or treatment with the investigated compound should be considered or at least documented for future considerations. The same pertains to treatment of cancer patients. The basis for improved predictions on the modulations of mutagenic and carcinogenic processes by disturbance of the natural circadian rhythms need much further research.

Physical activity protects against colon and breast cancer

It is known that a high level of physical activity can help reduce the risk of a number of diseases, including cancer. Physical activity can be achieved through deliberate exercise, through the effort exerted at work or just by going about the business of housework. The degree to which such different kinds of activity can help reduce the risk of cancer at different sites has been examined in the context of the large pan-European EPIC (European Prospective Investigation into Cancer and Nutrition) project which involves approximately half a million subjects. EPIC researchers, including a number of ECNIS partners (Carlos A. Gonzales from the Catalan Institute of Oncology, Barcelona, Jakob Linseisen from the German Cancer Research Center, Heidelberg, and Paolo Vineis from Imperial College, London), have recently reported the results of their investigations of the impact of physical activity on cancer risk. While finding little convincing evidence for an effect on risks of lung, pancreatic or rectal cancer, they did observe that physical activity led to a lower risk of colon cancer, especially among lean persons, while household activity was associated with a significantly reduced risk of breast cancer in pre- and postmenopausal women. More information at "ecnis.org, click on the "Science portal".

Use of new technologies ('omics') in environmental epidemiology

The rapid development of "omic" technologies generally refers to the study of the complete set of biological molecules present in living organisms with high-throughput techniques. This emerging field is enabling investigators to broadly explore biologic responses to exogenous and endogenous exposures, evaluate potential modification of those responses by variants in essentially the entire genome, and define disease at the chromosomal, DNA, mRNA and protein levels. The advantage of utilizing these techniques is that they can be employed purely as discovery tools, with no prior knowledge required.

• Genomics

In 'genomics', the study of the complete genome is divided into three areas. 'Genotyping', which focuses on gene sequencing and at identifying constitutional gene variants (Single Nucleotide Polymorphisms, SNPs), is used to associate variations to phenotypes of interest, using direct association studies and indirect association studies in environmental medicine. 'Gene expression profiling' is used to determine which genes are differently expressed as a result of changes in environmental conditions; while 'epigenomics' looks at epigenetic regulation of gene expression. While transcriptional profiling is a powerful method, proteins are generally the active agents in cells that execute the biological functions encoded by genes, affecting cellular metabolism and regulation. 'Proteomics' refers to the study of the complete set of

proteins present in a sample collected at a specific point in time. An important focus here is the identification of the presence of post translational modifications, the identification of proteins interacting in protein-complexes, as well as the quantification of protein abundance, which is assumed to be related to its role in cell function.

• Metabolomics

'Metabolomics' involves measuring collections of small compounds in cells or biologic fluids, providing considerable biochemical detail in that the measured molecules include both metabolized products of environmental chemicals and endogenous metabolites. Although there are still limitations in the current techniques, it is merely a matter of time before these techniques produce new leads in the discovery of novel intermediate markers. To achieve an accurate estimate of the association between biomarkers and biological endpoints, reliable and valid measurements of exposure and covariates, as well as better understanding and consideration of methodological issues are imperative.
The impact of gene-environment studies on our understanding of the distribution of environmentally induced disease could have major implications for public health policy. To understand environmentally induced diseases, studies of the putative mechanisms with integrated use of 'omics' technologies, are essential to establishing the biologic plausibility of epidemiologic information. The use of 'omics' is likely to play a major role in translating epidemiologic science into public health practices.

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Upcoming meetings

10-28 August 2009,
Rotterdam, The Netherlands
ERASMUS SUMMER PROGRAMME 2009

23-28 August 2009,
Island of Spetses, Greece
Spetses Summer School on Nuclear Receptor Signalling: From Molecular Mechanisms to Integrative Physiology

27-28 August 2009,
Venice, Italy
Workshop: Genomics in Cancer Risk Assessment

20-24 September 2009,
Charleston, South Carolina, USA
22nd International Symposium on Polycyclic Aromatic Compounds (ISPAC 22)

21-23 September 2009,
Porto, Portugal
ECNIS International Workshop on Biomarkers and Cancer

12-16 October 2009,
Stockholm, Sweden
Course in Philosophy of Risk in Health Risk Assessment

15-16 April 2010,
Lodz, Poland
ECNIS Final Meeting

26-29 September 2010,
Guarujá, Brasil
International Conference on Nutrigenomics (INCON) and 10th International Conference on Mechanisms of Antimutagenesis and Anticarcinogenesis (10th ICMAA)

ECNIS

Environmental Cancer Risk, Nutrition and Individual Susceptibility

Being a **Network of Excellence** within the EU 6th Framework Programme, ECNIS has as its overall objective the integration of European environmental carcinogenesis research in order to achieve a reduction in the cancer burden. To reach this objective, ECNIS activities are 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,

– **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, and

– **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.)

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22. International Agency for Research on Cancer, Lyon, France
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