

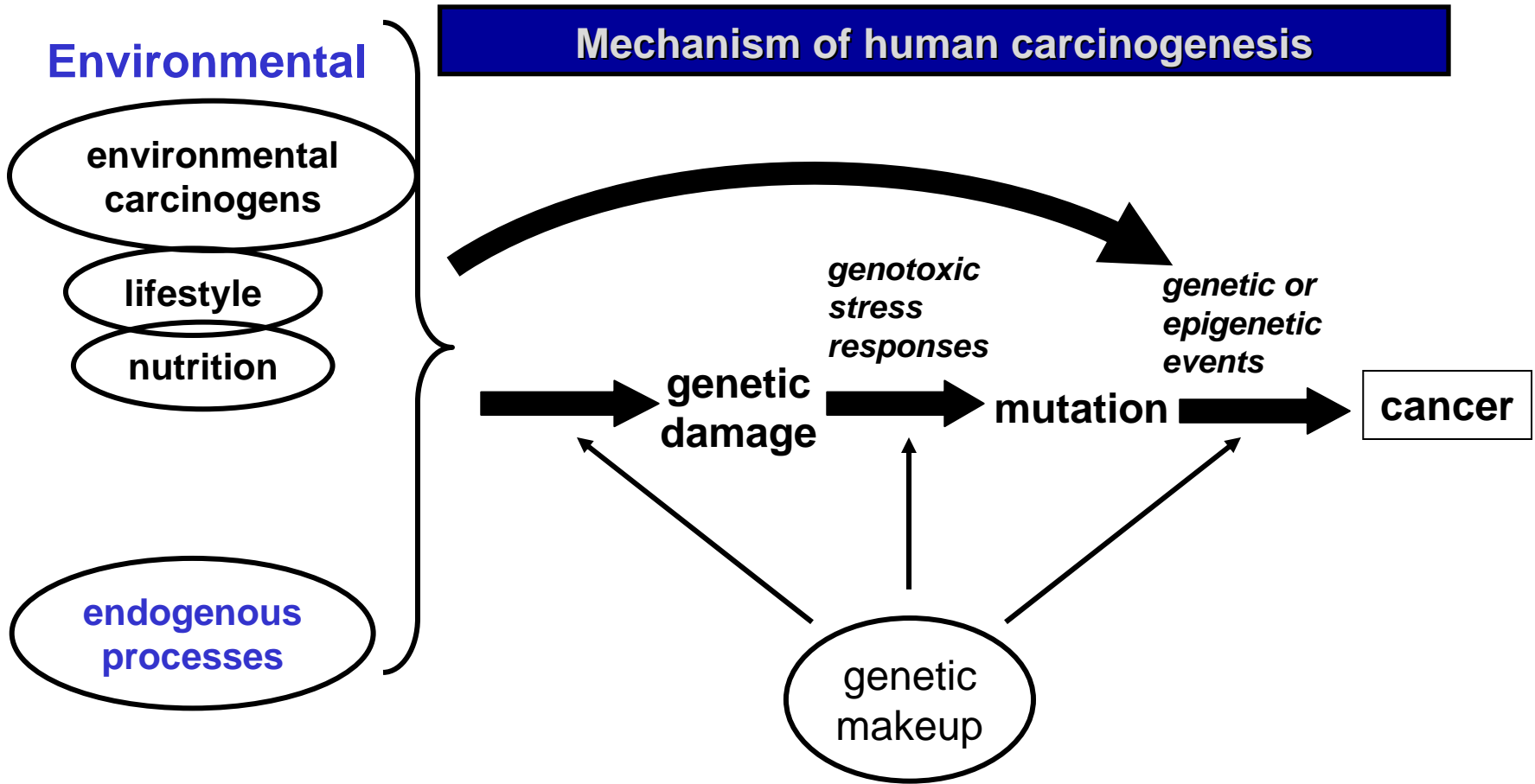


**ECNIS (Environmental Cancer Risks, Nutrition and Individual Susceptibility) Network of Excellence contribution to identifying factors and mechanisms by which dietary and lifestyle patterns modify cancer risks**

**Konrad Rydzyński - Coordinator  
Nofer Institute of Occupational Medicine  
Łódź, Poland**

## Cancer – major public health problem in Europe

- With an estimated 2.9 million new cases and 1.7 millions of deaths each year, cancer remains a major public health problem in Europe.
- Epidemiological studies show that the environment, including nutrition, is a major determinant of cancer risk in the general population.

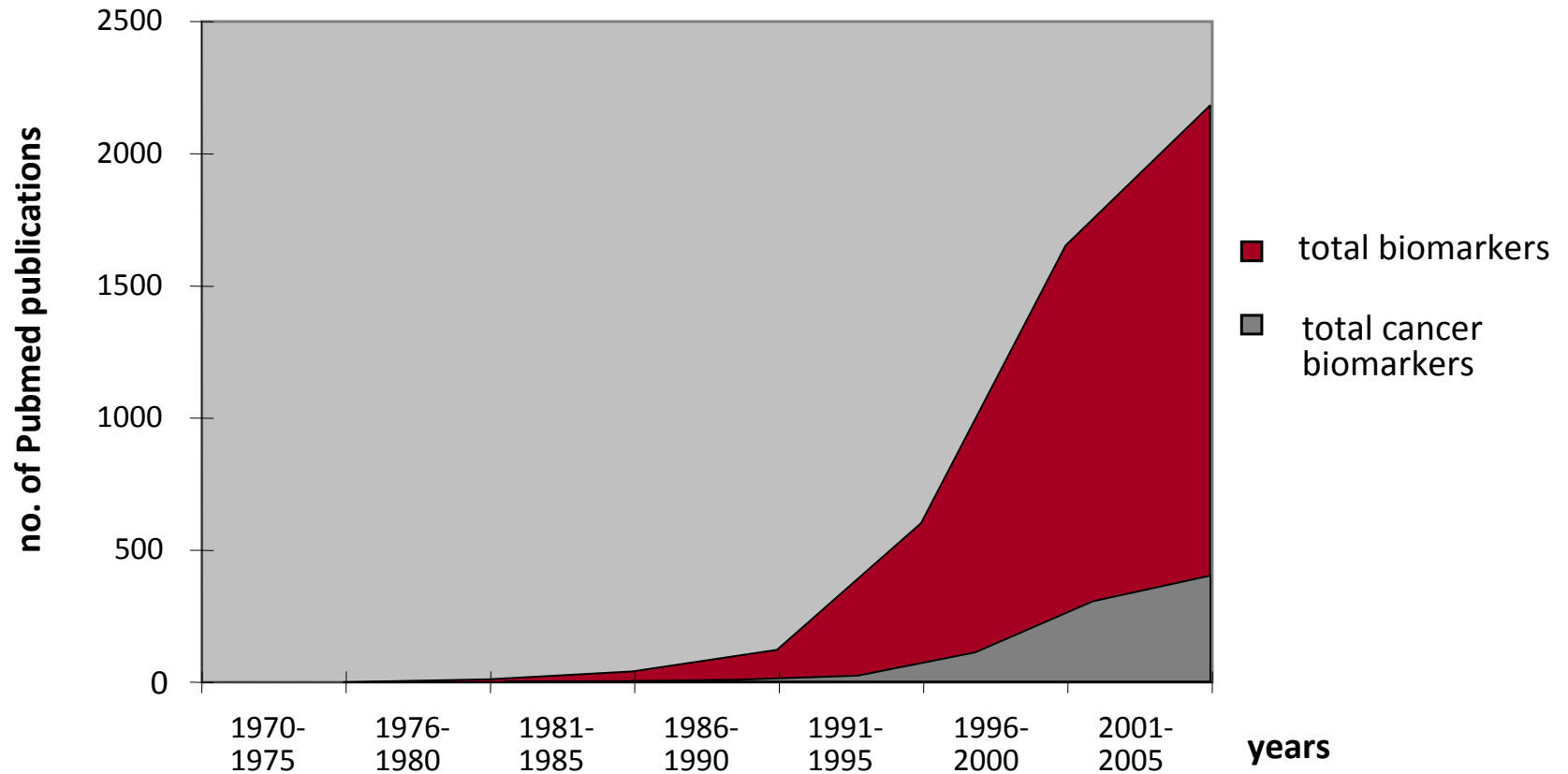


Environmental (non-endogenous) factors: 70-90% of cancer risk

## How to study environmental carcinogenesis?

- Human exposure to environmental carcinogens usually involves low levels of relatively weak carcinogens, frequently found as complex mixtures, and occurs over a prolonged period of time, making exposure assessments a major problem.
- There is a rapid increase worldwide in the use of biomarkers to monitor exposure and to determine the resultant biological effects, together with studies of human susceptibility factors.
- Also rapidly increasing worldwide is the study of food components which may modulate the effects of environmental carcinogens, and biomarkers are playing a major role in assessing the effectiveness of chemoprevention measures using these food constituents.

## PUBMED publications on biomarkers / molecular epidemiology & cancer

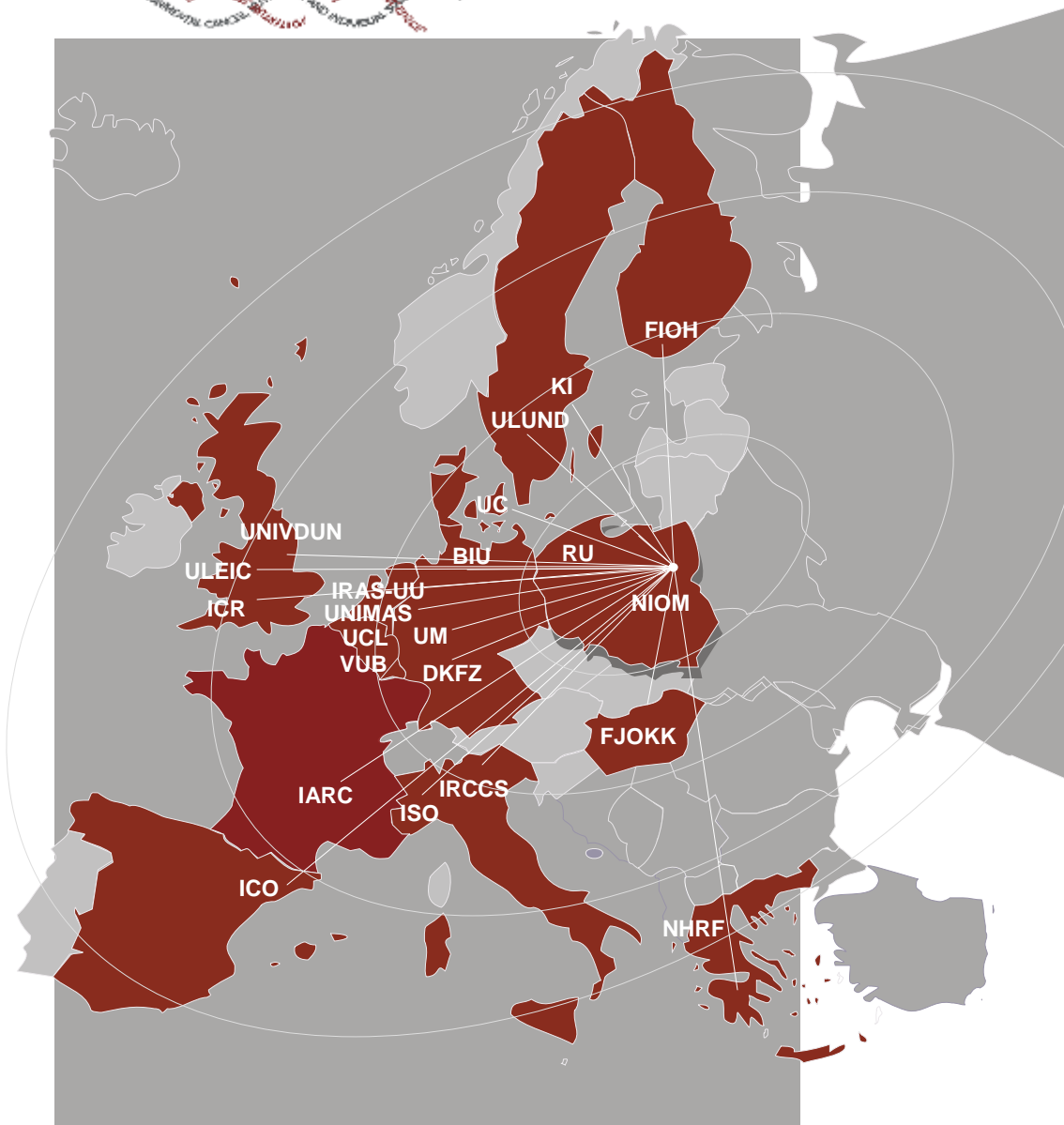


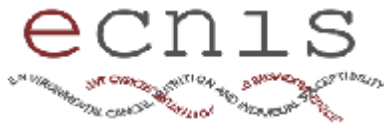
ECNIS & NewGeneris: Fifth Ministerial Conference on Environment and Health, Parma 2010

ECNIS includes 25 partners (3 SMEs) from 13 countries and 4 collaborating centers.



- NIOM** (Poland)
- VUB** (Belgium)
- UCL** (Belgium)
- UC** (Denmark)
- FIOH** (Finland)
- DKFZ** (Germany)
- UM** (Germany)
- BIU** (Germany)
- NHRF** (Greece)
- FJOKK** (Hungary)
- ISI** (Italy)
- IRCCS** (Italy)
- Collegium Med.** (Poland)
- ICO** (Spain)
- KI** (Sweden)
- ULUND** (Sweden)
- UNIMAS** (The Netherlands)
- IRAS-UU** (The Netherlands)
- ULEIC** (UK)
- ICR** (UK)
- UNIVDUN** (UK)
- IARC** (France)
- Imperial College** (UK)





The vision of ECNIS was the creation of a dynamic research network which would work to decrease cancer incidence by:

- identify chemicals or other factors in the environment and food which may cause cancer,
- elucidate the mechanisms by which dietary and lifestyle patterns modify cancer risk,
- develop and validate novel biomarkers of exposure, effect and susceptibility for environmental and occupational cancer risk assessment
- discover genetic (hereditary) factors which make individuals more or less susceptible to cancer,
- formulate improved approaches to the risk assessment of carcinogens,
- integrate joint training and mobility programs in area of environmental cancer molecular epidemiology

The initiatives undertaken within ECNIS was concentrated on integration to built “ECNIS added values”

- Molecular Epidemiology and Cancer (MEC) database
- Core facilities for: standardized chemicals, antibodies and analytical methodology
  - European Standards Committee on Urinary DNA Lesion Analysis (ESCUA)
  - European Comet Assay Validation Group (ECVAG)
- ECNIS Repository
- Training and educational program



## The ECNIS knowledge database on Molecular Epidemiology and Cancer (MEC)

Starting point for a re-evaluation of molecular epidemiology studies and for pooling ECNIS data with the results of other studies

MEC is currently accessible within ECNIS through its website [www.ecnis.org](http://www.ecnis.org)

- 19 molecular epidemiology datasets that represent epidemiological studies based on different types of biomarkers
- total 10,000 subjects, including cancer patients and healthy subjects with various biomarkers

## Current contents of MEC

- **EPISAT** (Epidemiologic Information Storage and Analysis Tool) that allows researchers to store, maintain and retrieve epidemiologic information and databases, analyze the content of the databases acquired, allow meta- and pooled-analyses
- **Examples of Studies:** pooled analysis of studies on DNA adducts and dietary vitamins; pooled analysis on lung cancer and bulky adduct levels

# Core facility

**virtual laboratory” conducting very specific studies in different location, but with fully integrated approach**

The current core facilities of ECNIS are for standards and antibodies applicable for studying exposure to **carcinogens** like: polycyclic aromatic hydrocarbons - **PAHs**’ (fruits, vegetables, grilled food, tobacco smoke), heterocyclic aromatic amines – **HCAs** (fried , grilled meat and fish), **N-nitroso compounds** (tobacco smoke, fruits,vegetables) **alcohol**

- **3'-phosphates of dA and dG adducts of PAH diol epoxides needed for application in <sup>32</sup>P-postlabelling studies**

*(±)-anti-BPDE-N2-dG-3'-monophosphate (mixture of diastereomers)*

*(±)-anti-B[c]PhDE-N6-dA-3'-monophosphate (mixture of diastereomers)*

- **2'-deoxyribonucleotides and 2'-deoxyribonucleosides required for characterisation of antibodies**

*N<sup>2</sup>-ethyl-2'-dG-3'-monophosphate*

*C8-PhIP-dG-3'-monophosphate*

*O<sup>6</sup>-Carboxymethyl-dG-3'-monophosphate*

*1,N<sup>6</sup>-Etheno-dA*

# European Standards Committee on Urinary DNA Lesion Analysis (*ESCULA*)

- International cross-validation exercise of the measurement of urinary 8-oxodG (biomarker of oxidative DNA damage).
- comprises **31 laboratories (including 4 SME)**, from **16 countries globally**
- Under ESCULA a urine biobank has been set up and works are going on to determine reference ranges for healthy and diseased people
- On-going studies and planned activities include investigations on the topics related to determining the DNA repair source(s) of urinary 8-oxodG;

## ***ECVAG - European Comet Assay Validation Group***

Assessment and reduction of comet assay variation in relation to  
**DNA damage and repair**

- comprises **12 laboratories from 9 different EU countries**
- **Ultimate goal:** development of standardized method for the measurement of DNA damage and repair applicable to high throughput molecular epidemiology studies on cancer
- to reach consensus on the likely level of DNA damage in lymphocytes and on procedures and values of the DNA repair incision assay,
- development of *bona fide internal standard* materials to minimise variability in the measures of comet assay endpoints.
- to determine whether or not there are regional differences in the level of oxidatively damaged DNA in lymphocytes in Europe




# ECNIS subject-specific repository

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. **Contains 400+ records**

Search:

Go



---

Advanced Search

**Browse by**

- Communities & collections
- Title
- Author
- Date issued
- Date submitted
- Subject
- Subject (MeSH)
- Researchers

**Listed communities**

- ECNIS - Environmental Cancer Risk, Nutrition and Individual Susceptibility
- ECNIS annotated biomarkers bibliographic database - test version

Home :: My ECNIS :: Submit :: Help! :: Feedback :: Register/Login

ECNIS Repository > Home

## Welcome...

Welcome to our open access repository of ECNIS research!

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 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** (February '09):

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)

Higher urine 1-hydroxy pyrene glucuronide (1-OHPG) is associated with tobacco smoke exposure and drinking maté in healthy subjects from Rio Grande do Sul, Brazil. (Fagundes, Renato B. et al)


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

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

Metabolic activation of carcinogenic aristolochic acid, a risk factor for Balkan endemic nephropathy. (Stiborova, Marie et al)

**Latest submissions**

- Prospective study of mesothelioma mortality in Turkish villages with exposure to fibrous zeolite.  
*Baris, Y. Izzettin; Grandjean, Philippe*  
13-Mar-2009
- Cytogenetic analysis of Pakistani individuals occupationally exposed to pesticides in a pesticide production industry.  
*Bhatti, Javed A.; Khan, Q. M.; Haq, M. A.; Khalid, A. M.; Nasim, A.*  
13-Mar-2009
- Rapid analysis of XRCC1 polymorphisms using real-time polymerase chain reaction.  
*Schneider, Joachim; Classen, Vera; Shilin, Monika; Helmig, Siegfried*



**Quick guides**

- Getting started
- Using search
- Browsing
- Submitting content
- Editing your details

[More help](#)

**RSS feeds**

[RSS 1.0](#) [RSS 2.0](#)

# Collaborative research projects

3 calls - 24 granted projects

## Priorities:

- 1. Interlaboratory biomarkers validation studies*
- 2. Development & validation of phenotypic biomarkers*
- 3. Development of novel nutritional biomarkers*
- 4. Studies on cancer induction mechanism for better prediction and prevention*
- 5. Integration of biomarkers into risk assessment*

## ECNIS Type B Projects

### 1<sup>st</sup> call:

- Validation of NNOC-related DNA adducts and assessment of their determinants in the general population; *P. Georgiadis, C.A. González, J. Linseisen, D. Segerback, P. Farmer, P. Boffetta, T. de Kok*
- Towards consensus for the measurement of urinary 8-oxo-7,8-dihydro-2'deoxyguanosine; *R. Olinski, M.S. Cooke, S. Loft*
- Use of lymphoblastoid cell lines for the identification of at risk genotypes: validation of cell lines for the dna repair response; *G. Matullo, S. Loft*
- Development of methods for determination of tobacco-smoke related collagen adducts in human lung – possible biomarkers of long-term exposure; *B. Jönsson, B. Schoket*
- Molecular dissection and potential cross-talk of the biological and genetic pathways affected by benzo[a]pyren (BaP) and dioxin (TCDD); *F. Oesch, S. Kyrtopoulos, J. van Delft, D. Segerbäck, J. Hayes, M. Kirsch-Volders, A. Seidel*
- Induction of oxidative stress by polycyclic aromatic hydrocarbons and its modulation by food components; *S.A. Kyrtopoulos, M.N. Alexis, M. Botsivali, V. Papadimitriou, T. Sotiroudis, V.L. Souliotis, J. Nair*
- Short-term effects of selenium on global gene expression in humans using selenium-rich milk and different selenium supplements; *B. Åkesson, L. Dragsted*
- Genetic and epigenetic alterations in plasma DNA of healthy and cancers subjects as biomarkers of exposure or tumorigenesis; *P. Hainaut, Z. Herceg, P. Vineis*
- A mendelian randomization study of cruciferous vegetables and lung cancer within the EPIC cohort study; *P. Brennan, P. Vineis, J. Linseisen*
- Is PPAR $\delta$  the “fat sensor” that mediates the promotion of intestinal cancer by high fat diets?; *C. Palmer, J. Rafter, S. Pettersson*

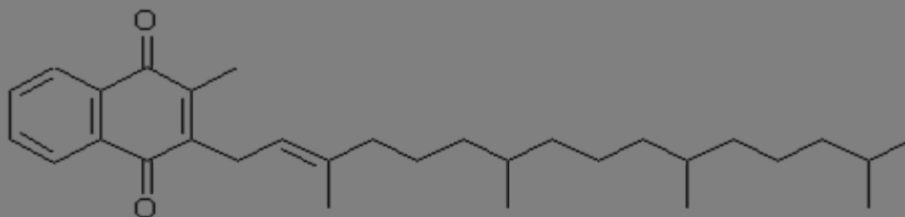
## 2<sup>nd</sup> call:

- Biomarker-based assessment of alcohol-related cancer risk; *P. Boffetta, R. Vermeulen, A. Hirvonen, B. Dumez*
- Early changes in immunological markers in Non-Hodgkin's Lymphomas; Development and validation of multi-analyte platforms; *R. Vermeulen, P. Vineis, S. Johnston, J. Linseisen, A. Nieters, C. Schroder*
- Integration of biomarkers in the estimate of cancers attributable to environmental and dietary factors in Europe; *P. Boffetta, R. Vermeulen, J. Linseisen, P. Vineis*
- Method development and validation of acetaldehyde induced DNA damage as a biomarker of alcohol intake; *J. Nair, D. Segerback, P. Farmer*
- Improving the throughput and efficiency of the 32P-postlabelling assay (ITEPA); *D. Phillips, L. Moller, B. Schocket, F-J van Schooten, J. Nair*
- Assessment and reduction of comet assay variation in relation to DNA damage and DNA repair phenotype; *P. Moller, L. Moller, R. Godshalk, G. Jones*
- Contribution of diet, cell turnover and DNA repair to production of urinary DNA damage products: validation of biomarkers of DNA damage and repair; *P. Farmer, R. Oliński, J. Nair, D. Phillips*
- Development and validation of phenotypical nucleotide excision DNA repair (NER) assays for use in molecular epidemiology; *M. Kirsch-Volders, FJ van Schooten, G. Matullo, S. Kyrtopoulos, A. Collins*
- Assessment of general population exposure to PAHs in northern Iran, a high risk area for esophageal cancer; *F-J van Schooten, A. Seidel, D. Phillips, P. Boffetta*

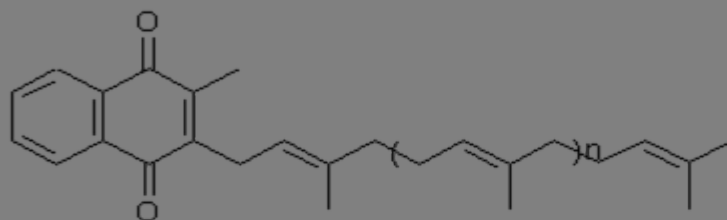
### 3<sup>rd</sup> call:

- European Standards Committee on Urinary DNA Lesion Analysis (ESCULA); *M. Cooke, R. Oliński, S. Loft*
- Use of new transgenic mouse models to study the metabolism of environmental and dietary carcinogens; *D. Phillips, V. Arlt, C. Henderson, R. Singh, H. Schmeiser*
- Assessment and reduction of comet assay variation in relation to DNA damage; *P. Moller, L. Moller, R. Godschalk, G.D.D. Jones*
- Preliminary assessment of general population exposure to mycotoxins in northern Iran, a high risk area for esophageal cancer; *P. Boffetta, P.C. Turner, Y.Y. Gong*
- Validation of N2-ethylidenedeoxyguanosine as a biomarker of alcohol intake; *D. Segerback, P. Farmer, J. Gromadzińska*

# Vitamin K (Blood coagulation, bone metabolism, cancer prevention?)



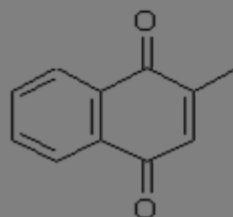
**Phylloquinone (Vitamin K<sub>1</sub>)**



**Menaquinone (Vitamin K<sub>2</sub>, MK-n)**



(bacterial origin)



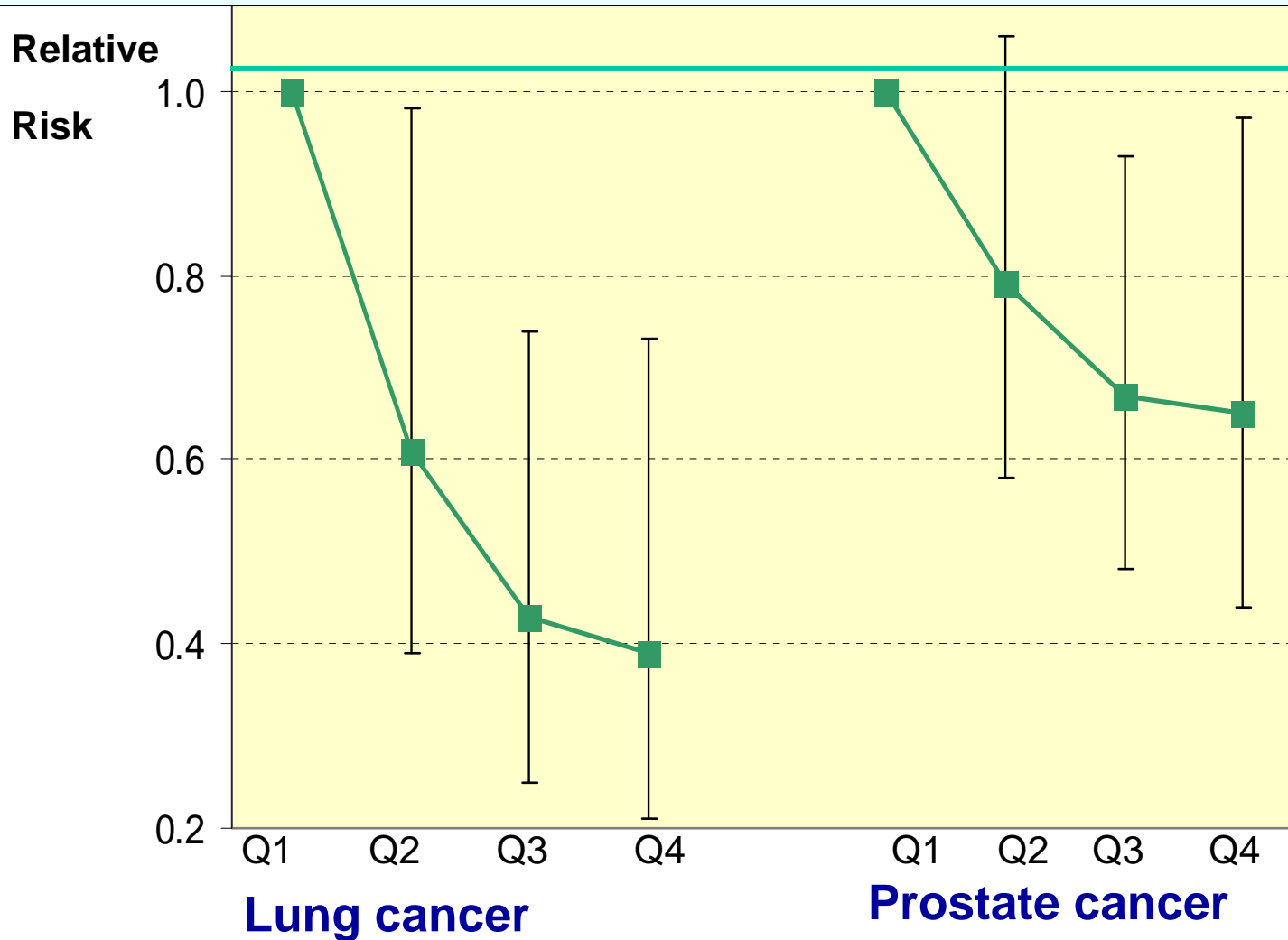
**Menadione (Vitamin K<sub>3</sub>)**

## EPIC-Heidelberg, a prospective cohort study

- **25 540 study participants**  
(men 40-65 years, women 35-65 years old at recruitment)
- **Recruitment: 1994-1998**
- **Assessment instruments:**
  - Lifestyle questionnaire
  - Personal interview: SES, health status, medication, etc.
  - Food frequency questionnaire
  - Anthropometric measurements
  - Blood samples
- **Follow-up (1997-2005):**
  - Active, by questionnaires
  - Medical validation of self-reported diseases



# Menaquinone intake, lung cancer, prostate cancer incidence



((Fully adjusted models; Nimptsch, Rohrmann, Linseisen, Am J Clin Nutr 2008))

## Conclusions

- **Menaquinone intake is associated with a lower cancer mortality**
- **With respect to cancer incidence, significant associations exist only in men.**

**This result is mainly driven by the strong inverse associations of menaquinone intake and lung and prostate cancer**

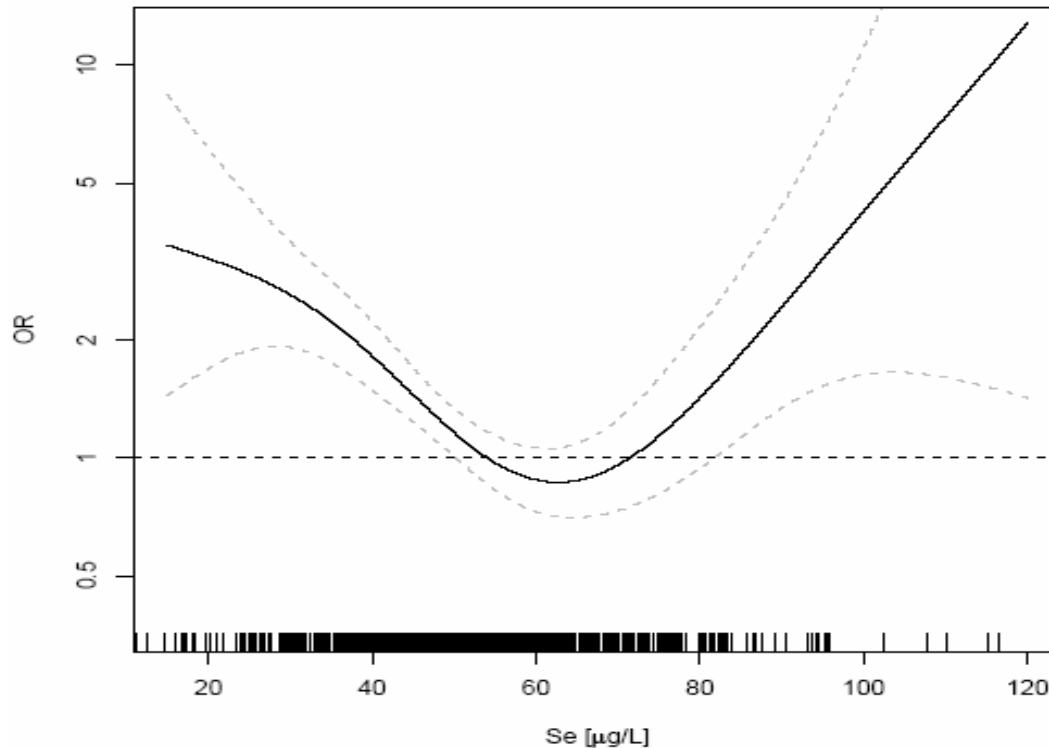
- **There is no association between menaquinone intake and the incidence of breast or colorectal cancer**
- **We found no effect of phylloquinone intake and cancer risk or mortality**

# Selenium may protect against cancer ...

- Numerous **animal studies** have shown chemopreventive activity of selenium in cancer development induced by chemical carcinogens, viruses or transplanted cancer cells
- Some **human ecological studies** have reported that low Se intake is associated with increased cancer mortality
- Some **human intervention studies** have shown decreased incidence of some cancers in Se supplemented individuals (liver, lung, prostate and colorectal cancers)



# Selenium: U-shaped dose response in lung cancer incidence

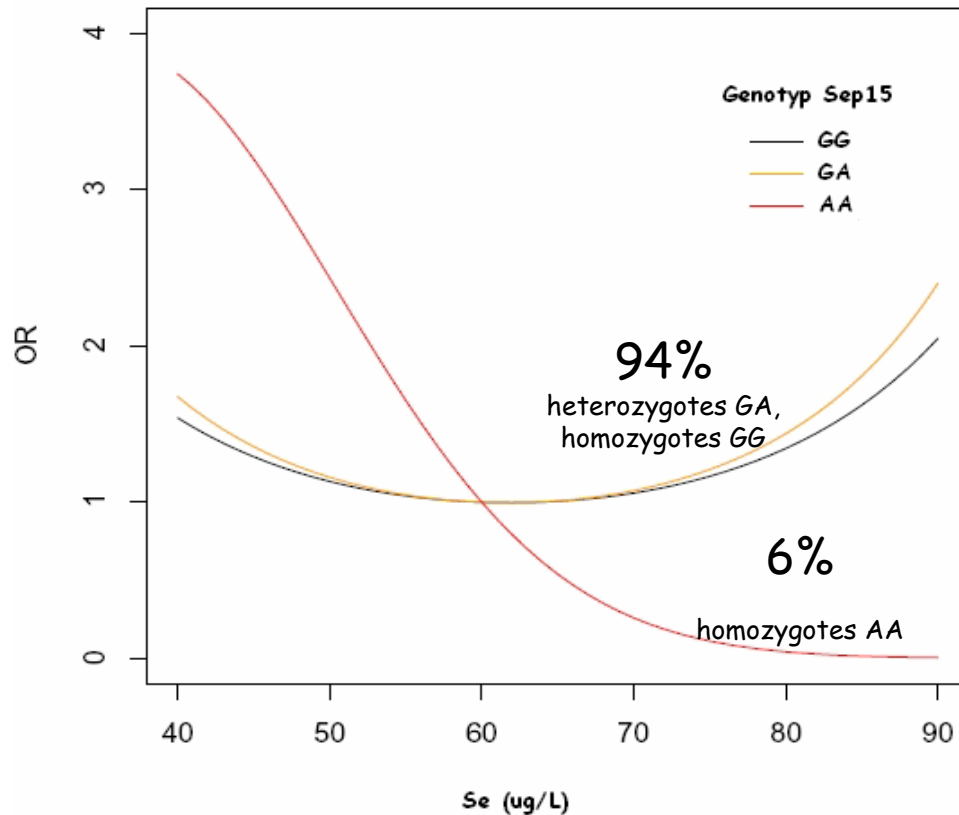


**Case control study**

**325 cases**

**287 controls**

Jabłonska et al., Eur J Nutr 47: 47-54, 2008

Ewa Jablonska  
Jolanta Gromadzinska  
Wojciech Sobala  
Edyta Reszka  
Wojciech Wasowicz**Lung cancer risk associated with selenium status is modified in smoking individuals by *Sep15* polymorphism**Joint effect of *Sep15* polymorphism and Se status on lung cancer risk

Test for trend differences:

AA vs GG  $p = 0,049$ AA vs GA  $p = 0,025$ 

Jablonska et al., Eur J Nutr 47: 47-54, 2008

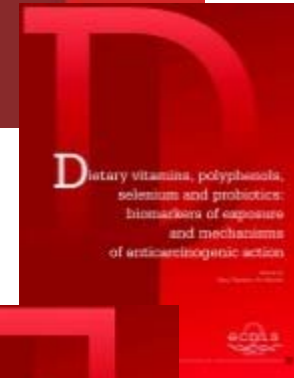
# Selenium may protect against cancer ... but only under certain circumstances

1. Se may act chemopreventive only in the individuals with **low** baseline Se status
2. Additional Se supplementation in those with **high** Se status may increase the risk of some cancers
3. Se supplementation should be based on individual's genotype profile



## 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 biomarker studies

- Quantative exposure assessment for epidemiologic research (*in preparation*)



# Ethics and data protection in human biomarker studies

*„In research on biological material of human origin emphasis is primarily on decisional autonomy and protection of individual's rights whilst the collective need to protect health as 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. .. A critical analysis shows that diverse implementations of EU regulations in various EU countries may hinder transnational research and bring about inequalities in the level of protection .„*

*In the volume current ethical and legal framework is outlined, important challenges analyzed, concrete situations described and solutions suggested.*



# October 2009: ECNIS joins CommNet

(Network of communication officers of food-related EU projects)

Network of 30 EU projects

**CommNet** What is CommNet?

- Network of communications managers in FP6 & FP 7 projects
- Focus on food science – quality, safety & health
- Started in 2005 CASCADE initiative – now 30 projects
- Unique network with expertise across communications and food science!

[www.commnet.eu](http://www.commnet.eu)

**ECNIS participated in events organised by CommNet**

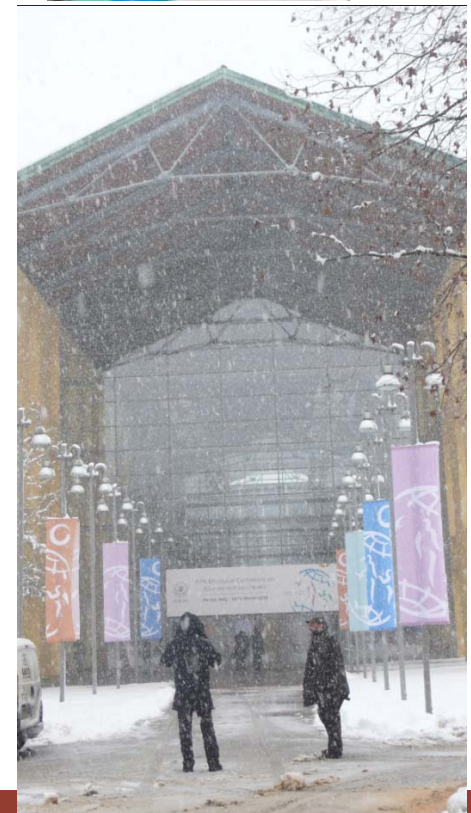
**Next CommNet meeting to be hosted by NHRF, Athens, October 2010**

**ECNIS at the Fifth WHO Ministerial Conference on environment and health: Protecting children's health in a changing environment  
Parma, Italy, 10-12 March 2010**



**Participation in the Workshop “How Human Biomonitoring supports Environment & Health policy – European feasibility study on mothers and children “**

**Dr. Maria Botsivali: Presentation on “Trends in biomarkers research and their potential for biomonitoring strategies: A NewGeneris and ECNIS overview”**





## **Planned stakeholders event:**

**Workshop for EC policymakers, co-organised by ECNIS, NewGeneris and EnviroGenomarkers, in collaboration with DG Research and the support of ECNIS project officer V. Lefevre**

**“Utility of biomarkers in the assessment of environmental and food cancer risk”**

**28 September 2010, Brussels**



## Contacts with other projects

1. NewGeneris & EnviroGenomarkers: co-organisation of stakeholder events
2. COPHES: participation in meetings (Parma)
3. PHIME: presentation of ECNIS at PHIME AGM 2010 after invitation
4. Participation in CommNet – network of 30 food-related EU projects



**Thank you for your attention**