

European Science Foundation  
Standing Committee for the European Medical Research Councils (EMRC)

**ESF EMRC EXPLORATORY WORKSHOP**

**Drinking Water Chlorination and  
Bladder Cancer**



**Athens, Greece, 2-4 November 2004**

**Convened by:  
Peter J. Goebell**



### **Convenor:**

**Peter J. Goebell**

[peter.goebell@uni-due.de](mailto:peter.goebell@uni-due.de)

Tel: +49 201 723-3210

Fax: +49 201 723-5931

University Clinic of Essen

Hufelandstrasse 55

45122 Essen

Germany

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### **Main Objectives of the Workshop:**

Drinking-water might contain harmful load for European citizens, since its chlorination generates trihalomethanes and other by-products (CBPs) with mutagenic and carcinogenic properties. Epidemiological studies have associated CBPs with an increased risk of bladder cancer; but limitation of most studies has been relatively crude methodology, in particular for exposure assessment.

Thus, only a multi-centric and comprehensive approach will have sufficient power to analyze the potential harmful disinfection-dependent and disinfection-independent water components in the light of established risk-factors for bladder cancer, such as smoking, exposure to aromatic amines or arsenic. Aim of this study is to determine the potential risk European citizens may be imposed to. The identification, quantification and assessment of risk factors in drinking-water will also improve current knowledge on measurement-techniques, including new methodological approaches and standards. Elucidation of dose-relationships will be available for implementation into decision-making processes.

This workshop took place partly within the frame and partly alongside the annual *International Bladder Cancer Network (IBCN)* meeting, thus taking advantage of its well established network, and enabling participants to gain access to the large variety of experience and excellence needed for such interdisciplinary investigations.

The aim of this Europe-wide investigation and the workshop was to strengthen the scientific, evidence-based knowledge to foster problem-solving strategies for the provision of safe, high-quality water for the European citizens and reduction of bladder cancer incidence of the population.

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**Note:** *The meeting is organised back to back with the 16<sup>th</sup> congress of the ESUR to lower costs.*



## **1. Assessment of the results**

The growing body of evidence from epidemiological studies, that our drinking water, as fundamental source of life and health in the broadest sense, might contain harmful load for the European citizen, lead the participants to evaluate strategies and explore possibilities to provide a basis for scientists and policy-makers with approaches to better understand the risks and their avoidance. The increasing numbers of allergies and cancers as environmentally related health issues are among the threats the EU as a consortium of modern industrialized countries is confronted with.

The results of the workshop lead into the identification of tasks to be addressed in future research and measures to be considered in future strategies to lower risk derived through the provision of chlorinated drinking water as indicated and outlined in the Outcome section below.

The proposed future work of the established consortium will help to create and maintain research synergies between relevant disciplines and methodologies with a view to assessing, limiting and controlling exposure to chemical, biological and physical environmental hazards, including occupational settings.

In addition, the consortium itself as a European network aims to support and be part of the networking at a European level. It will contribute towards providing the evidence base for the development of adequate environmental and health policy measures with the ultimate aim to decrease morbidity and mortality attributable to factors distributed to the European citizen through the provision of drinking water.

## **2. Contribution to the future direction of the field**

The water frame work of the European Commission, but even more pertinent, the drinking water quality directive [(80/778/EEC) and its revision (98/83/EC)] reflect the obligation for sound scientific approaches to identify and evaluate risk factors to which Europeans are inescapable exposed. The provision of clean water in reasonable quantities is clearly within the responsibility of public authorities and industry supporting municipal water suppliers to achieve this. The aspired formation and support of loco-regional task groups to ensure the implementation into decision-making processes will contribute to this aspect. In addition, the results from the proposed comprehensive analysis of the divers risk factors, related and unrelated to



the exposure and use of drinking-water aim to support the accomplishment of the before mentioned directives through the provision of new evidence-based data.

It is a recognized prerequisite that in order to successfully reduce environmental health effects refined and more effective methods for diagnosis and risk assessment, as well as innovation in the risk management processes are needed. There is need for the collection of adequate exposure data and its analyses to yield knowledge on dose-response relationships to provide the basis for better and effective prevention. The first steps towards a better and effective prevention will be provided with the results of the proposed study: the collection of individual matched probes and epidemiological data combined with the comprehensive analysis of risk factors. This is a unique undertaking, also because of its European dimension and its ability to be implemented in decision-making and problem-solving processes with Pan-European impact.

This consortium takes with its ambitious goals advantage of the cross-border environmental diversity of the EU, since it expects this to be crucial to better identify, quantify and evaluate the impact of the diverse factors and their combination. The delivered standardized methods for assessing exposure and effect within the scope of this proposal will also be an important tool to be used for the support of regulatory bodies in their efforts to achieve and maintain European water quality standards.

The inclusion of many different European centers in this large consortium will help to standardize incidence and prevalence of drinking-water and environment related bladder cancer among other diseases taking into account geographical and/or climatic variation, since the obtained measures will allow the comparison of data and interventions at E.U. level.

This proposal will study influencing factors through the inclusion of knowledge on the various methods of pretreatment of drinking water in the direct analysis of its compounds. The implementation of new technologies and innovative methodologies to investigate and compare the health effects of mixtures of pollutants, toxic substances as well as combined and low dose effects of agents will also be addressed.

In summary, this proposal aims to contribute to the Programme and its priorities by identification, quantification and assessment of the impact of risk factors Europeans are exposed to through drinking-water and thereby their environment. The gained knowledge on measurement, including new technological and methodological approaches, new standards and the elucidation of dose-relationships will be available



for the implementation into decision-making processes on a EU level. This will strengthen the scientific and evidence-based knowledge to foster problem-solving strategies to accomplish the European aim to provide clean and high-quality water to the European citizen.

### **3. Outcome**

In brief, the following areas and fields were identified and discussed and do also directly reflect outcomes from the various discussions at the mini-symposia/workshops for specific tasks. The summary below thus reflects the general discussion after the work-groups reported their vision to the attendees.

- the evaluation and determination of occupational and/or environmental sources of carcinogenic potential is a complex task and requires thoughtful planning. The multiplicity of effectors influencing the risk for cancer needs to be monitored with great care and more importantly with the most valid instrument of a comprehensive approach.
- The provision and updates on new analytic procedures throughout an evaluation are as essential as the access to the latest developments in the field. The formation of local expert-groups to work with the municipal water suppliers and decision-making authorities may be regarded as another key-element, since local/regional conditions may change over the time course. This may include new municipal politics or changes in the water supply.
- Due to the differing chemical and physico-chemical properties of the parameters to be analyzed, different approaches and equipment are required for their analysis: Volatile chlorination by-products will be quantified by head-space GC, halogenated anions by ion-chromatography and non-volatile disinfection by-products by LC/MS/MS. The latter methodology has not yet been used for the identification and quantification of the respective compounds and has first to be established. Total arsenic in water samples and in urine specimens of patients and controls will be quantified by atomic absorption spectroscopy; the renally eliminated organic arsenic metabolites will be specifically determined by LC/MS/MS. The hemoglobin adducts hydroxy- and cyanoethylvaline, used as long-term indicators of smoking, and the



hemoglobin adducts of carcinogenic aromatic amines may be quantified in a future research project by established GC/MS procedures.

- The establishment of local expert groups may provide data on disinfection procedures and collaborate with municipal water suppliers. They will also help with the execution of the established and validated guidelines for sample collection, storage and shipping in a future project. The person-to-person interviews may ensure the collection of high-quality epidemiological and clinical data.
- The establishment of a consortium and its consolidation as a working group like the participants of this workshop agreed to form, may serve as the basis for establishing a European bladder cancer network to be implemented and combined with existing cancer registries.
- The establishment of local expert groups which will provide data on disinfection procedures and collaborate with municipal water suppliers are essential. In addition, guidelines for sample collection, storage and shipping are mandatory.
- To evaluate the role of the complex environmental and occupational factors for the development of bladder cancer they have to be compared and associated with epidemiological data of equal valid quality and precision.
- The ability to ensure the safe transportation of water samples containing volatile compounds and of blood samples, respectively, to a central laboratory within 24 hours is a key-element to be ensured the high quality of the analyses.
- The determination of the following confounders may be crucial:
  - oxyhalides (chlorite, chlorate, bromate) and bromide trace level concentrations in samples of drinking water.
  - non-volatile halogenated disinfection by-products, volatile halogenated compounds need to be determined in water samples obtained from the individual water sources of patients and controls to find out, how geographical differences and disinfection procedures influence the formation and the distribution pattern of these compounds.
  - To improve the precision of the estimated risk of bladder cancer associated with ingested arsenic from drinking-water, the individually based measures of exposure as well as the matched water samples



need to be investigated. This may lead to data on individual exposure to arsenic in drinking-water and the establishment of a “arsenic burden score” for risk assessment in future epidemiological studies.

- The analytical results will reveal if statements on cigarette consumption made by the study participants to the interviewers are trustworthy. Thus, hemoglobin adducts as cyanoethylvaline and hydroxyethylvaline may be quantitatively determined to obtain an objective measure of the long-term smoking habits of study participants. From these statements, the contribution of smoking to bladder cancer incidence in the study population may be derived.
- Since exposure to specific aromatic amines, such as 4-aminobiphenyl, is a long established risk factor for developing bladder cancer, it may be of interest to investigate the oxidized metabolites of aromatic amines which form hemoglobin adducts. In non-smokers, levels of hemoglobin adducts of 4-aminobiphenyl above 4,9 ng/l are indicative of the slow acetylator phenotype. Taken this phenotype assignment into consideration, the hypothesis may be tested whether “slow acetylators” are at a higher risk of developing bladder cancer.

In summary, the workshop has also lead to the initiation of the assembly of a European consortium to apply for the framework of the European Commission. In specific, the Priority 5: Food Quality and Safety has in its 3rd Thematic call a Work Programme for the specific programme for research, technological development and demonstration: "Integrating and strengthening the European Research Area" a call under T5.4.8.6, which reads: Investigation of potential health impacts of long-term exposure to disinfection by-products in drinking water (STREP [specific targeted research project]).



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Here, the aim is to investigate potential human health risks (e.g., cancer, premature births, miscarriage, birth defects, reproductive effects) associated with long-term exposure to low levels of disinfectants and disinfectant by-products occurring in water for human consumption and use in the food industry. The studies should include quantitative assessments of risk associated with microbial contamination of drinking water versus chemical risk. The main outcome will be improved risk assessment/management. SMEs specialised in measurement of water contamination would be encouraged to take part.

The discussed first draft of a proposal on “chlorination by-products in drinking water” would fit into the topic. We are confident, that we could tailor the proposal to a successful submission to the EU for the upcoming funding period.





## 4. FINAL PROGRAMME

To provide a comprehensive overview of workshop schedule and sessions, both IBCN meeting and ESF workshop programmes are shown below. **IBCN sessions/events also attended by ESF participants are indicated in red, while ESF-only sessions are marked in green.** Common ESF-IBCN sessions of particular relevance to ESF workshop attendees are additionally highlighted in green.

### Tuesday, 02.11.2004

*Individual arrival*

**20:00 Reception / dinner for all**

### Wednesday, 03.11.2004

09:00	Welcome	<b>A. Giannopoulos</b> <i>Athens, Greece</i>
09:10	The "classic" introduction of the IBCN meeting	<b>H.B. Grossman</b> , <i>Houston, TX, USA</i>
<i>Session I: Achievements – ongoing activities- perspectives</i> Chairs: F. Waldman, B.J. Schmitz-Dräger		
09:30	The ISBC trial – what ´s next ?	<b>P.J. Goebell</b> <i>Essen, Germany</i>
09:45	Phases of marker development – Statistical implications	<b>S. Groshen</b> <i>Los Angeles, CA, USA</i>
10:00	IBCNS/SPOR	<b>C. Dinney</b> <i>Houston, TX, USA</i>
10:15	Array studies – To understand the <u>two</u> entities of bladder cancer	<b>R. Simon</b> <i>Basel, Switzerland</i>
10:30	Stockholm hypothesis – Introducing the <u>four</u> entities of bladder cancer	<b>G. Steineck</b> <i>Stockholm, Sweden</i>
<i>Session II: IBCN - putative Network partners</i> Chairs: R.J. Cote, J.A. Schalken		
10:50	Opportunities for international collaborations through the National Cancer Institute	<b>C. Dinney</b> <i>Houston, TX, USA</i>
11:05	Establishing and maintaining a collaborative research network – European Community funded research	<b>J. A. Schalken</b> <i>Nijmegen, The Netherlands</i>
11:20	Presentation of the European Science Foundation (ESF)	<b>C.E. Sekeris</b> <i>(Standing Committee for the European Medical Research Councils)</i>
11:35	The Spanish tissue arrayer – a multi-institutional approach	<b>P. Real</b> <i>Barcelona, Spain</i>
11:50	Introduction of a United Kingdom bladder bank proposal	<b>M. Zeegers</b> <i>Birmingham, England</i>
12:05	Discussion	<b>Chairs</b>



<b>12:20</b>	<b>Buffet Lunch</b> with the IBCN participants
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### Continued Sessions

Session III: IBCN – A need for formal structure ? <i>Chairs: H.B. Grossman, B.J. Schmitz-Dräger</i>					
<b>13:15</b>	<b>Introduction of a putative structure</b> <span style="float: right;"><i>B.J. Schmitz-Dräger</i> Fürth, Germany</span>				
	<b>Open discussion</b>				
<b>14:15</b>	<b>Summary</b> <span style="float: right;"><i>Chairs</i></span>				
<b>14:30</b> – <b>15:00</b>	<b>Coffee break and gathering of the groups</b>				
<b>15:00</b> – <b>18:30</b>	<b>Working groups (sessions in parallel)</b>				
	<table border="1" style="width: 100%; text-align: center;"> <tr> <td style="width: 25%;">Tissue arrayer IBC/NCI SPORE Prognostic markers</td> <td style="width: 25%;">Diagnostic markers</td> <td style="width: 25%;">Epidemiology / predictive uro-oncology</td> <td style="width: 25%; color: blue;">ESF workshop "Drinking water chlorination and bladder cancer"</td> </tr> </table>	Tissue arrayer IBC/NCI SPORE Prognostic markers	Diagnostic markers	Epidemiology / predictive uro-oncology	ESF workshop "Drinking water chlorination and bladder cancer"
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<i>ESF workshop</i> <i>"Drinking water chlorination and bladder cancer"</i>	
<b>15:00</b>	<b>Introduction to environmental risk factors for bladder cancer</b> <span style="float: right;"><i>P.J. Goebell</i> Essen, Germany</span>
<b>15:15</b>	<b>Factors influencing the formation of disinfection by-products (DBPs) in Mediterranean drinking water</b> <span style="float: right;"><i>E.G. Stephanou</i> Heraklion, Greece</span>
<b>15:45</b>	<b>Analytical procedures to detect risk factors for bladder cancer</b> <span style="float: right;"><i>A.W. Rettenmeier</i> Essen, Germany</span>
<b>16:15</b>	<b>Study design and conceptual approach of a proposal to the European Commission</b> <span style="float: right;"><i>A.W. Rettenmeier</i> Essen, Germany</span>
<b>16:45</b>	<b>Organization and Procurement (Core 1)</b>
<b>17:10</b>	<b>Analytic Procedures and Measurement (Core 2)</b>
<b>17:35</b>	<b>Biometry and Epidemiology (Core 3)</b>
<b>18:00</b>	<b>Discussion and outline for the upcoming tasks</b>
	<i>Plenum moderated</i>
<b>19:30</b>	<b>Dinner together with the IBCN participants</b>



## Thursday, 04.11.2004

08:00 – 12:00	<b>Working groups (sessions in parallel)</b>			
	Tissue arrayer IBCN/NCI SPORE Prognostic markers	Diagnostic markers	Epidemiology / predictive uro-oncology	<b>ESF workshop</b> "Drinking water chlorination and bladder cancer"



<i>ESF workshop</i> <i>"Drinking water chlorination and bladder cancer"</i>	
08:00	<b>Introduction</b> <b>Definition of Workpackages, Milestones and Deliverables</b> <b>Definition of local tasks prior and throughout the project</b>
08:20	<b>WP1:</b> <b>Network and Logistic basis</b>
08:40	<b>WP2:</b> <b>Oxyhalides (chlorite, chlorate, bromate) and bromide - trace levels in drinking-water</b>
09:00	<b>WP 3:</b> <b>Volatile halogenated compounds in drinking-water</b>
09:20	<b>WP 4:</b> <b>Non-volatile halogenated by-products in drinking-water – identification and quantification by LC/MS/MS</b>
09:40	<b>WP 5:</b> <b>Arsenic in drinking-water and biomonitoring of arsenic exposure in study participants</b>
10:00	<b>WP 6:</b> <b>Hydroxyethylvaline and cyanoethylvaline – long-term indicators of smoking</b>
10:20	<b>WP 7:</b> <b>Hemoglobin adducts of aromatic amines</b>
10:40	<b>WP 8:</b> <b>Data management, epidemiological and statistical analysis</b>
11:00	<b>Regulatory issues for the entire proposal – for national/local groups</b>
11:20	<b>Time frame – definition of next steps</b>
11:40	<b>Summary</b>
12:00	<b>Lunch</b> together with the IBCN participants



## Continued Sessions

<i>Presentation and reports from the working groups (IBCN/ESF)</i>		
<i>Chairs: H.B. Grossman, B.J. Schmitz-Dräger</i>		
<b>13:00</b>	<b>Tissue arrayer IBCN/NCI SPORE</b>	<b>C. Dinney</b> <i>Houston, TX, USA</i>
<b>13:20</b>	<b>Statistical needs &amp; GCP</b>	<b>S. Groshen</b> <i>Los Angeles, CA, USA</i>
<b>13:40</b>	<b>Prognostic markers</b>	<b>R.J. Cote</b> <i>Los Angeles, CA, USA</i>
<b>14:00</b>	<b>Diagnostic markers</b>	<b>H.B. Grossman,</b> <i>Houston, TX, USA</i>
<b>14:20</b>	<b>Epidemiology / predictive uro-oncology</b>	<b>N. Malats</b> <i>Barcelona, Spain</i>
<b>14:40</b>	<b>European Science Foundation "Drinking water chlorination and bladder cancer"</b>	<b>P.J. Goebell</b> <i>Essen, Germany</i>
<b>14:30</b> - <b>15:00</b>	<b>Summary, outline regarding the future of the IBCN, and assignments</b>	<i>Chairs</i>

## **16:00** End of Workshop

*16:00* Joining the official Opening of the 16<sup>th</sup> Congress of the ESUR



## 5. Participants of the workshop

**Albert W. Rettenmeier**  
Hygiene & Occupational Medicine  
University Clinic Essen  
Hufelandstrasse 55  
D-45122 Essen  
Germany  
e-mail: [a.w.rettmeier@uni-essen.de](mailto:a.w.rettmeier@uni-essen.de)

**Anna Sankila**  
Helsinki University Hospital  
Department of Urology  
Helsinki  
Finland  
e-mail: [Anna.Sankila@hus.fi](mailto:Anna.Sankila@hus.fi)

**Arndt Hartmann**  
University of Regensburg  
Department of Pathology  
Germany  
e-mail: [arndt.hartmann@klinik.uni-regensburg.de](mailto:arndt.hartmann@klinik.uni-regensburg.de)

**Ashish Kamat**  
MD Anderson Cancer Center  
Department of Epidemiology  
Houston  
USA  
e-mail: [akamat@mdanderson.org](mailto:akamat@mdanderson.org)

**Bernd J. Schmitz-Dräger**  
EuromedClinic  
Department of Urology  
Fürth  
Germany  
e-mail: [bsd@euromed.de](mailto:bsd@euromed.de)

**Colin Dinney**  
MD Anderson Cancer Center  
Department of Urology  
Houston, TX  
USA  
e-mail: [cdinney@mdanderson.org](mailto:cdinney@mdanderson.org)

**Euripides G. Stephanou**  
Environmental Chemical Processes  
Laboratory  
School of Sciences and Engineering  
University of Crete  
P.O. Box 1470  
71409 Iraklion  
Greece  
e-mail: [stephanou@chemistry.ucl.ac.uk](mailto:stephanou@chemistry.ucl.ac.uk)

**Feliksas Jankevicius**  
Department of Oncology  
Institute of Oncology  
Vilnius University  
Santariškiu 1,  
2021 Vilnius  
Lithuania

**Fred Waldman**  
UCSF, Cancer Center  
San Francisco  
USA  
e-mail: [waldman@cc.ucsf.edu](mailto:waldman@cc.ucsf.edu)

**Gunnar Steineck**  
Clinical Epidemiology  
Radiumhemmet Karolinska Institute  
S-171 76 Stockholm  
Sweden  
Email: [gunnar.steineck@onkpat.ki.se](mailto:gunnar.steineck@onkpat.ki.se)

**H. Barton Grossman**  
MD Anderson Cancer Center  
Department of Pathology  
Houston, TX  
USA  
e-mail: [hbgrossman@mdanderson.org](mailto:hbgrossman@mdanderson.org)

**Jack A. Schalken**  
University Medical Center  
Nijmegen  
The Netherlands  
e-mail: [J.Schalken@uro.umcn.nl](mailto:J.Schalken@uro.umcn.nl)

**Kristina Hotakainen**  
Department of Clinical Chemistry  
University Central Hospital  
Haartmaninkatu 2  
FIN-00290 Helsinki  
Finland

**Lars Dyrskjøt**  
Aarhus University Hospital  
Klinisk Biokemisk Afdeling  
SKS Skejby Sygehus  
Brendstrupgårdsvej  
8200 Århus N  
e-mail: [LARS@KI.AU.DK](mailto:LARS@KI.AU.DK)

**Maurice P.A. Zeegers**  
Department of Public Health and  
Epidemiology  
University of Birmingham  
Edgbaston  
B15 2TT  
United Kingdom  
e-mail: [M.P.Zeegers@bham.ac.uk](mailto:M.P.Zeegers@bham.ac.uk)



**Núria Malats**

Institut Municipal d'Investigacio  
Medica, IMIM  
Doctor Aiguader, 80  
Barcelona E-08003  
Spain  
e-mail: [Nmalats@imim.es](mailto:Nmalats@imim.es)

**Francisco (Paco) Real**

Institut Municipal d'Investigacio  
Medica, IMIM  
Doctor Aiguader, 80  
Barcelona E-08003  
Spain  
Email: [preal@imim.es](mailto:preal@imim.es)

**Peter J. Goebell**

Department of Urology  
University Clinic Essen  
Hufelandstrasse 55  
D-45122 Essen  
Germany  
e-mail: [peter.goebell@uni-essen.de](mailto:peter.goebell@uni-essen.de)

**Richard J. Cote**

USC Keck School of Medicine  
Department of Pathology  
Los Angeles  
USA  
e-mail: [Cote\\_R@norsur.hsc.usc.edu](mailto:Cote_R@norsur.hsc.usc.edu)

**Robert Stoehr**

Department of Urology  
University of Regensburg  
D-93042 Regensburg  
Germany

**Ronald Simon**

University of Basel  
Department of Pathology  
Basel  
Basel  
Switzerland  
e-mail: [Ronald.Simon@unibas.ch](mailto:Ronald.Simon@unibas.ch)

**Susan Groshen**

USC Keck School of Medicine  
Department of Preventive Medicine  
Los Angeles  
USA  
e-mail: [groshen\\_s@ccnt.hsc.usc.edu](mailto:groshen_s@ccnt.hsc.usc.edu)

**Tapani Liukonen**

Mikkeli Central Hospital  
Department of Urology  
Mikkeli  
Finland  
e-mail: [tapani.liukkonen@esshp.fi](mailto:tapani.liukkonen@esshp.fi)

**Tevita Aho**

Department of Oncology  
University of Cambridge  
Cambridge  
UK  
e-mail:

**Vladimir Bencko**

Institute of Hygiene & Epidemiology  
Charles University in Prague  
First Faculty of Medicine  
Studnickova 7  
CZ 128 00 Prague 2  
Czech Republic  
e-mail : [vbencko@lf1.cuni.cz](mailto:vbencko@lf1.cuni.cz)

**Xifeng F. Wu**

MD Anderson Cancer Center  
Department of Epidemiology  
Houston, TX  
USA  
e-mail: [xwu@mdanderson.org](mailto:xwu@mdanderson.org)

**ESF representative**

Prof. Constantin Sekeris  
National Hellenic Research Foundation  
Institute of Biological Research and  
Biotechnology  
48 Vassileos Constantinou Avenue  
116 35 Athens  
Greece  
Email: [minali@eie.gr](mailto:minali@eie.gr)



## 6. Statistical information on invited participants

### Type of affiliation of participants

University	18
Research institution	7
ESF representative / others	2

### Origin of participants

Germany	5
Finland	3
USA	7
Greece	2
Sweden	1
The Netherlands	1
Denmark	1
UK	2
Spain	2
Switzerland	1
Czech Republik	1

### Disciplines involved

Hygiene / Occupational Medicine	2
Urology	5
Pathology	4
Epidemiology	6
Molecular Biology	2
Environmental / Clinical Chemistry	2
Oncology	4
Biostatistics	2