EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

Exploratory Workshop Scheme

Standing Committee for the European Medical Research Councils (EMRC)

Standing Committee for Life, Earth and Environmental Sciences (LESC)

ESF Exploratory Workshop on

SETTING THE FUTURE FOR WATER AND HEALTH RESEARCH

Barcelona (Catalonia, Spain), May 21-22, 2012

Convened by:
Cristina M. Villanueva, Patrick Levallois
Manolonis Kogevinas and Mark Nieuwenhuijsen

SCIENTIFIC REPORT

Contents

1. Executive summary

The workshop was held at the Centre de Recerca en Epidemiologia Ambiental (CREAL) located in the Barcelona Biomedical Research Park (PRBB) over a day and half. It was organized by Cristina M Villanueva (CREAL, Barcelona, Spain), Patrick Levallois (Université Laval, Québec, Canada), Manolis Kogevinas (National School of Public Health, Athens, Greece) and Mark Nieuwenhuijsen (CREAL, Barcelona, Spain). The workshop was funded by the European Science Foundation (ESF) with additional financial support from the International Center for Scientific Debate (B-Debate). This agency contributed to cover part of the travel expenses of the participants from countries outside Europe.

The workshop brought together a total of 27 participants from 11 countries (Belgium, Canada, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, UK, and USA). The background of participants was multidisplinar with a mixture of the following specialties: chemistry, biology, toxicology, epidemiology, exposure science, civil engineering, regulator, water industry representative and independent consultant. The general atmosphere of the workshop was excellent. In particular, the interventions during the discussion were done in a constructive and positive way and the breaks and meals facilitated the interactions between participants. Also, as most of the participants were located at the same hotel, synergy was facilitated between them. The general organisation of the workshop helped to stimulate the emergence of new ideas and the collaboration between participants.

The main topic of the workshop was the improvement of epidemiologic research on the health impact of drinking water chemical contamination. The first morning was devoted to the review of current knowledge regarding the occurrence of chemical contaminants in drinking water (with a special focus on disinfection by-products, perfluorinated chemicals and pharmaceuticals and illicit drugs) and to the use of global indicators of water toxicity (with a focus on genotoxicity and endocrine disruption) in risk assessment and management. The afternoon was devoted to a review of the methodology and results of published epidemiologic studies on reproductive outcomes and cancer. Also a special lecture was given on improving exposure assessment to waterborne contaminants. The end of the first day focussed on the use of biomarkers in different epidemiologic studies on water contaminants. Discussion after each talk was very productive and helped to understand the limits of traditional epidemiologic approaches and the necessity to generate new studies more able to answer to the present challenges.

The next half-day was divided in two parts. First, one lecture was presented on the potential impact of climate change on water quality and two lectures were given on the procedures and requirements to derive water standards. The second part of the session was devoted to an open discussion on identifying priorities to fullfill knowledge gaps and improving methods of investigation. The participants agreed upon the following conclusions:

- Epidemiologic results based on solid method and good exposure assessment are crucial to evaluate the risk to human health associated with drinking water chemicals;
- New studies should not repeat previous studies with the same limitations and shortcomings but try to better answer current research questions with improved methods;
- Evaluation of water contaminants occurrence is important and it should not be limited to regulated contaminants, nor to public water distribution systems;
- Chemicals of concern that deserve further epidemiological research include some regulated chemicals (e.g. nitrate, metals, and disinfection by-products) and several emerging chemicals (e.g. perfluorinated compounds, UV filters, nanoparticles, etc.);

- Access to public and private sector (water industry) water contaminants monitoring and assessment data should be encouraged and facilitated;
- Collaboration between water utilities, regulators and researchers is important and should be promoted;
- Multidisciplinary approaches are necessary to improve research on the health effects of water contaminants;
- Epidemiological studies need large numbers of study subjects and measurements, which may constitute a challenge in the collaboration with other disciplines (chemistry, toxicology);
- Global indicators of water toxicity might be useful to evaluate the global effect of mixtures, and to identify "hot spots" for more in-depth analysis of specific contaminants, but they need further validation and high throughput development to be used in epidemiological studies
- Studies with contrast (wide range) of exposure are essential, thus it is therefore important to estimate water contamination of study participants locations before undertaking an epidemiological study;
- Better exposure assessment to water contaminants and to other sources of contaminants is crucial to derive valid dose-response curves, necessary for risk assessment and regulatory purposes
- Retrospective assessment has limits particularly for outcomes with long latency (cancer) and prospective evaluation (as in cohort studies) should be encouraged
- Mechanistic studies trying to identify pathways of toxicity might be necessary for some contaminants to guide design for further epidemiologic studies;
- Geographical Information systems and fate/transport modelling of chemicals in water sources could help to improve exposure assessment (external exposome);
- But individual data collection is essential and requires questionnaires and or biological samples;
- The new –omics markers seem promising to study modes of biological actions of certain exposures but there is a need to clarify how to use them and when.

A detailed list of water contaminants that would be useful to study was also set but further work should be done on that matter to prioritize those chemicals with some objective criteria. Participants also agreed that the most important problems currently are found with small utilities and private wells (especially where source water quality is poor and treatment cost-prohibitive) but no concrete solution was proposed to stimulate research in this area.

Finally, participants agreed to create a formal network of researchers and professionals on drinking water contaminants. The possibility to join existing organisations on water (e.g. the International Water Association which presently focuses on microbiological quality) should be evaluated. There is a need to continue exchange and collaboration between professionals and researchers involved in drinking water quality in Europe. Possible funds available for water research in Europe were discussed. Some of these funds seem also accessible for US or Canadian researchers.

Globally, this workshop fulfilled its objectives and demonstrated the need to conduct a multidisciplinary and high quality research on chemical contamination of water and public health. It was the first step to improve and prioritise epidemiologic research on this topic in Europe. It has also served to stimulate collaboration between European and North American researchers.

2. Scientific content of the event

The workshop aims to advance in the field of epidemiology and chemical water contaminants with the following specific objectives:

1) Prioritise water contaminants for further research and suggest a research agenda;
2) Evaluate current exposure assessment methodologies and make recommendations for improvement when possible;
3) Review and make recommendations on the use of biomarkers;
4) Find and evaluate databases (including data access) of water contaminants for future use in epidemiological studies;
5) Bring together researchers from different fields to foster European networks for further projects, including where possible stakeholders, such as the water supply industry and environmental regulators.

The workshop lasted one day and half. The first day focussed on evaluating exposure to drinking water chemical contaminants and their toxic effects with epidemiologic methods. During the second day, participants discussed new challenges and future direction to evaluate the effects of human exposure to those contaminants. The program included time allocated for discussion after each session. Also, at the end of the second day a discussion was held about research priorities and follow-up activities.

Monday, May 21st

The workshop was opened by Cristina Villanueva (CREAL, Barcelona, Spain), the leader of the project, who summarized the objectives and expectations of the workshop and gave some practical information to participants. Then, Carlos Segovia Perez (Instituto de Salud Carlos III, Madrid, Spain), acting as a representative of ESF, explained the different actions taken by its organization to stimulate research in Europe.

The first session was on the occurrence of chemical contaminants in drinking water and was moderated by Mark Nieuwenhuijsen (CREAL, Barcelona, Spain). He set the scene by presenting a summary of current violations of drinking water guidelines in Europe and then proposed a list of emerging contaminants that are commonly reported in source water. Michael Templeton (Imperial College, London, UK) presented an overview of the many disinfection by-products (DBPs) found in disinfected water. He put the emphasis on nitrogenous DBPs which are more toxic than non-N containing DBPs and are not presently regulated, as well as the need to conduct more targeted searches for new groups of DBPs that may better explain the observed health outcomes from epidemiologic studies. Gunilla Lindström (Örebro University, Örebro, Sweden) presented data on the presence of perfluorinated compounds in drinking water and food. In particular, she reported data from Catalonia on the presence of PFOA in source water and this compound was considered unusually high in Barcelona tap water. Ettore Zuccato (Mario Negri Institute for Pharmacological Research, Milan, Italy) presented results of its studies on the presence of pharmaceuticals and illicit drugs in surface and tap water in the area of Milan and Florence. These contaminants are excreted by patients and consumers and water treatment facilities do not remove them completely.

The second session was on global indicators of water toxicity and was moderated by Tamara Grummt (Federal Environmental Agency, Bad Elster, Germany). She started the session giving examples of how such global indicators are used in Germany to help water managers to produce drinking water of better quality. Michael Plewa (University of Illinois,

Urbana, USA) presented on the use of cytotoxicity and genotoxicity bioassays for ranking toxicity of different DBPs. He developed thereafter his study on the mechanism of genotoxic effect of haloacetic acids (HAA) trough the modulation of intracellular calcium by the inhibition of the metabolite enzyme glyceraldehyde-3- phosphate deshydrogenase (GAPDH). Minne Heringa (KWR Water Research Institute, Nieuwegein, Netherlands) presented the use of different genotoxicity tests for drinking water management. She emphasised that currently the best test battery is the combination of Ames (fluctuation) test with the Comet assay or micronuclei assay. With these bioassays, potentially harmful compounds have been detected in water where chemical analysis failed to detect anything and vice versa, showing the added value of these tools. Merijn Schriks (KWR Water Research Institute, Nieuwegein, Netherlands) presented data on the use CALUX bioassays to evaluate global hormone activity in waste water and tap water in Netherlands. Glucocorticogenicity was found the main component of hormone activity for waste waters. A follow-up investigation revealed that several glucocorticoids were present in such waters: dexamethasone, cortisone, cortisol and triamcinolone acetonide acting in a dose-additive manner. Other bioassays used to evaluate other biological effects (hepatoxicity, immunotoxicity, and neurotoxicity) were also presented briefly at the end of the talk.

The afternoon was dedicated to human exposure and toxicity. Elena Righi (Universitià di Modena, Modena, Italy) set the scene by introducing the potential effects of water contaminants and the complexity of human exposure evaluation. Sylvaine Cordier (INSERM, Rennes, France) presented a review of the association between diverse reproductive outcomes and water contaminants. There are some limited evidence linking metals, nitrates, pesticides, and DBPs to small-for-gestational age (SGA) babies and birth defects. Emerging contaminants have not yet been studied but might be a concern. Patrick Levallois (Université Laval, Québec, Canada) reported on the association between some water contaminants (arsenic, DBPs, nitrates, asbestos, fluorides, and trichloroethylene) and diverse cancer sites (skin, bladder, colorectal, stomach, and leukaemia). He discussed the need for better exposure assessment of exposure in order to improve the use of epidemiologic data in water quality standards establishment. Jay Nuckols (Colorado State University, Fort Collins, Colorado, USA) explained the different components of the exposure assessment to water contaminants putting the emphasis on the use of geographical-based fate/transport models to quantify contamination of tap water over time and space when you have limited data. He concluded that adequate resources (financial and expertise) are required to evaluate both internal and external exposome (the complete exposure history of a person) in order to improve exposure classification in epidemiological studies.

The last part of the day focussed on mechanisms and biomarkers. This session was chaired by Manolis Kogevinas (National School of Public Health, Athens, Greece and CREAL, Barcelona, Spain). After a short introduction of the chairman, Roel Vermeulen (Institute of Risk Assessment Sciences, Utrecht, the Netherlands) presented an overview of the different possibilities of molecular analyses with an emphasis on the study of intermediate endpoints. Different -omic approaches (genomics, epigenomics, transcriptomics, proteomics, metabolomics, and adductomics) could be used as well as more traditional approaches (ex: micronuclei (MN) in nucleus cells). He concluded on the need for large sample size studies and replication/validation of results. Theo de Kok (Maastricht University, Maastricht, Netherlands) presented on the use of genomics to evaluate the association between nitrate/nitrite exposure and colorectal cancer. He studied in particular, the link between gene expression levels and N-nitroso compound (NOC) urinary excretion as well as MN frequency in lymphocytes. With this approach, he identified possible pathways linking NOC to colo-rectal cancer. Finally, Alfred Bernard (Louvain, Brussels, Belgium) presented an overview of

the studies he conducted in adolescents and DBPs exposure at swimming pools using different biomarkers of effect (airway epithelial changes and inflammation, aeroallergen-specific IGE, serum inhibine B). Those studies suggest that early exposure to DBPs in swimming pools can predispose children to asthma and other allergic diseases and possibly to decrease male fertility.

Tuesday, May 22

This half day was divided in two parts. The first part was on the new challenges and regulatory aspects and was chaired by Tamara Grummt (Federal Environmental Agency, Bad Elster, Germany). She presented briefly how risks associated with water quality might be managed. Then, Paul Hunter (University of East Anglia, Norwich, UK) presented a lecture on the impact of climate change on water quality with an emphasis on microbiological quality. Possible impacts on chemical quality were also discussed. John Fawell (Independent consultant, Buckinghamshire, UK), as a WHO expert committee representative, summarised the main issues regarding the establishment of water quality standards by the WHO. He emphasised the need of relevant and systematic and high quality data on the occurrence of chemicals (regulated and unregulated) in drinking water. He then proposed a list of priorities for further epidemiologic studies. Peter Marsden (Drinking Water Inspectorate, London, UK) closed this session presenting the EU directive on drinking water and its challenges. He then went through diverse cases (DBPs, Cryptosporidium, pesticides, NDMA) and suggested some priorities for further research.

The second part of this half-day was devoted to a thorough discussion on the questions raised all along the meeting. Mark Nieuwenhuijsen (CREAL, Barcelona, Spain) proposed a summary of the chemical contaminants that were discussed by speakers during the workshop as well a list of emerging contaminants. Discussion went on the adequacy of those lists but also on the difficulties of access to the data occurrence on those chemicals in drinking water. The global indicators of toxicity were also briefly discussed. Manolis Kogevinas (National school of public health, Athens, Greece and CREAL, Barcelona, Spain) introduced its discussion section presenting knowledge on the link between exposure to water contaminants and health effects and challenged the need for studies of better quality using new technology tools. Finally, Cristina Villanueva (CREAL, Barcelona, Spain) discussed with participants the importance of setting a network on these issues and Carlos Segovia Perez (Instituto de Salud Carlos III, Madrid, Spain) proposed possible opportunities for funding such a network but also new research on the topics covered during this workshop.

3. Assessment of the results, contribution to the future direction of the field, outcome

Globally, this was a successful workshop that fulfilled the proposed objectives and demonstrated the need to conduct high quality multidisciplinary research on drinking water and health. It was the first step to stimulate and prioritise epidemiologic research on drinking water chemical contaminants in Europe. It has also stimulated collaboration between European and North American researchers.

The participants agreed upon the following conclusions:

- Epidemiologic results based on solid method and good exposure assessment are crucial to evaluate the risk to human health associated with drinking water chemicals;
- New studies should not repeat previous studies with the same limitations and shortcomings but try to better answer current research questions with improved methods;
- Evaluation of water contaminants occurrence is important and it should not be limited to regulated contaminants, nor to public water distribution systems;
- Chemicals of concern that deserve further epidemiological research include some regulated chemicals (e.g. nitrate, metals, and disinfection by-products) and several emerging chemicals (e.g. perfluorinated, UV filters, nanoparticles, etc.);
- Access to public and private sector (water industry) water contaminants monitoring and assessment data should be encouraged and facilitated;
- Collaboration between water utilities, regulators and researchers is important and should be promoted;
- Multidisciplinary approaches are necessary for improving research on the health effects of water contaminants;
- Epidemiological studies need large numbers of study subjects and measurements, which may constitute a challenge in the collaboration with other disciplines (chemistry, toxicology);
- Global indicators of water toxicity might be useful to evaluate the global effect of mixtures, and to identify “hot spots” for more in-depth analysis of specific contaminants, but they need further validation and high throughput development to be used in epidemiological studies
- Studies with contrast (wide range) of exposure are essential, thus it is therefore important to estimate water contamination of study participant location before undertaking an epidemiological study;
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- Retrospective assessment has limits particularly for outcomes with long latency (cancer) and prospective evaluation (as in cohort studies) should be encouraged
- Mechanistic studies trying to identify pathways of toxicity might be necessary for some contaminants to guide design for further epidemiologic studies;
- Geographical Information systems and fate/transport modelling of chemicals in water sources could help to improve exposure assessment (external exposome);
- But individual data collection is essential and requires questionnaires and or biological samples;
- The new –omics markers seem promising to study modes of biological actions of certain exposures but there is a need to clarify how to use them and when.

Also two subjects were discussed but did not lead to a formal conclusion:

1) Prioritizing contaminants:
Although a detailed list of water contaminants would be useful, further work need to be done to prioritize those chemicals with some objective criteria.

2) Small utilities:
Participants stated that the most important problems currently are found with small utilities and private wells (especially where source water quality is poor and treatment cost-prohibitive) but no solution was proposed to stimulate research in this area.

These two topics deserve further discussion in another meeting.

The follow up activities of the meeting include:

- An article will be written and submitted for publication in an international journal, including the main discussion points and the conclusions met by the group.
- Participants agreed to create a formal network of researchers and professionals on drinking water contaminants and health. There is a need to continue exchange and collaboration between professionals and researchers involved in drinking water quality in Europe. Possible funds available for water research in Europe were discussed. Some of these funds seem also accessible for US or Canadian researchers. This could stimulate the collaboration with North American researchers. The possibility to join existing organisations (e.g. the International Water Association which presently focuses on microbiological quality) should be evaluated. The COST applications will be considered.
- Write a letter to the European Commission on behalf of the group asking for access to regulatory data on water contaminants, which could be used in epidemiological studies on-going in Europe.

4. Final programme

Monday, May 21st 2012

08:45-9:00	**Registration, coffee** (informal meeting)
09.00-09.10	**Welcome by Convenor** **Cristina M. Villanueva** (CREAL, Barcelona, Spain)
09.10-09.20	**Presentation of the European Science Foundation (ESF)** **Carlos Segovia Perez** (ESF Standing Committee for the European Medical Research Councils - EMRC / Standing Committee for Life, Earth and Environmental Sciences - LESC)
09.20-13:30	**Session 1. DRINKING WATER QUALITY**
	Occurrence of chemical contaminants (Chair: Mark Nieuwenhuijsen)
09.20-9:25	**Setting the Scene** **Mark Nieuwenhuijsen** (CREAL, Barcelona, Spain)
9:25-9.55	**DBP Formation, Occurrence, and Control: Knowns and Unknowns** **Michael Templeton** (Imperial College, London, UK)
09.55-10:25	**Is Drinking Water a Significant Contributor to Human Exposure to Perfluorinated Chemicals?** **Gunilla Lindström** (MTM Research, Örebro University, Örebro, Sweden)
10.25-10:55	**Pharmaceuticals and Illicit Drugs in Surface and Drinking Water** **Ettore Zuccato** (Mario Negri Institute for Pharmacological Research, Milan, Italy)
10:55-11.25	*Coffee / Tea Break*
	Global Indicators of Water Toxicity (Chair: Tamara Grummt)
11.25-11.30	**Setting the Scene.** **Tamara Grummt** (Federal Environmental Agency, Bad Elster, Germany)
11.30-12.00	**Biological and Molecular Mechanisms for DBP toxicity** **Michael J. Plewa** (University of Illinois, Urbana, USA)
12.00-12.30	**Testing Drinking Water for Water Genotoxic activity** **Minne Heringa** (KWR Watercycle Research Institute, Nieuwegein, Netherlands)
12.30-13.00	**Endocrine Disruption and other Toxicity Markers** **Merijn Schriks** (KWR Watercycle Research Institute, Nieuwegein, Netherlands)
13.00-13.30	**Discussion** (Moderator: P. Levallois)
13.30-14.30	*Lunch*
14.30-18:30	**Session 2. HUMAN EXPOSURE AND TOXICIY**
	Human Exposure and Effects *(*Chair: Elena Righi)
14.30-14.35	**Setting the Scene** **Elena Righi** (Universtià di Modena e Reggio Emilia, Modena, Italy)
14.35-15.05	**Drinking Water Contaminants and Reproductive Health** **Sylvaine Cordier** (INSERM-U1085/IRSET, Rennes, France)
15.05-15.35	**Drinking Water and Cancer: the Epidemiologic Evidence** **Patrick Levallois** (Université Laval, Québec, Canada)
15.35-16.05	**Application of Environmental and Geospatial Sciences in Epidemiology Studies concerning Waterborne Contaminants** **Jay R. Nuckols** (Colorado State University, Fort Collins, Colorado, USA)
16.05-16.25	*Coffee / tea break*
	Mechanisms and Biomarkers *(*Chair: Manolis Kogevinas)

16.25-16.30 **Setting the Scene**
Manolis Kogevinas (CREAL, Barcelona, Spain)

16.30-17:00 **Use of Molecular Markers to Quantify Risk and Identify Mechanisms of Action**
Roel Vermeulen (Institute for Risk Assessment Sciences, Utrecht, Netherlands)

17.00-17:30 **Nitrate, nitrite, endogenous nitrosation and colorectal cancer risk: Genomics markers for risk evaluation**
Theo de Kok (Maastricht University, Maastricht, Netherlands)

17.30-18.00 **Risk Associated with Exposure to Chlorinated Pools**
Alfred Bernard (Catholic University of Louvain, Brussels, Belgium)

18.00-18.30 **Discussion** (Moderator: Cristina M Villanueva)

20.30 *Dinner*

Tuesday, May 22nd, 2012

09.00-13:30 **Session 3. NEW CHALLENGES AND FUTURE DIRECTIONS**

New Challenges and Regulatory Aspects *(*Chair: Tamara Grummt)

09.00-09.05 **Setting the Scene**
Tamara Grummt (Federal Environmental Agency, Bad Elster, Germany)

09.35-10.10 **Climate Change and Risks to Drinking Water Water Supplies in Europe**
Paul Hunter (University of East Anglia, Norwich, UK)

10.10-11.35 **Drinking Water Guideline Setting at the WHO**
John Fawell (WHO Expert Committee on the Guidelines for Drinking Water Quality, Independent consultant, Bourne End, Buckinghamshire, UK)

10.35-11.00 **Challenges for Drinking Water Regulation**
Peter Marsden (Drinking Water Inspectorate, London, UK)

11:00-11.30 *Coffee / Tea Break*

Future Directions

11.30-12.10 **Research priorities 1: Occurrence and Global indicators of toxicity**
All Participants (Moderator: Mark Nieuwenhuijsen)

12.10-12.50 **Research priorities 2: Epidemiology/Exposure/Biomarkers**
All Participants (Moderator: Manolis Kogevinas)

12.50-13.30 **Discussion on Follow-up Activities/Networking/Collaboration**
(Moderator: Cristina M Villanueva/Patrick Levallois)

13.30 *End of Workshop and lunch* (informal meeting)

5. Final list of participants

Convenor:

1. **Cristina M VILLANUEVA-BELMONTE,** Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain

Co-Convenor:

2. **Patrick LEVALLOIS,** Université Laval, Québec, Canada, on *sabbatical stay at CREAL*
3. **Manolis KOGEVINAS,** National School of Public Health, Athens, Greece
4. **Mark NIEUWENHUIJSEN,** Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain

ESF Representative:

5. **Carlos SEGOVIA PEREZ,** Instituto de Salud Carlos III (ISCiii), Madrid, Spain

Participants:

6. **Alfred BERNARD,** Department of Public Health, Catholic University of Louvain, Louvain-la-Neuve, Belgium
7. **Sylvaine CORDIER,** Université de Rennes 1, INSERM-U1085 – IRSET, Rennes, France
8. **Theo DE KOK.** Department of Toxicogenomics, Maastricht University, Maastricht, Netherlands
9. **John FAWELL,** Independent consultancy and advisory services on drinking water and environment, Bourne End, UK
10. **Anna GÓMEZ,** Agència de Salut Pública de Barcelona *(Public Health Agency of Barcelona),*Barcelona, Spain
11. **Joan GRIMALT,** Institute of Environmental Assessment, and Water Research (IDÆA), Spanish Council for Scientific Research (CSIC), Barcelona, Spain
12. **Tamara GRUMMT,** Department of toxicology of drinking water and swimming pool water, Federal Environment Agency, Bad Elster, Germany
13. **Minne HERINGA,** KWR Watercycle Research Institute, Nieuwegein, Netherlands
14. **Paul HUNTER,** The Norwich School of Medicine, University of East Anglia, Norwich, UK
15. **Gunilla LINDSTROM,** Örebro University, Man-Technology-Environment Research Center (MTM), Örebro, Sweden
16. **Peter MARSDEN,** Drinking Water Inspectorate, London, United Kingdom
17. **John R NUCKOLS,** Colorado State University, Department of Environmental and Radiological Health Sciences, Fort Collins, Colorado, United States
18. **Marie PEDERSEN,** Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain
19. **Michael PLEWA,** University of Illinois at Urbana-Champaign, Urbana IL, United States
20. **Elena RIGHI,** Università degli Studi di Modena e Reggio Emilia, Modena, Italy
21. **Merijn SCHRIKS,** KWR Watercycle Research Institute, Nieuwegein, Netherlands
22. **Leslie STAYNER,** University of Illinois, School of Public Health, Chicago, IL, United States
23. **Mike TEMPLETON,** Imperial College London, London, United Kingdom
24. **Fernando VALERO,** ATLL (Aigües Ter-Llobregat), Barcelona, Spain
25. **Roel VERMEULEN,** Institute for Risk Assessment Sciences, Utrecht University, Utrecht, Netherlands
26. **Elisabeth D WAGNER,** University of Illinois at Urbana-Champaign, Urbana IL, United States
27. **Ettore ZUCCATO,** Mario Negri Institute for Pharmacological Research, Milano, Italy

6. Statistical information on participants

	Number of participants	% from the total of participants
Total participants	27	100
Gender distribution		
Men	18	67
Women	9	33
Country of origin		
Belgium	1	4
Canada	1	4
France	1	4
Germany	1	4
Greece	1	4
Italy	2	7
Spain	7	26
Sweeden	1	4
The Netherlands	4	15
UK	4	15
USA	4	15
Discipline		
Chemistry	4	15
Toxicology	7	26
Epidemiology	10	37
Exposure science	1	4
Public health surveillance	1	4
Regulator	1	4
Industry	1	4
Consultant	1	4
Other	1	4
Age group		
30-40	6	22
41-50	7	26
51-60	7	26
61-70	7	26

Appendix: Abstracts of the communications presented at the workshop

DBP Formation, Occurrence, and Control: Knowns and Unknowns

Michael Templeton (Imperial College, London, UK)

This presentation summarised the current state of knowledge and ongoing research into the formation, occurrence and control of disinfection by-products (DBPs) in drinking water. It should always be kept in mind that chlorination has saved countless lives over the past century, so the benefits of disinfection should be emphasised when discussing DBPs. That said there is currently significant interest in identifying and quantifying the hundreds of DBP compounds which are formed (or theorised to be formed) by the common disinfection processes that are used in water treatment and a need to prioritise them in terms of their relative health relevance. Trihalomethanes (THMs) and haloacetic acids (HAAs) remain the only regulated DBPs in many countries however there is now a significant amount of information regarding the presence of a range of other DBPs, including several groups of nitrogen-containing DBPs (N-DBPs), some of which may be of greater health relevance than THMs and HAAs. N-DBPs include nitrosamines, haloacetonitriles, haloacetamides, halonitromethanes, aromatic amines, and cyanogen halides. Data from the first round of a 2011-12 UK drinking water sampling survey for several N-DBPs was presented; so far, all N-DBPs have only occurred at concentrations < 10 µg/l and several of the N-DBPs are only rarely detected, if at all. There is also a need to better understand the precursors of DBPs, to better inform precursor removal/control strategies and/or adjust disinfection processes to minimise DBP formation. In some cases treatment strategies which aim to minimise THMs or HAAs may enhance the formation of other DBPs; for example, chloramination is a common strategy to reduce THM and HAA formation but may enhance nitrosamine formation. Lastly, current DBP research is moving towards investigating the drinking water occurrence of a range of new potential DBPs which may present more plausible explanations than THMs or HAAs for the reported epidemiological outcomes associated with exposure to chlorinated water, including several bladder carcinogens; new chemical standards and analytical methods are needed to analyse for many of these compounds.

Is Drinking Water a Significant Contributor to Human Exposure to Perfluorinated Chemicals?

Gunilla Lindström (MTM Research, Örebro University, Örebro, Sweden)

Human exposure to perfluorochemicals (PFCs) is due to a variety of environmental and product based sources. Temporal and spatial trends of some PFCs in human blood show increasing levels since the mid 70's and on the other hand declining trends in some cases since 2000. The exposure pathways to humans have not been fully understood, even if food has been known to contain PFCs. During the last five years there has been a fast growing interest in monitoring of PFCs in drinking water as one possible contributor to human exposure. In 2011 Web of Science lists 30 publications and 500 citations on drinking water and PFCs. This can be compared to only 4 publications and 25 citations in 2007.

A number of studies were performed in 2007-2011 in Catalonia to assess the exposure of PFCs in a general population [1]. The aim was to evaluate the contribution from food, drinking water, indoor air and dust to the total exposure. The levels of up to 27 PFC congeners were determined in human blood (in ng/mL), foods (in ng/g), drinking water (in ng/L), dust (in ng/g) and air (in pg/m^3). The major PFCs detected in blood were PFOS (mean 7.6 ng/mL), PFHxS (mean 3.6 ng/mL) and PFOA (mean 1.8 ng/mL). In general PFOS was also the major compound present in most sources of exposure.

Exposure through the diet for an adult man in the Catalonian study was estimated to 62.5 ng/day for PFOS and 24 ng/day for PFOA. Fish followed by dairy and meet products were the main contributors. However, the intake of PFOS and PFOA was not considered enough to solely contribute to the corresponding blood levels. Therefore, the contribution by drinking water was estimated by determination of levels of PFCs in 40 different water suppliers in Catalonia. Surprisingly, the levels of 7 PFCs from the different locations showed big variations in contamination. Assuming a human water consumption of 2 L per day, the daily intake of PFOS and PFOA by the population in the most polluted area of Barcelona (worst case scenario 57.4 ng/L respectively. 58.1 ng/L) was estimated to 1.7 ng/kg bw/day (PFOS) and 1.6 ng/kg bw/day (PFOA).

In conclusion, food was found to be the dominant pathway for human PFC exposure in Catalonia and accounting for more than 70% of the total intake of PFOS and PFOA. In the most populated area (the Barcelona province), where the highest levels in drinking water were measured, water can contribute to adults' respectively toddlers' total exposure substantially (> 70% respectively >50%). Indoor dust and air sources were negligible when compared to food and water intake. However, for toddlers under worst case scenario the intake from dust and food were estimated to be equal (19%).

[1] Ingrid Ericson Jogsten, In Assessment of human exposure to per- and polyfluorinated compounds (PCDs) – Exposure through food, drinking water, house dust and indoor air. In *Örebro Studies in Chemistry* 10, ISBN 978-91-7668-811-3, 2011

Pharmaceuticals and Illicit Drugs in Surface and Drinking Water
Ettore Zuccato (Mario Negri Institute for Pharmacological Research, Milan, Italy)

The term pharmaceuticals refers to a class of widely used compounds and includes thousands of different active molecules, with different physico chemical properties, which are currently used in the world to treat or to prevent diseases, with hundreds of new molecules synthesized every year to replace obsolete compounds. Once administered, pharmaceuticals can be excreted as the parent compound or active metabolites in urine and stool, and can reach surface and ground water. Industrial pollution and improper disposal may play a role but the patient is recognized as the major source of the contamination. The same apply to illicit drugs which have been recently recognized as another emerging environmental issue. Monitoring surface water and drinking water contamination by pharmaceuticals and illicit drugs is advisable for several reasons, including reliable assessment of risks for the environment and, through the food chain, for man. Moreover, environmental levels might reflect the amounts consumed by the local population and can be used to estimate consumption of licit and illicit drugs. However, at least for pharmaceuticals, blanket monitoring is difficult because of the excessive number of compounds and metabolites, with different chemical structures and physico-chemical properties. It is therefore best to focus on a restricted list of molecules. The tendency is to establish priorities so as to restrict monitoring and risk assessment to a limited number of hazardous molecules, but proposals on how to do this selection are scarce. Pharmaceuticals are usually ranked according to tonnage, though some molecules with low sales volumes but high biological activity and toxicity are included (hormones, anticancer drugs) . Here we describe an approach based on two steps to identify molecules of concern for the environment and the human health. The first step is to pre-select the pharmaceuticals according to prescription or to biological activity, and the second is to refine the list by measuring them in surface and drinking waters. For illicit drugs a similar approach was implemented, measuring predicted urinary excretion products of major drugs of abuse, including cocaine, opioids, amphetamines and THC. Licit and illicit drugs were subsequently measured in surface and drinking water in some locations in Italy. Results showed that these compound can be considered widespread pollutants, frequently contaminating surface and drinking waters for human use.

Biological and Molecular Mechanisms for DBP toxicity
Michael J. Plewa (University of Illinois, Urbana, USA)

For decades the U.S. Environmental Protection Agency (U.S. EPA) and the World Health Organization have regulated DBPs to protect the public health and the environment. However, no systematic, quantitative biological molecular mechanism exists that explains the toxicity of a regulated class of DBPs. We propose a comprehensive model for the toxicity of the haloacetic acids (HAAs). The HAAs are a major class of drinking water DBPs with five HAAs regulated by the U.S. EPA. These agents are cytotoxic, genotoxic, mutagenic, teratogenic and carcinogenic. We discovered that the decreasing toxicity rank order of the monohaloacetic acids (monoHAAs) was iodo- > bromo- >> chloroacetic acid. We present data that the monoHAAs inhibit the activity of the metabolic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in a concentration-dependent manner with the same rank order as above. MonoHAA-mediated GAPDH inhibition kinetics and many metrics of toxic potency of the monoHAAs were highly correlated (r >0.9) with their alkylating potential and the propensity of the halogen leaving group (*Environ. Sci. Technol.* 2011, *45*, 5791–5797). Our working hypothesis argues that this irreversible inhibition of GAPDH

generates a molecular cascade that decreases cellular ATP and pyruvate (which may be the basis of HAA induction of cytotoxicity, neurotoxicity and teratogenicity), as well as modulation of intracellular Ca^{2+} levels which leads to the generation of reactive oxygen species (ROS). ROS may be generated by altering the homoeostasis of mitochondria or by modulating the arachidonic acid pathway. Our mammalian cell toxicity data and human cell toxicogenomic data indicate that HAA-mediated ROS generation may be the primary route in HAA-induced genotoxicity and perhaps carcinogenicity. Of interest is the fact that GAPDH, the target molecule for HAA-induced toxicity, is also associated with the etiology of neurological dysfunction including Alzheimer's disease.

Testing Drinking Water for Water Genotoxic activity

Minne Heringa (KWR Watercycle Research Institute, Nieuwegein, Netherlands)

To safeguard its good quality and safety, drinking water and is sources must be continuously screened for the presence of contaminants. Besides chemical analysis, toxicity analysis is recommended, to enable detection of unknown hazardous contaminants and to measure the total effect of the mixture of compounds present in the water. Because of the relatively low levels of contaminants in these waters, only low-dose toxic effects, such as genotoxicity, are of relevance.
There are many different assays available to screen for genotoxic chemicals. For the choice of a test battery, it is important that it detects as many different types of genotoxic substances a reasonably possible, that the assays are fast, sensitive and cheap and that fractionated water samples can efficiently be analyzed, for subsequent contaminant identification. Currently, the best test battery is found to be the Ames (fluctuation) test with the comet assay or micronucleus assay.
Application of these tests shows that, indeed, the previously unknown presence of genotoxic compounds can be detected in water. Also, the decrease of the levels of these compounds due to a certain treatment step, or the decrease in surface water over time, due to environmental measures, can be monitored. An important issue is at what response of these assays one should be worried and take action. An alarm value can be derived using the Threshold of Toxicological Concern (TTC). This exercise shows that the current setup of the Ames fluctuation test is nearly, but not fully sensitive enough yet.
Future challenges to be tackled are the increase of the sensitivity of the Ames fluctuation test setup (e.g. by higher concentration of the water), the determination of the sensitivity of the comet assay, the comparison of the comet assay with the micronucleus assay, the translation of genotoxicity test responses to possible consumer health risk, the determination of any possible added value of other, new genotoxicity tests and the validation of tests for non-genotoxic carcinogens for application on water.

Endocrine Disruption and other Toxicity Markers

Merijn Schriks (KWR Watercycle Research Institute, Nieuwegein, Netherlands)

Thousands of chemicals are emitted to natural waters leading to nanogram to microgram per liter levels. A number of these Micropollutants may lead to toxic effects even at very low concentrations or as mixtures. The large number and variety of Micropollutants make it very difficult to assess such effects which are often in the sub-acute range.
Besides applying advanced analytical chemical tools such as LC-mass spectrometry, we therefore aim in our research for more holistic methods such as Effect Directed Analysis (EDA). In one of our earlier studies we applied a panel of so-called CALUX bioassays to screen a number of (waste)water extracts for various modes of endocrine disruption, namely estrogenicity, androgenicity, glucocorticogenicity and progestagencity. A striking result was the glucocorticogenic activity observed in various extracts. Glucocorticoids are mainly applied as anti-inflammatory drugs and on the top 10 list of most prescribed pharmaceuticals. However, CALUX bioassays provide an integrated biological response and do not provide the identity of the responsible bioactive compounds. In an attempt to unravel the identity of the responsible compounds, we used a high resolution Orbitrap mass spectrometer. The results showed a broad range of glucocorticoids such as dexamethasone, cortisone, cortisol and triamcinolone acetonide in the low microgram per liter range. In an attempt to study the behavior of the individual constituents in a complex mixture, we spiked stripped wastewater with the various glucocorticoids. The results showed that the contribution of the individual constituents is dose-additive and that the identified glucocorticoids explain the observed CALUX results to a fairly high extent. Finally, in an attempt to put the results in the perspective of (adverse) human health we are developing bioassay trigger values to define a bioassay level below no adverse effects are to be expected. The results show that low risk for humans can be expected from exposure to glucocorticogenic compounds. At the end of my

presentation I will take the opportunity to discuss a number of toxicity pathways that may be relevant for drinking water as well.

Drinking Water Contaminants and Reproductive Health
Sylvaine Cordier (INSERM-U1085/IRSET, Rennes, France)

The presentation will be limited to health risks associated with the presence of chemicals in drinking water. In some areas, water quality is threatened by geochemical inputs (ie arsenic), by point-source or diffuse pollutions of water resources or by inadequate characteristics of the distribution network (ie lead pipes). In these situations, the presence of metals, fertilizers or pesticides, or persistent pollutants in drinking water can represent a significant part of the exposure to these chemicals in the general population. High concentrations of arsenic in drinking water for instance have been associated with an increased risk of fetal loss and congenital malformations when ingested during pregnancy. Increased risks of spontaneous abortions, fetal growth restriction and birth defects have been linked with nitrate intake in some studies but the evidence is still not conclusive. The long-standing limit value of 50 mg/l for concentration of nitrates in public water supplies may not adequately protect users exposed to higher levels.
Chemical mixtures present in treated waters and in distribution networks are also those derived from the disinfection step of water treatment (disinfection by-products, or DBPs). Their potential impact on pregnancy outcomes has generated an abundant literature. Evidence regarding the risk of spontaneous abortions or stillbirths, or of congenital malformations is inconclusive. Studies have quite consistently reported no association between maternal DBPs exposure and preterm delivery. Studies on small-for-gestational-age showed more consistent results, the majority reporting increased risks overall. However the components of the mixture responsible for this increased risk, if any, are still unidentified.
Today it is recognized that emerging pollutants, in particular drug residues acting as endocrine disruptors, present in the range of ng/L in drinking water, may result in health risks that have not yet been studied.
In summary, most chemical contaminants in drinking water are not monitored, most studies focus on one class of contaminants at a time, and health risks potentially resulting from exposure to these mixtures have not been fully evaluated.

Drinking Water and Cancer: the Epidemiologic Evidence
Patrick Levallois (Université Laval, Québec, Canada)

Drinking water is a source of several carcinogens that could expose populations continuously through ingestion, and eventually by inhalation or dermal absorption. Only three water chemical contaminants have been studied deeply with epidemiology: arsenic, disinfection by-products and nitrates. Arsenic, mostly from natural source, is a well proved human carcinogen. In countries as Taiwan and Chile where there was high contamination levels, it was associated with skin, lung and bladder cancer. Many studies were done with lower levels but to date there is still uncertainty regarding the effect of arsenic at low level. Disinfection by-products are very numerous and most of the studies have used total trihalomethanes as the indicator of toxic effect those chemicals. Bladder cancer has been repeatedly associated with higher levels of contamination; however the dose-response curve for low level contamination is still imprecise and there is no explanation for the apparent vulnerability of men compared to women. The study of nitrates exposure is very challenging since most of the exogenous nitrates come from food and that endogenous exposure is not negligible. Also, their carcinogenic effect is mediated through the formation of N-nitroso compounds which is enhanced in population with low antioxidants intake. Few studies have evaluated the possible impact of water nitrate and no conclusion could be reached from their results. Other contaminants effect has been less studied. Asbestos is a well accepted carcinogen by inhalation but its effect by ingestion is still uncertain. Tricholoroethylene is a solvent that is probably carcinogen in human based on animal and occupational studies but studies on the effect of water contamination are few and very limited. Fluorides are added to water for the prevention of dental carries. To date most of the ecological studies done on their possible relationship with cancer have been reassuring but recent case-control studies of osteosarcoma in youth have given contradictory results. Globally, the contribution of epidemiological studies to risk evaluation of water carcinogens is very limited. One of the major weakness of those studies is the exposure assessment which needs to consider a very long period of time (at least 40 years and if possible all

the life) and take into consideration all the routes of exposure. There is a real need for coordinating efforts to improve studies on water contamination and cancer.

Application of Environmental and Geospatial Sciences in Epidemiology Studies concerning Waterborne Contaminants

Jay R. Nuckols (Colorado State University, Fort Collins, Colorado, USA)

The purpose of epidemiology is to understand the etiology of a disease to the point that prevention strategies can be developed and employed. Exposure assessment is a critical component of epidemiology when this etiology is associated with contaminants in our environment. Exposure is the physiological ingestion, inhalation, or dermal transfer of a contaminant. Each of these "routes of exposure" requires contact between humans and their physical environment, thus dictating a spatial dimension to environmental epidemiology. The amount of exposure is also a very important factor in disease etiology. The integration of environmental and geospatial sciences in epidemiology promotes better understanding of the relationship between where contaminants occur (source), how they move in our environment (transport), and the levels to which we come in contact over space and time (exposure). Better understanding of these relationships can greatly facilitate disease prevention by reduction or elimination of contaminant emissions from the source, or by minimizing opportunity for contact between humans and contaminants in their environment. Human exposure to waterborne contaminants can occur as a result of consumption of water (ingestion), breathing airborne vapors or emissions from water sources (inhalation), and/or water contact activities (dermal transfer). Waterborne contaminants associated with adverse health impacts include anthropogenic chemicals (e.g. byproducts of water disinfection), naturally occurring elements (e.g. arsenic), and biological pathogens (e.g. Vibrio cholera). Most human exposure to these contaminants occurs through home water use, recreation activities, and occupations involving water use activities. A major public health tradeoff in modern times is increased exposure to waterborne chemical compounds generated by disinfection procedures designed to reduce pathogen contamination in public water supply distribution systems (piped water). Other emerging issues include the water scarcity and waste management coupled with population growth and global climate change. Advances in geospatial science such as remote sensing and geographic information systems allow surveillance and mapping of source, occurrence, and human activities associated with water resources. Advances in environmental sciences such as simulation modeling and micro-sensors allow better estimation of the fate, transport, and amount of a contaminant in the aqueous environment. By integrating these sciences in public health sciences such as epidemiology, we should be able to facilitate optimal strategies for disease prevention and protection of environmental health.

Use of Molecular Markers to Quantify Risk and Identify Mechanisms of Action

Roel Vermeulen (Institute for Risk Assessment Sciences, Utrecht, Netherlands)

Nitrate, nitrite, endogenous nitrosation and colorectal cancer risk: Genomics markers for risk evaluation

Theo de Kok (Maastricht University, Maastricht, Netherlands)

Increased intake of nitrate in drinking water has been shown to raise endogenous formation on N-nitroso compounds (NOC). Epidemiological studies have shown that dietary factors linked to the stimulation of endogenous nitrosation, a process resulting in the formation of this class of compounds, are associated with increased risk of various diseases, including cancer, thyroid malfunction and neural tube defects. These factors include high consumption of red and processed meat in combination with low intake of antioxidants. Although NOC are known rodent carcinogens, there is only very limited direct evidence for a carcinogenic potential of NOC in humans. Therefore, we performed a series of human studies to link drinking water nitrate concentrations, combined with specific dietary factors, to the urinary excretion levels of NOC as markers of exposure. Subsequently, exposure levels were related to lymphocytic micronuclei (MN) levels, well-validated biomarkers of human cancer risk and whole genome transcriptomic responses. We used lymphocytes, from adult females participating in the pan-European biomarker research project NewGeneris, as a surrogate tissue for analysing such potentially carcinogenic gene expression and MN formation.

We demonstrated a significant association between MN frequency and urinary and identified modifications in among others cytoskeleton remodelling, cell cycle, apoptosis and survival, signal transduction, immune response, G-protein signalling and development pathways, which indicate a response to NOC-induced genotoxicity. Moreover, we established a network of genes, the most important ones of which include FBXW7, BUB3, Caspase 2, Caspase 8, SMAD3, Huntingtin and MGMT, which are involved in processes relevant in carcinogenesis. Although this is the first study linking gene expression profiles to human NOC exposure measurements and the results need to be validated, it demonstrates the potential added value of using transcriptomics biomarkers in human studies to investigate carcinogenic risks associated with specific exposures in humans.

Risk Associated with Exposure to Chlorinated Pools
Alfred Bernard (Catholic University of Louvain, Brussels, Belgium)

Recent studies suggest that the rise of allergic diseases in the developed world might be linked at least in part to the increasing and largely uncontrolled exposure of children to the toxic chlorination products (CPs) contaminating the air and water of swimming pools (Bernard et al., 2003, 2011). According to this "chlorine" hypothesis, the disruption of epithelial barriers caused by these chlorine-based oxidants would exert adjuvant effects in the development of atopic diseases such as asthma, hay fever or allergic rhinitis. In order to provide further insight into the respiratory effects of CPs, we recently conducted several studies among school adolescents and children with a variable attendance of chlorinated pools and for comparison of a swimming pool disinfected by the copper-silver ionization method. In addition to classical outcomes (respiratory diseases, exhaled nitric oxide, total and aeroallergens specific IgE), we measured various airways epithelium biomarkers in serum, urine or nasal lavage fluid (NALF), including the lung-specific Clara cell protein (CC16). In adolescents (n=845, 14-18 years), the serum concentration of CC16 (a marker of Clara cell damage) decreased dose-dependently with the cumulated time spent in chlorinated pools. Atopic adolescents in the lowest tertile of serum CC16 were approximately 2.5 times more likely to suffer from asthma (OR, 2.57, 95%CI 1.00-6.61) or allergic rhinitis (OR, 2.39, 95% CI 1.26-4.53) than those in the highest tertile. In a two-year follow-up of 205 young children (5 years), we found that the early attendance of chlorinated pools (for more than 10 hours before the age of 3 years) was associated with an increased risk of elevated nitric oxide (OR, 4.45, 95% 1.34-14.8) and of house-dust mite sensitization (HDM, OR, 2.6, 95% 1.01-6.67). These risks were again associated with airways epithelial damage as evidenced by an increased leakage of CC16 from the lung. In both adolescents and young children, the CC16/albumin ratio in NALF, which integrates both the permeability and cellular integrity of the nasal epithelium, also decreased with time spent in chlorinated pools. In boys, a lower CC16/albumin ratio in NALF was associated with an increased risk of HDM sensitization. These findings add to the growing evidence that CPs in swimming pools can cause epithelial barriers defects that predispose children to allergic sensitization and later to the development of asthma and other respiratory diseases.

Bernard A, Carbonnelle S, Michel O, Higuet S, De Burbure C, Buchet JP, Hermans C, Dumont X, Doyle I. Occup Environ Med. 2003;60:385-94.
Bernard A, Voisin C, Sardella A. Am J Respir Crit Care Med 2011;183:570-2.

Climate Change and Risks to Drinking Water Water Supplies in Europe
Paul Hunter (University of East Anglia, Norwich, UK)

In recent years waterborne disease has been identified as one of the particularly climate vulnerable diseases. In the recent report on water, the IPCC have recently identified the main vulnerable groups as being those communities that are infrastructure poor. For most high income nations this means those people reliant on very small and private water supplies. To date however, most statements in the literature have been fairly general and not attempted to quantify any potential impact of climate change on human health in this group.
We have been undertaking a series of modelling studies to estimate the impact of climate change on water quality for consumers of private water supplies in England. Climate data was obtained from the UK CIP09 climate projections using the Weather Generator. For each site the weather generator was run for the years 2040 and 2080 under the SRES B1 low and the SRES A1F1 high carbon emission storylines. Data from 100 runs of 100 years duration were obtained for each site in the UK. One thousand consecutive years of data were chosen for each model. The relationship between E. coli count and precipitation variables were determined by regression analysis of the

PHLS dataset which has previously been described. Although mean daily precipitation over the course of the year was not that different between the baseline and 2080 High emission scenario, the model predicted more dry days in summer and more frequent heavier rainfall events during the winter in 2080. The impact on probability of failing E coli counts was not that different between the baseline and high emission two scenario. However, where positive, there were differences in the actual counts observed depending on which part of the UK was being modelled. The impact of climate change on waterborne disease and water quality is dependent on the location. In some areas, the main risk would appear to be from seasonal aridification. The impact on risk from cryptosporidiosis may be minimal or even negative.

Drinking Water Guideline Setting at the WHO

John Fawell (WHO Expert Committee on the Guidelines for Drinking Water Quality, Independent consultant, Bourne End, Buckinghamshire, UK)

The Guidelines for Drinking-water Quality were first published in 1984 with subsequent revisions in 1993, 2004 and 2011. The Guidelines are designed to be a point of departure for member states to develop their own standards, which differ from the guidelines by having legal force. It is intended that the guidelines should be adapted to local circumstances in both the range of parameters and the values, except for microbiological pathogens. The guidelines are not just a list of numbers but are based around a framework for safe water that takes a proactive approach to identifying and correcting problems in any supply. Part of the approach is however built around water quality targets. For chemicals these are guideline values. For microbial pathogens the approach is based around acceptable risk of disease and establishing suitable treatment barriers. Since it is not appropriate or particularly feasible to monitor individual pathogens most of the time *E. coli* is used as an indicator of faecal contamination.

The chemical contaminants often generate the greatest concern even though there is little evidence that this is the case except for very high concentrations of naturally occurring arsenic and fluoride. Since the Guidelines are intended as a basis for standards all over the world, it is important that they are relevant in a wide range of different countries. In order to achieve this substances are selected on the basis of widespread occurrence and concentration, presence does not necessarily equate to significance. It is important that such data are systematic and of known good quality. In addition, we seek data on the impact of different interventions and treatments, not just advanced treatment in highly developed countries as well as analytical methods that can be used widely. Practical considerations are important in developing guideline values.

Increasingly, epidemiological data, particularly clinical epidemiology, from highly exposed populations is needed to determine whether animal data are appropriate. It is vital that exposure from all sources is considered and that the data can be used where there is a known endpoint. Examples of substances for which better data are required are barium and selenium and an example of a substance for which the epidemiology data has shown that humans are not as susceptible as might be inferred from laboratory animal studies is uranium.

Challenges for Drinking Water Regulation

Peter Marsden (Drinking Water Inspectorate, London, UK)

The main drivers behind drinking water regulation are discussed. Principal amongst these are the World Health Organisations (WHO) guidelines. Examples are given of how both WHO guideline values and the WHO Water Safety Plan (WSP) approach have been implemented in to legislation. In Europe, the Commission's proposals and subsequent negotiations that result in the Drinking Water Directive are key drivers. At the national level, the consideration of expert committees can inform standards and associated guidance.

Research can feed into all these drivers, usually on the basis of a balanced judgement that reviews all the available data. It is rare for a single study to directly affect regulation.

Some case studies are discussed to highlight the interface between research and regulation. One of the challenges is in the area of disinfection by products (DBPs) where the undoubted benefits of disinfection need to be balanced against the small risks that may exist from DBPs. This example reinforces the need for a balanced approach to considering the data that informs regulation.

Further case studies focus on examples where the threshold is low or may even be zero. Any pathogen with a low infective dose can pose a challenge to regulation. The resistance of *Cryptosporidium* to chlorination provides a unique challenge to both water treatment and regulation. In England and Wales, *Cryptosporidium* was regulated by means of a treatment standard, though now a more holistic WSP approach is adopted.

The nitrosamine, NDMA, provides an example of a chemical that is also a challenge and current national advice is that exposure should be as low as is reasonably practical. Some further areas for research are highlighted. In all cases, the risks are likely to be small though some may pose the challenge of having very low or zero thresholds.

Finally access to data is discussed at the national and European level.