Project No. 036224

HiWATE

HEALTH **I**MPACTS OF LONG-TERM EXPOSURE TO DISINFECTION BY-PRODUCTS IN DRINKING **WAT**ER

SPECIFIC TARGETED RESEARCH PROJECT

FP6 Food quality and safety

Publishable Final Report

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Project full title: HEALTH **I**MPACTS OF LONG-TERM EXPOSURE TO DISINFECTION BY-PRODUCTS IN DRINKING **WATE**R

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Publishable Executive Summary

Project objectives

The overall aim was to investigate potential human health risks (e.g. cancer, premature births, small for gestational age, semen quality, stillbirth, congenital anomalies) associated with long-term exposure to low levels of disinfectants (such as chlorine) and disinfectant by-products (DBPs) occurring in water for human consumption and use in the food industry. The study comprised risk-benefit analyses including quantitative assessments of risk associated with microbial contamination of drinking water versus chemical risk and compared alternative treatment options. The outcome will contribute to improved risk assessment and management. The study made use of existing studies/databases and newly collected information. It was the first large research effort in Europe in the area of DBPs and health.

The specific objectives of the proposed work are as follows:

I) To determine the DBP composition and levels in drinking water in various regions in Europe (Spain, United Kingdom, Lithuania, France, Italy, Greece). Samples were collected and analysed for a range of DBPs, depending on the type of water disinfectant treatment used.

II) To identify the determinants of DBPs and develop predictive models. In addition to the analysis for a range of DBPs (see objective I), the consortium obtained information regarding the possible determinants of the DBPs including organic matter content, water source, temperature, pH, (residual) disinfectant levels e.g. chlorine and bromide level.

III) To assess the risk of reproductive effects in relation to disinfection practices and levels of disinfection by-products, we conducted epidemiological studies to examine the relationship between DBPs and the following outcomes:
- Congenital anomalies (>2.6M subjects including 22000 cases), and stillbirth in an intervention study (>277,000 subjects including >1400 cases) and a large nation-wide cross-sectional study (almost 2.8M subjects including >14,000 cases), using registry data in the UK,

where mainly chlorination was used as a disinfectant. Low birth weight was also investigated in the intervention study (almost 260,000 subjects and >18,000 cases) and in the cross-sectional study (100,000 subjects and almost 6,300 cases). - Congenital anomalies using registry data in a case-control design (>1200 cases, almost 5000 controls) in Italy in regions, where mainly chlorine dioxide was used as a disinfectant.
- Birth weight and premature birth in birth cohorts in Spain, Greece, France and Lithuania (N>14000 subjects), where a range of disinfectant treatments were used. We also examined gene-environment interactions (e.g. metabolic polymorphisisms, oxidative stress and folate metabolism) in these populations.
- Semen quality, using a case-referent design (>1500 subjects) in the UK, where mainly chlorination was used for water disinfection.
We also conducted meta-analyses for disinfection by-product exposure and birth weight, premature birth, still birth and congenital anomalies using data from the study and the literature.

IV) To assess the risk of cancer, particularly bladder cancer and colon cancer, in relation to disinfection by-product practices and disinfection by-products levels, including the examination of any gene-environment interactions. The study obtained risk estimates from existing bladder case control cancer studies in Spain, France (includes ozonation as treatment) and Finland, and conducted summary analysis (>2300 cases, >3000 controls). New epidemiological studies were conducted, using a large case-control design (1000 cases, 1000 controls) to examine the relationship between DBPs and colon cancer in Spain and Italy.

V) To conduct risk-benefit analyses including quantitative assessments of risk associated with microbial contamination of drinking water versus chemical risk, compare alternative treatment options, and produce burden of disease estimates (e.g. DALYs). It built on and made use of expertise and experience of EC funded projects such as MICRORISK and INTARESE.

VI) To review water disinfection in Europe and worldwide in relation to drinking water and water use for food processing. Best practice in terms of water disinfection and a brief assessment of disinfection alternatives completed the study. A final workshop, was organised as an open conference brought together scientists working on environmental, toxicological, epidemiological and policy aspects of chlorination DBPs, microbiologists, policy makers, and representatives from the water industry and consumer organisations in Europe to develop guidelines for policy across Europe and the future research agenda.

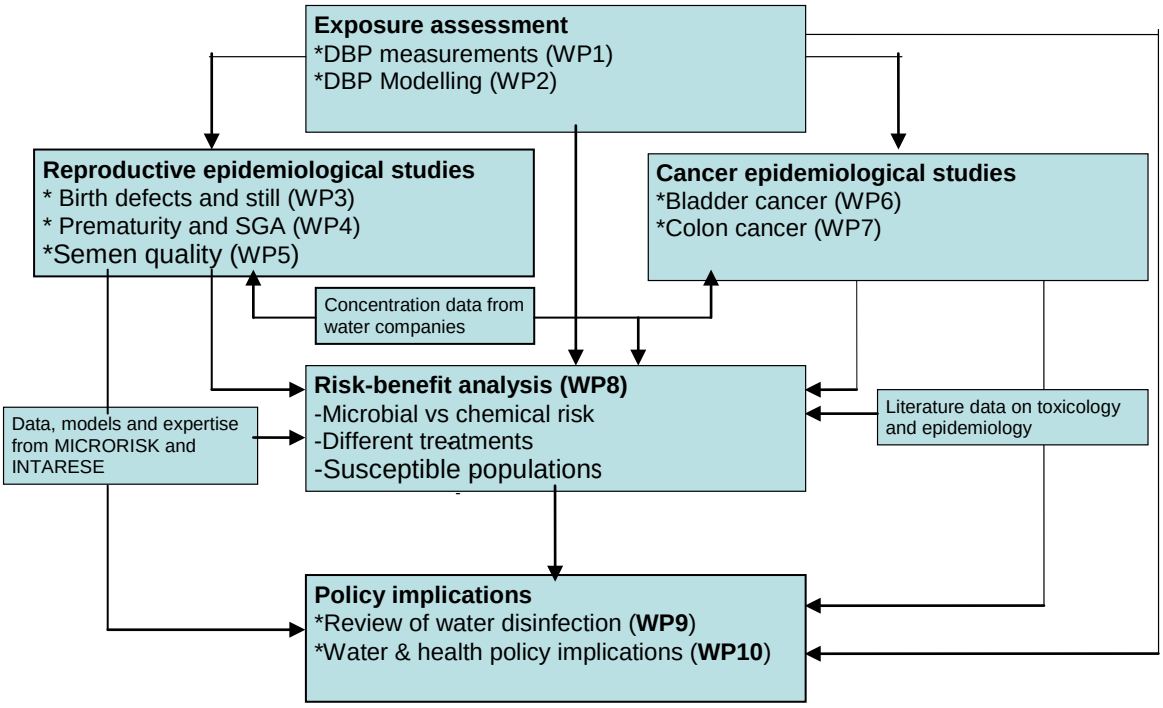
VII) To assess the water and health policy implications of current disinfection practices, taking into account recent environmental, toxicological and epidemiological findings and the findings of the HiWATE study. These various aspects were examined, including the measurement and modelling of DBPs and the results of the epidemiological and risk-benefit studies.

Project Consortium:

Participant role	Participant no.	Participant organisation name	Participant organisation short name	Country
CO	1	Imperial College London	Imperial	United Kingdom
CR	2	University of the Aegean	UA	Greece
CR	3	Finnish National Institute for Health and Welfare	THL	Finland
CR	4	Vytautas Magnus University	VMU	Lithuania
CR	5	University of Crete	UoC	Greece
CR	6	Université de Rennes	INSERM	France
CR	7	Municipal Institute of Medical Research Foundation	FIMIM	Spain
CR	8	Centre for Genomic Regulation	CRG	Spain
CR	9	University of Modena and Reggio	UNIMORE	Italy
CR	10	Istituto di Ricerche Farmacologiche "Mario Negri"	MN	Italy
CR	11	Swedish Institute for Infectious Disease Control	SIIDC	Sweden
CR	12	Hylobates Consulting Srl	HCS	Italy
CR	13	IC Consultants Ltd	ICON	United Kingdom
CR	14	Scarab	SCARAB	Sweden
CR	15	Centre de Recerca en Epidemiologia Ambiental	CREAL	Spain
CR	16	Institut Català d' Oncologia	ICO	Spain

CO Coordinating partner **Fig. 1**
CR Contracted partner

The work was divided into 10 work packages (WPs), within 4 Research Areas that are detailed as linked in the following figure:



Main findings of the project were:

There was substantial variation in trihalomethane (THM) concentrations across the study region with very low levels (mostly below 10 µg/l) in Lithuania and Crete and high levels, well above the current guidelines of 100 µg/l, in the Barcelona area, Spain. Medium levels were found in France and the UK (around half the guideline). Within Spain, medium levels were also measured in Asturias and Valencia and low levels in the Basque Country. Barcelona area samples were specifically high in brominated species because of high bromide levels in the water. Haloacetic acid (HAA) concentrations followed a similar pattern to the THMs but actual levels were lower. Haloacetonitrile (HAN) concentrations were a least an order of magnitude lower than the corresponding THM values and trichloroacetonitrile (TCAN) was hardly detected in any samples. Chloropicrin (CP) was only observed in a few samples. Very low levels of haloketones were detected in samples from UK and Spain. Concentrations of chloral hydrate (CH) were detected with the highest concentrations in Spain, and low concentrations in the rest of Spain, France and the UK. Chlorite and chlorate levels were fairly high at times in Italy because of the use of chlorine dioxide as treatment. 3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone) (MX) levels were generally low but noticeably higher in Bradford, UK compared to the other study regions. Some predictive models were constructed with UV-absorbance, temperature and total and free chlorine as the main predictors.

We found little evidence of any effects of THMs on reproductive outcomes including semen quality, congenital anomalies, stillbirth, pre-term delivery, and birth weight in any of the studies. Also, there was little evidence for gene-environment interaction for THMs and preterm delivery and birth weight. However in Italy there were statistically significant associations between exposure to chlorite (> 700 µg/l) and chlorate (>200 µg/l) and a number of congenital anomalies (urinary tract defect, cleft lip and palate, renal defects, abdominal defects, spina bifida), but the number of cases were relatively small and there were generally no monotonic exposure response relationships. Also, the meta-analyses generally found little

evidence for an association between disinfection by-products and birth weight, premature birth, still birth and congenital anomalies except for ´´small for gestational age´´, which is the 10%ile of babies with the lowest weight for a given gestational age, which showed a 1% increase in risk for every 10 µg/L increase in total THMs.

The pooled analyses of bladder cancer showed an exposure-response relationship between exposure to THMs and bladder cancer in men (OR=1.32; 95%CI 1.01 to 1.71 for average level of THM4 > 50 µg/L), but the relationship appeared less steep compared to North American studies. There was little evidence for a relationship between THMs and colon cancer.

The comparative risk assessment framework that was developed allowed for the risks from chemical and microbial agents associated with drinking water to be compared in a structured and transparent way, drawing on the available experience, expertise, literature and data for characterizing the occurrence, fate and health impacts of the different agents. The tool synergized existing scientific knowledge into a cohesive decision-making tool for water safety management, with potential for direct implementation by water utilities.

In the case study example, for bacterial and viral pathogens, chlorine was the most important barrier for protection of infectious risks. The risk trade-off between THM and pathogens occurred at very low chlorine concentrations (<0.1-0.15 mg.L-1), well below current dosage practice in that case study city (1-2mg.L-1). Above the trade-off point, bladder cancer DALYs increased slowly with respect to chlorine dose, implying that a safety factor to account for resistant pathogens and shielding was tolerable. Treatment techniques such as enhanced coagulation showed benefits in both pathogen and THM reduction and related health impacts. Despite the low trade-off level, the conclusion could not be drawn that the current dosage was unnecessarily high due to uncertainties in the model.

The review of the best available technologies suggested that the first step in reducing DBP formation is to use the best available source(s), which in preferential order are: groundwater; surface water subject to soil passage such as bank filtration; surface water sources. However, it is acknowledged that in many regions, a wide choice of drinking sources is unavailable, in which case alternative strategies should be adopted. DBP control strategies that limit both levels of total organic carbon (TOC)/Dissolved organic carbon (DOC) and THMs are recommended, although care should be taken to ensure that reduction in THM concentrations does not lead to an increase in other DBPs, which may be more toxic than THMs. In principle, precursor removal is the preferred option to switching disinfectants to control DBPs. Most treatments form alternative DBPs, however, DOC removal will reduce concentration of a variety of DBPs (monitored and unmonitored), albeit to varying degrees. There is a recent international and European trend for legislating for risk-based quality management, using the water safety plans (WSP) or similar multi-barrier/risk-based approaches would be sensible approaches to promote.

Based on the findings, the consortium recommends that based on the current health evidence for bladder cancer and birth weight 1) the current guidelines for DBPs in drinking water should be reviewed, 2) a stronger effort should be made to obtain information on DPBs levels and profiles in tap water in all regions in Europe, and other pathways than drinking water such as in industrial and food processes where little information exists, 3) routinely collected information on DBPs and its determinants should be made publicly available and easily accessible to the general public and the research community, 4) health evidence database for many DBPs should be expanded, specifically for DBPs other than THMs and HAAs, disinfectants such as chlorine dioxide, outcomes not included in this work, and the possible biological mechanisms 5) water treatment plants should lower there DBP levels as far as possible without compromising the effectiveness of the disinfection through e.g. source water selection and use of appropriate technologies 6) evidence based risk assessment methods and tools should be used to estimate the potential health impacts of water treatment 7) possible health impact of climate change should be further assessed

Using and disseminating the knowledge

A wide range of dissemination methods were employed, aimed at different stakeholder groups (science community, policy makers, water companies, water consumers, food industry). The principle of dissemination was to ensure an active dialogue, and to provide opportunities for exchange of expertise and experience, and transfer of knowledge. The stakeholder forum was created and utilised for this. Key approaches included:

1. An active tiered website (www.hiwate.eu), set up in the early phases of the project, targets both lay and professional people. This provided information on the project, updated on progress and results, a gateway to other relevant research, and a forum for discussion, comment and feed-back.
2. A web-based project brochure announcing the project, and providing a simple information sheet for interested parties.
3. Regular project news was distributed both via the web and, for targeted individuals, in hard copy. This was aimed at alerting users to key developments and headline results, events, and personnel involved in HiWATE, and to provide links to other related activities (e.g. parallel studies). It also provided brief commentaries on the implications of these developments for policy, and invited similar commentaries and reviews from users or other researchers.
4. Publication in leading, international, peer-reviewed journals, and presentations at major national and international conferences and symposia (in all the relevant disciplines), in order to disseminate results to the scientific community. Because of the broad scope and interdisciplinary nature of the project, publication will deliberately be aimed at different journals, in order to access different audiences. Some have been published.
5. Organisation of a series of workshops and seminars, at key stages in the project, with the last workshop (HiWATE, London) being open to everyone.
6. Publication of final materials and results (e.g. brochure, dedicated journal issue) for the non-specialist audience, on the health risks and benefits of disinfection and disinfection by-products in Europe, and the role in this on policy, lifestyle/behaviour etc.
7. Production of press releases to attract media attention to significant events and publications.