
February 27, 2004

Technical Working Group on

Research Needs
This report reflects the opinions of the members of the Working Group and it highlights the different opinions contained within the group where appropriate. It should not be considered as an official statement of the position of the European Commission.

This baseline report is provided by the Technical Working Group Research Needs

that has been appointed by the European Commission within the Environment & Health Strategy.

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1 Introduction

Environment and Health includes the understanding of the effects of several environmental factors on human health. The issues are complex and, whilst some have been studied relatively extensively, others are still largely unknown. However, there can be no policy for “Environment and Health” without good knowledge of the associations and interactions between environmental variables and human health. Therefore research - the gaining of new information, the integration of existing information in new approaches and the development of the new tools to assess the complex environment and health interactions – is an essential part, a “cornerstone”, in the European Strategy on Environment and Health. Promotion of research in this field is one of the priorities for the Community action plan for Environment and Health currently under development. The baseline report gives a selected overview of the European research within the area of Environment and Health in general and in the priority areas identified in the Communication in particular. Research needs and priorities are indicated together with input for the action plan to be developed at a later stage.

To implement efficient environmental management policies, essential information and input from research must be made available. Thus, a good estimate of the population exposure distribution is needed. Whilst the lack of the “ideal” exposure study should not hinder the application of policies aiming at reducing environmental exposures and, ultimately, protecting human health, the objective should always be to get more accurate exposure information. Further, knowledge of the effect size and the shape of the exposure-response are essential. These latter tasks are the main focus of research in environmental health.

A technical working group (TWG) has been dedicated to research issues and research needs. The group consists of project leaders, project coordinators and project managers from projects funded under the 5th and the 6th Framework programs. Additional members have been appointed from the other technical working groups and through an open nomination procedure on Internet launched by DG ENV in summer 2003. These research nominees from the other TWG’s act as intellectual bridges between the groups with a role to communicate research needs and priorities to the Research Needs TW Group. The present Baseline Report is based on input from the other TWGs and from individual members of the TWG on Research Needs, as listed in the contributors list. The purpose of the Report is mainly to review existing knowledge and point to the most important gaps which will form the basis for the corresponding Action Plan. The first part is an executive summary of the different contributions.
2 Short summary of individual reports

Report on the implementation of the London Declaration and European Research

The London Conference recommendations have been addressed both to the national and international bodies responsible for funding research. This had a visible impact on the formulation of the EC Fifth Framework Programme on research (1999-2002). Environment and Health was the subject of one of its Key Actions (KA 4), with allocated budget amounting to €160 million. The programme has financed 83 collaborative research projects implemented in the EU Member States. It has also started thematic research networking, facilitating transmission of the research results to a variety of user groups. Areas included are risk assessment methodology, endocrine disrupters, allergy and allergens, pesticides, neurological effects genotoxicity, health impacts of air quality, water quality and drinking water, environmental factors and cognitive functions and electromagnetic fields. Additionally research efforts were undertaken to study health consequences of climate change in line with the recommendations of the London conference in the key action “Energy, Environment and Sustainable Development”. For the future it is recommended to concentrate on long-term funding to support cohort studies (birth cohorts, biological sample banks), multidisciplinary approaches, increased training of environment and health specialists, risk perception and communication and a strengthening of environment and health monitoring systems.

Research in the priority areas of the Environment and Health Communication

Traffic pollution, childhood allergy and asthma, and effects of long-term exposure on mortality

Traffic is likely the largest source of exposure to outdoor air pollution in Europe today. Traffic pollution has been implicated in many adverse effects on health. In the past 15-20 years, research on air pollution and health has re-emerged in Europe. European research has contributed to our understanding of short-term effects of particles, ozone, and sulfur and nitrogen oxides on mortality and hospital admissions for respiratory and cardiovascular disease; and on symptoms, lung function and cardiovascular changes in panels of asthma and cardiovascular disease patients. Similarly large contributions have been made to our understanding of effects or traffic-related pollution on respiratory disease and allergy in children; and of effects of large-scale changes in pollution levels on mortality and morbidity. Also, European researchers have been very instrumental in making quantitative assessments of the health impact related to air pollution exposures. More recently, concentrated efforts have started to better understand the toxicological mechanisms underlying effects of particles and potentially carcinogenic air pollutants on human health.

Throughout the 4th and 5th Framework Programmes, the Commission has played a vital role in fostering research with a European dimension on air pollution and health. The successive APHEA studies (Air Pollution and Health – a European Approach) have not only enormously improved our understanding of short term effects of air pollution on health. They have also stimulated the development of entirely new methods of analysis, and have spread excellence by training participants in many countries (including CEE countries) to use these methods. Similarly, EU funding has supported research that has improved understanding of Europe-wide exposures to PM10, Black Smoke and their effects on asthmatic children (PEACE study, Pollution Effects on Asthmatic Children in Europe). Emerging issues such as the effects on ultrafine particles have been the subject of successive studies conducted in Finland, Italy, Germany, Netherlands, UK, Spain and Greece (ULTRA studies, HEAPSS, RUPIOH). In the field of traffic pollution, EU funding has contributed to development of methods of exposure
assessment using Geographic Information Systems (SAVIAH) and application of such methods in birth cohort studies on development of allergy and asthma in young children (TRAPCA and AIRALLERG). Recent and ongoing toxicology studies are contributing significantly to our understanding of carcinogenic and non-carcinogenic effects of airborne particles (EXPAH, HEPMEAP, RAIAP). Research priorities for the future are: 1) Assessment of human exposure to traffic exhaust; 2) epidemiological and toxicological field studies of current exposures and of changes in exposure, 3) Health impact & risk assessment, 4) Toxicological evaluation of exhausts of different engine and fuel types, 5) Physico-chemical characterisation of traffic exhaust.

Impact of environmental factors on allergy and asthma

Allergic diseases and asthma pose an important and increasing problem for populations and health care systems around the world. During the past 30 years the prevalence of allergic diseases and asthma has doubled in the EU countries and it is rapidly increasing in Central Europe. Over 50% of the population of Europe is likely to be allergic within the next 10-15 years. The reasons for the rise in allergy and asthma remain unclear but epidemiological evidence indicates that this rise has been driven by changes in the social and physical environment. Research in this area is intense and there are at the moment 11 on-going or planned integrated projects or networks of excellence funded by EU. The overall objective of future research is to identify the environmental factors that are detrimental to allergy and asthma and moreover to understand the mechanisms involved and determine how to prevent or minimise these effects and risks. One of the key questions about children’s and adult environmental is why and when children respond differently to toxic agents as well the variation in human susceptibility to indoor and outdoor pollution is one the future issues to tackle. Furthermore the increasing complexity of the research questions in this field calls for better integration of studies, by standardisation of methods, health effect assessment and analysis, and by increasing sample sizes. A solution to tackle this fragmented knowledge is an internationally competitive network of European centres of excellence and European research projects. There is also a need for more prevention and precaution and the identification of the risks for human health, taking account of particularly vulnerable groups such as children.

Heavy Metals

A number of sub-options are proposed, supporting the Option Plan for Heavy Metals (consisting on four actions) detailing the work programmes needed to fill the knowledge gaps in our understanding of the exposure, effects, and the identification of new risks posed by toxic metals (not all toxic metals are ‘heavy metals’ in the traditional sense). These include programmes of work to:

a) determine the exposure to metals, metal compounds, and metal combinations from:
   1. known sources - where they may be included in existing monitoring programs,
   2. new sources, or routes, of exposure i.e. catalysts and additives, etc

b) that,
   • develop new effect assessment methodologies, for various media and exposure vectors, for metals, particularly soluble forms, (i.e. arsenic, cadmium, nickel, platinum, chromium, palladium, antimony); metal compounds (organ tins, nickel compounds, Cr$^{+3,+6}$, As$^{+3,+5}$); and combination of metals depending on the sources and different medium (for example: platinum & rhodium & palladium in air; mercury & arsenic in fish)
- Innovative work to increase the sensitivity and specificity of traditional methodologies as an aid to the establishment of dose-response relationships for low-level heavy metal exposures.

- Development of non invasive biomarkers for children

- Examine the possible effects of chronic exposures.

- Determine the increased risk due to genetic susceptibility.

c) develop risk assessment methodologies for metals, metal compounds, and metal combinations from previously unrecognised sources, which are found in the exposure vectors for children.

**Endocrine Disruption**

Endocrine disrupters have received considerable political and scientific attention recently. In 1999, the European Commission published a Communication on Endocrine disrupters (COM 706, 1999) which lists information gathering and research as priorities. In the 5th framework program, 60 MEuro has been spent on direct research on endocrine disrupters of which 20 MEuro were “earmarked” to as result of the Community communication (CREDO cluster). In future years, European research in the area of endocrine disruption should pursue the following topics: 1) Integrated exposure assessments of the full spectrum of endocrine active chemicals in human tissues and environmental media, including air, water and soil. 2) Establishment of biobanks with suitable human reference material, covering European countries with marked differences in relevant human disorders, 3) Research into biomarkers of effects and mechanisms underlying male and female disorders, strengthening links to fundamental research into mechanisms of hormonal carcinogenesis, 4) Systematic explorations of the relationship between exposure time and dose and of mixture effects, with a view to underpin better risk assessment by defining chronic effects of both single chemicals and mixtures, 5) Investigations of the link between exposure and health effects in males and females, building on better exposure information, differences in disease incidence between countries and taking account of combination effects, exposure timing and individual susceptibilities, 6) Research into the impact of lifestyle/environment factors on fecundity, precocious puberty and on fetal origins of male and female reproductive disorders.

**Dioxins and PCBs**

The existing situation is reflected in the WG’s Baseline Report. The research needs identified initially include:

- Information on the dioxin and PCB situation in some accession countries

- Understanding of the chain of events leading from industrial and other emissions to food, especially Baltic fish, and possibilities to clarify these steps

- Time series information is highly important for predicting future.

- Information on problems with Baltic herring and salmon; generally fish requires special attention

- Human intake (risk groups such as fishermen)

- Level of dioxin and PCB intake in the female population before the first pregnancy and the consequent body burdens.
• Research should be promoted in the EU to advance understanding in risk comparison and risk benefit assessment, in order to make more informed and better decisions possible in important environmental health issues.

• New groups of chemicals, such as brominated diphenylethers and other brominated compounds.

**Biomonitoring of children**

Surveys of children’s exposures to environmental factors eg heavy metals, dioxins, endocrine disrupters are ongoing in some European countries

• several EU-funded and nationally funded research activities focus on environmental impacts on the health of children

• a common European monitoring system is suggested to ensure sound and harmonised study design, availability of reliable tools for sampling and analysis, harmonised data treatment and adequate quality control

• collaboration of epidemiologists, toxicologists, exposure assessors and regulators, in order to develop and implement systematic biomonitoring systems to produce useful results for regulatory and/or policy decision-making is lacking in many of the activities reported.

• adherence to existing collaborative and supporting administrative systems within the research structure in EU is suggested to initiate integration and interdisciplinarity

**Research in Environment and Health of significance for the Communication**

**Environment and Health Implications of Electromagnetic Field Exposure**

Electromagnetic field (EMF) exposure from equipment such as power lines or mobile phone base stations and TV and radio transmitters are seen as a potential source of risk for the public health and the environment that present a difficult set of challenges for decision-makers. Research on possible health implications of EMF exposure is being carried out by a number of industrial, national and international funding bodies and by the European Commission (about 10 research projects in the 5th Framework Programme).

Future EMF research needs and priorities can be summarised as: **Extremely Low Frequency (ELF)**: studies on the role of duration and intermittency of exposure and on interaction mechanisms; **Radiofrequency Radiation**: studies on blood brain barrier, heat shock proteins, immune system, neural damage, hypersensitivity, genotoxic effects and molecular interaction; **Epidemiological studies**: prospective cohort studies of mobile phone users, studies on potential long-term effects of whole-body exposure to radio-frequency radiation, development of exposure and personal assessment; **Exposure of children**: studies on the association found between exposure to ELF and leukaemia; studies on potential higher sensibility and vulnerability of children to exposure to EMF; **Emerging technologies**: previously unexpected research, with an increased need for proactive measures due to the continuing introduction of new EMF technologies and devices at new frequency and modulation; **Long-term and occupational exposure**: exposure of workers, health operators and patients to high level of EMF; **Combined exposure**: exposure to both EMF and other physical, chemical or biological factors, as well as personal conditions (e.g., health status, pregnancy).
Climate change and climate variability

The European Science Foundation Report in 1999 made recommendations regarding research tasks for the health impacts of climate change and stratospheric ozone depletion:

- Improve the epidemiological and mechanistic science base and develop predictive methods for assessing the future health risks of human induced climate change and increased UV radiation.

This research priority is still valid and there is a need to develop appropriate strategies and interventions to reduce impacts on health. "The climate in Europe is changing, and extreme weather events in recent years have had a significant impact on human health (e.g. the August 2003 heat waves in France). Three projects funded in the EC Fifth Frameworks programme are currently addressing climate change and health. Several proposals are being reviewed under the 6th Framework Programme, and one Integrated Project that includes quantitative health risk assessment has been funded (ENSEMBLES). Future research should focus on: 1) Develop appropriate methods for quantifying and understanding of potential impact of climate change on human health. 2) Improve our quantitative evidence on the effects of heat waves and hot weather in order to understand the underlying mechanisms and how heat-related illness and premature mortality can be prevented. 3) Improve our quantitative evidence on flood-related health impacts and how they can be prevented. 4) Improve projections of the impact of climate on air quality, particularly tropospheric ozone. 5) Clarify the relationship between changing climate, allergens and allergic disorders and to improve forecasting accuracy and effectiveness. 6) Assess the potential effect of climate change on current and emerging vector-borne diseases in Europe, and develop risk management strategies. 7) Clarify the mechanisms by which changes in temperature and rainfall will increase the risk of infectious diseases. 8) Evaluate the health benefits and costs of measures for adaptation and mitigation. 9) Improve understanding of individuals' perceptions of, and responses to, climatic changes and resulting health impacts.

Environmental Health Genomics and Biomarkers

The recent completion of the sequencing of the human genome, in combination with technological advances in high-throughput characterisation of DNA sequences as well as RNA and protein expression, are revolutionizing biological research. By permitting a global view of cellular processes, these advances, which are covered by the areas of genomics, transcriptomics, proteomics, metabolomics (“-omics”) are driving a novel, systems-biology approach to the understanding of the working of the cell and how it responds to environmental stresses. The opportunities provided by these advances to environmental health research are immense and there is an urgent need for the European Union to formulate a concrete strategy for their development and application on a continent-wide scale. A concerted and sustained effort is required to develop a European-wide effort in the area of Environmental Health Genomics and Biomarkers which is expected to impart a major boost to our understanding of the basis of environmental disease. This effort should be based on the co-ordination and integration of multi-disciplinary activities, including 1) the discovery and characterisation of environmental response-relevant genes, 2) the charting of genetic variation in human populations, 3) the assessment of the functional impact of genetic variants on environmentally relevant genes, 4) environmental exposure assessment, and 5) the development, validation and exploitation of molecular biomarkers.
Water

Water is essential for life. Nevertheless, water as a carrier of chemicals and pathogens is at the same time one of the most severe threats to human health and well-being. Water quality — that every European citizen has access to good drinking water— has a high priority on the political agenda and several European directives ensure different quality aspects of the water cycle. Therefore, health-related water research has to be undertaken in an integrated way considering all parts of the water cycles (natural and anthropogenic). European research on water has been strongly supported in both the 4th and 5th Framework programs. In the 5th FP the key action “Sustainable management and the quality of Water” with a budget of 254 MEuro dealt with projects on management and monitoring of water resources, with pollutants in ground- and surface waters, regulation of water stocks in deficient regions and surveillance, early warning and communication of events in the global water cycle. Major future research challenges remains. They can be divided into technological, quality monitoring and surveillance and maintenance and management of water resources. The technological challenges include water purification, desalination, and wastewater reclamation and reuse in order to achieve sustainable water supply. The quality monitoring challenges include water-borne diseases (cholera, shigellosis, viral hepatitis A, typhoid fever) and new emerging threats (Legionella, viruses, protozoa, Cyanobacteria, low concentration of chemical pollutants) which all will require new surveillance methods. Research priorities are solar energy-driven purification and desalination, rapid sensors, biofilm analysis, molecular biology techniques, microbial source tracking methods, etc. An example is the development and validation of a DNA-chip technology for the assessment of the bacteriological quality of bathing and drinking water, in order to identify and quantify pathogenic bacteria directly in any water sample and to assess their state of activity.

From the health point of view it seems paramount to develop all water research considering risk and the precautionary principle in all cases.

Noise

Environmental noise has a major impact on the quality of life of those exposed and may in time lead to other health effects. In Europe 450 million people (65%) are exposed to noise levels above 55dBA, of which 113 million (17%) are exposed to levels above 65dBA and 9.7 million (1.4%) are exposed to levels above 75dBA. Levels above 65dBA, are thought in most people to cause annoyance and lead to sleep disturbance. Other adverse health effects include interference with communication, performance and learning as well as cardiovascular and immunological problems. Furthermore, leisure time activities can also produce noise levels potentially damaging to hearing. From results of research until today, 65-70 dB(A) outdoor sound level during day and 55-60 dB(A) during night (LAeq) may be quality targets for environmental policy regarding cardiovascular diseases based on current knowledge from research carried out in this area. Further, we do not see sufficient evidence for health effects in children exposed to community noise, however the current data base does not allow to conclude that effects may not occur in susceptible children or in a susceptible contexts (socio-cultural, environmental.). Stress hormones can be useful stress indicators in field and laboratory noise studies but their clinical relevance in noise studies is not clear compared to classical risk factors. Future research priorities include the health effects of a combination of exposures, for example air and noise pollution from road traffic or poor housing conditions and noise, environmental exposure to chemicals and noise as combined exposures may be more detrimental to health than each acting alone and particularly in vulnerable groups such as children and the elderly. Methodological issues including quantification of noise and health effects measures need to be further addressed.
Cost Benefit Analysis (CBA) + Health Impact Assessment (HIA)

Cost-Benefit Analysis (CBA) and Health Impact Assessment (HIA) are linked methodologies for assessing the costs and benefits of past, current and future policies. To date, research in and applications of HIA and CBA have focussed on outdoor air pollution, especially the ‘classical’ air pollutants, and on policies that affect them. There has been work on some other areas (e.g. metals, dioxins, noise). We see two kinds of research priorities: 1) There is a need to expand and include HIA of many other kinds of environmental issue 2) The work to date has highlighted a number of general methodological needs, specific to HIA and CBA, which will apply across all applications.

Indoor air

Exposure to indoor air pollutants is now recognised as participating significantly to a wide range of environmentally related diseases including allergies, short term and long term respiratory pathologies. Numerous chemical, physical and biological contaminants have been found indoors. They result from various sources including outdoor air, building materials and systems, indoor activities, etc... for many of them the concentrations found indoors are higher than outdoor. Several projects at European level have been conducted in this field during the last two decades. Among those, exposure surveys to air pollutants have underlined the prominent contribution of indoor spaces to the global exposure for most pollutants even for those being already regulated outdoors like benzene, particles, NO₂, CO, etc. Research needs should consider to what extent indoor air pollution is affecting health of the European citizens and in particular what is its contribution to acute and chronic health impacts (including asthma and respiratory allergy) and what are exposure patterns, determinants and implications for safety thresholds. Future research should address indoor air exposure surveys, exposure measurements, health effects measurements, risk assessments, networking Indoor exposure data bases, modeling of exposures and effects in buildings, standardization and harmonization and facilitate cross fertilization across Europe and multidisciplinary approaches. Few emerging issues in direct or indirect connections either with general scientific progress or with buildings construction and management changes are also to be considered.

Environmental exposure and the risk of adverse reproductive outcomes

An assessment of the state of research on the role of environmental hazards in the development of adverse reproductive outcomes has been focused on three exposure scenarios recognised as the most prevalent in Europe, and four additional ones that are of importance for specific local populations. The first group included air pollution, environmental tobacco smoke (ETS) and environmental noise, and the second one trihalomethanes (THMs) in drinking water, hazards from waste landfill sites, residential exposure to pesticides and organochlorine-contaminated food. All major adverse reproductive health outcomes have been considered, taking into account their high prevalence in the European population: infecundity, spontaneous abortions, birth defects, fetal deaths, low birth weight (LBW) and SGA. The increased risk of LBW was the most consistent finding of the studies on populations exposed to ETS, environmental noise, waste landfill sites and organochlorine contaminated food. The increased risk of SGA infants was associated with exposure to air pollution, environmental noise and THMs. The elevated risk of infecundity was related to exposure to THMs, organochlorine-contaminated food and to residence close to waste landfills. Spontaneous abortions were mainly linked to exposure to THMs and organochlorine-contaminated food. As regards birth defects, an increased risk was confirmed only in populations living in the vicinity of waste landfill sites, while excess risk of fetal deaths was observed in rural residents exposed to pesticide drifts. The biological mechanisms by which the examined environmental factors affect reproductive outcomes have not been...
clearly established for any of them. The most advanced research in this field so far has been performed in relation to the effects of exposure to air pollutants, ETS, environmental noise and organochlorine contaminants in food.

Environmental factors and cardiovascular disease

Evidence has been found that environmental exposures such as environmental tobacco smoke (ETS), ambient air pollution, noise, and extreme weather conditions are associated with mortality and morbidity from cardiovascular diseases, in particular ischemic heart diseases. However, little is known on the role of these environmental exposures in young adults in initiating and promoting asymptomatic states of cardiovascular disease, their role in determining the severity of cardiovascular disease latter in life, and their potential to trigger acute events of cardiovascular disease like myocardial infarction. European research has addressed these issues. Health effects of ambient air pollution and noise are being addressed as part of the “Quality of Life” program – key action 4 as part of the 5th framework. While its major focus for air pollution is on respiratory health there are studies being funded assessing acute health effects of air pollution in patients with cardiovascular disease. Future research priorities are 1) acute exacerbation of cardiovascular disease by environmental exposures in triggering myocardial infarction, arrhythmia, sudden cardiac death, acute coronary disease based on pre-existing cardiovascular disease, on genetic predisposition and on individual risk factor profiles including early physiological changes in different population subgroups ranging from children to patients with cardiovascular disease. 2) Chronic effects of environmental exposures on cardiovascular disease, ie cardiovascular disease morbidity and mortality, role of socio-economic status and unhealthy life-styles in augmenting the impact of environmental exposures, genetic susceptibility to develop cardiovascular disease and role of chronic environmental exposures on initiating and promoting atherosclerosis.

Cocktail effect – cumulative risk assessment – combined exposure

Exposure - the assessment of relevant exposures, the methodology to assess exposure and the models to develop a global Environment and Health exposure concept – are key issues in the assessment of environmental impacts on human life. Human health risk- and exposure assessment has until now principally been dealing with one “threat” at a time, being it a chemical, a pesticide or radiation to name a few. However, when targeting environmental factors and human health we have to realise that we in our normal life never are exposed to a multitude of risk factors at a time. Currently the methodology to assess and deal with these complex exposure situations is weak or non-existing. The “cocktail-effect” problem is highlighted in several EU policy documents, but only in few European scientific reviews. Most research exists out in the area of air pollution/respiratory diseases and asthma, but it must be expanded also to other priority diseases. Science on interactions, multi-exposure and biomarkers must be prioritised, but at the same time be more policy relevant using different assessment concepts. A strong research initiative is needed in this field and this is one of the real challenges for environment and health research for the future.

Environmental stress and children

Children represent a very particular type of user of the living environment. Physiologically and psychologically they may respond/adapt to and cope with these stressors differently from adults. Also their time-use pattern is different from adults, the former spending more time outdoors than the latter. Various index number specific to children are not formulated: prevalence, dose-response curves are missing. More general little, is known of the impact of context (when, where, with whom) on the exposure to and perception of ambient stressors. Finally, long-term effects have been studied seldom due to lack of studies with longitudinal
designs. What we need are large scale epidemiological studies to assess prevalence and establish dose-response curves, in-depth studies (e.g. diary studies) to collect data on time, place and person and studies with longitudinal design to assess long-term (health) effects of exposure to ambient stressors in children in their daily life.
3 Report on the implementation of London Declaration decisions

Environmental Health Research for Europe

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Situation assessment

- A substantial number of research projects on environment and health was funded in the years 1999-2002 in the scope of the 5th Framework Programme of the EC DG RTD. This programme covered many, though not all, priority research areas identified in preparation to the London Conference. The projects provided, or will provide soon, important information supporting environmental health policy making, e.g. in relation to health impacts of air pollution.

- However, the lack of clearly identified area of European research on environmental health in the current EC research programme, coupled with limitation in national funding of the research, restricts the possibility for dedicated collaborative studies. We recognise that this might result in a significant reduction of new information available for the support of environmental health policies in Europe and inevitably have an impact on the level of available expertise in the near future.

Fulfilment of the commitments

The London conference recommendations were addressed both to the national and international bodies responsible for funding the research as well as to the research community applying for the funding and shaping their work according to the research priorities formulated in the process leading to the London conference. To disseminate the conclusions of the London and to discuss its possible role in the follow up, the ESF convened a conference of the interested parties in Munich in October 1999. At that time, the 5th Framework Programme was covering more than 80% of the research priorities identified in London. Lack of specific resources assigned in WHO to actively promote and systematically monitor the implementation of the London conference recommendations restricted ability to provide a comprehensive assessment of the national activities which might have been developed according to the London conference recommendations. Therefore, evaluation of progress in environmental health research over the recent four years is mostly based on the results of the conference “An Environment for better health” organised in Aarhus, Denmark, on 8-10 May 2003, by ESF and WHO in collaboration with the Research Centre for Environment and Health of the Danish Ministry of the Interior and Health in Aarhus and with the contribution of EEA, and supported by the EC DG Research funds. It provided a concise overview of the main research projects related to environment and health implemented in Europe in the recent five years. Invited speakers reviewed the progress in their research areas based on published reports and their knowledge of the subject. This overview was supplemented by the oral or poster presentations of (mostly EC sponsored) individual projects. Close to 100 conference participants contributed to the discussion and formulation of conclusions and recommendations. Brief analysis of the conclusions from the Conference is presented in the next section of this report.

The discussion on the environmental health research in the framework of the ESF-lead programme and implemented in collaboration with the EC and WHO prior to the London conference had a visible impact on the formulation of the EC Fifth Framework Programme on research (1999-2002). Environment and Health was a subject of one of its Key Action 4, with
allocated budget amounting to €160 million. The programme has financed 83 collaborative research projects implemented in the EU Member States. It has also started thematic research networking, facilitating transmission of the research results to a variety of user groups. Most of the projects funded in the framework of this EU programme were presented at the Aarhus conference. Final conclusions from this research are still to be seen, as many projects are still going on, but it can be expected with confidence that this intensive effort will provide a valuable input to the knowledge base of the future environmental health policies.

In line with the recommendations of the London conference, research was undertaken to study health consequences of climate change. WHO, for example, coordinates a project “Climate change and adaptation strategies for human health” (cCASHh) financed by the 5th FP of the EC DG Research (key action Energy Environment and Sustainable Development). This 25-country project has the objective to enhance communities’ capacities to adapt to climate change. The areas covered are heat stress, floods, food borne diseases and vector borne diseases. For each of these areas health impact assessment, policy analysis, cost benefit analysis and integrated assessment methodologies are used.

Important role of environmental health research in shaping European policies and actions on environment and public health is stressed in, respectively, 6th Environmental Strategy (adopted in 2002) and in the Public Health Strategy of 2003. Unfortunately, the European Union’s 6th FP on RTD does not contain a specific set of actions related to this topic. Though certain possibilities for funding environmental health projects exist in the scope of other areas of research, such as “Food Safety and Health Risks”, the chances for a substantial funding of research successfully initiated under the 5th FP are significantly limited.

Analysis

The Aarhus conference (May 2003) provided an opportunity to review many, though not all priority areas of research selected in the process preceding the London Conference. The main conclusions concerning these selected areas are as follows:

Cross-cutting issues: risk assessment: New studies address several health outcomes of public health concern, deal with exposure levels relevant for environmental situations and elaborate methods possibly enabling quick and effective risk assessment of new compounds. In particular, the following issues have been considered:

- **Endocrine disruption:** An European Research Cluster on Endocrine Disruption (CREDO) has been established. The aims of CREDO, that involves more than 60 laboratories, are to produce scientific data to support the Community Strategy on Endocrine Disrupters and to establish a focus for endocrine disrupter research in the EU. The projects include both epidemiological and mechanistic studies on effects of prenatal and early life-stage exposure to organo-halogens on different biological endpoints, e.g. osteoporosis or fertility. An important goal for some studies is to develop biomarkers to assess human exposure.

- **Allergens:** Three networks deal with children and allergy e.g. placental uptake and transfer of environmental chemicals relating to allergy in childhood years. Several projects focus on development of new testing procedures for skin allergens and on methods to increase the safety standard of fragrance compounds. One project focuses on timing and seasonality of allergens and their health impacts.
• Pesticides: Several projects assess immunotoxic activity and effects on embryonic development of low doses of pesticides. Exposure models and scenarios for assessing the predicted environmental concentrations of pesticides in groundwater and air will have been developed.

• Neurological effects: The role of genetic, environmental and occupational risk factors for the development of Parkinson’s disease is studied in one project. New methods for predictive toxicity testing of neurotoxic volatile chemicals are being developed.

• Genotoxicity. A limited number of mechanistic studies in this area are ongoing with focus on different known carcinogens, e.g. PAH or asbestos substitute fibers. New methodologies to detect aneugenic chemicals to be used in risk identification are being validated.

Specific research areas:

• Air quality: Several projects were conducted, and results of some were already included in WHO synthetic analysis prepared to support the development of European Clean Air for Europe programme. The topics studied include the impacts of air pollution on incidence and prognosis of allergy, allergic disease and lung function, and on respiratory health in children. New studies include assessment of exposure to fine particles, e.g. in a study on inflammatory responses to the exposure in a high-risk group and in the study on cardio-respiratory toxicity of particles. Several studies addressed the role of exposure to microbiological factors in the farming environment during pregnancy and early infancy on the development of immune function. Biomarkers of exposure and markers of genetic variation are used in several studies related to PAH or traffic-related air pollution exposure. Several studies focused on improvement of methods of exposure assessment and on screening tools to assess new technologies affecting air quality (e.g. fuel additives, combustion technologies etc.). Integration of the research from various studies is planned to be achieved by comprehensive risk assessment projects and through the activity of thematic network AIRNET which collects, interprets and disseminates data from individual EU-funded projects on air pollution and health, in order to strengthen the science-policy interface and to draw policy-relevant recommendations.

• Water quality and drinking-water: Major challenge to research in this area remains effective surveillance of water-borne diseases, in particular of cholera, shigellosis, viral hepatitis A and typhoid fever. New emerging threats (e.g. protozoa, cyanobacteria, low concentration of chemical pollutants) require new surveillance methods as well. New solutions in water treatment and monitoring technologies will be needed to achieve sustainable water supply. The research focuses on rapid sensors, biofilm analysis, molecular biology techniques, microbial source tracking methods etc. An example is the development and validation of a DNA-chip technology for the assessment of the bacteriological quality of bathing and drinking water, in order to identify and quantify pathogenic bacteria directly in any water sample and to assess their state of activity.

• Environmental effects on cognitive functions. Several studies address the impacts of noise on various aspects of health, and in particular on health and development of children. This research will provide guidance for location and new building codes for the building of new schools. Biomarkers for assessment of hazardous exposures for neurotoxicants and for early detection of cognitive effects are being developed, taking advantage of a birth cohort.
- Climate changes and ozone depletion. The studies look at the consequences of exposure to UV radiation on the skin as well as on the immune system and its adaptation. Effects of environmental and climatic variables on health are studied using database of meteorological variables, health indicators, and air pollution data with the overall objective is to develop a Human Health Watch Warning System.

- Electromagnetic fields. The ever-present exposure to EMF is of high concern to the public. Intensive research has not been able, until now, to provide conclusive results regarding a potential health risk of the exposure.

**Recommendations**

High quality environmental health research reminds a cornerstone of effective environmental health policies and actions, and the knowledge that it generates is a pre-condition for creation of environments supporting population health. The previous Public Health and Environmental programmes of EC acknowledge this conclusion of London ministerial conference. Therefore further effort of international and national research organizations is needed to assure appropriate resources for this research. As indicated by the analysis of the recent developments, the following issues should be taken into consideration:

- **Effective research on numerous environmental health issues involves long term (multi year) study, requiring long term sustainable funding.** Lack of such European funding for environmental health is one of the reasons that badly needed studies based on a long term follow up of cohorts (e.g. birth cohorts, particularly relevant to the environmental impacts on children health) are scarce in Europe. Examples of such European studies having a sustainable, long term funding for core activity, such as maintenance of a biological samples bank, exist in other areas of health research. They prove high effectiveness of this approach and its value for both advance in knowledge on aetiology of major diseases, including identification of genetic susceptibility and the role of risk factors (e.g. EPIC study on nutrition and cancer). They are crucial contributions to the development of effective disease prevention programmes.

- **The multi-disciplinary research approaches are needed to effectively tackle health consequences of various environmental situations.** Funding mechanisms should facilitate and encourage organization of such multidisciplinary research as well as multidisciplinary, policy-oriented discussions formulating topics of the research.

- **Training** of environmental health specialists both for further research and for public health practice is an important output of the research projects. Decreasing emphasis on environment and health in university curricula and in research funding restricts inflow of capable individuals to this discipline limiting expertise base for the future public health policy making and interventions.

- **An important area of research necessary for effective use of the knowledge accumulated by the environmental health research is risk perception and communication.** Better understanding of the factors determining response of the society to public health messages would enable more effective public health interventions.

- **Environmental health monitoring** should be strengthened and based on the best available knowledge of the environmental health links. Though often considered to be marginal for environmental health research, it is an essential tool for implementation of environmental
health policies. Results of the monitoring should be also used by the research as a guide in selection of research topics the most relevant for current public health problems.

- Future European research funding mechanisms (e.g. the next EC RTD framework programmes) should enable and clearly promote the highest quality European collaborative research on environmental health.

However, one should emphasise that these conclusions have to be considered as indicative and should be a subject of further discussions to reflect the complexity and diversity of the present status of research related to health-environment interactions.
4 Input from other technical working groups (TWGs)

4.1 TWG neurodevelopmental disorders

The baseline related to neurodevelopmental disorders is described in detail in the baseline report of the corresponding technical working group\textsuperscript{1}.

4.2 TWG respiratory diseases

The baseline related to neurodevelopmental disorders is described in detail in the baseline report of the corresponding technical working group\textsuperscript{1}.

Compilation of the proposals from Paul van Cauwenberge, Thibaut Van Zele and Peter Helms

Key words:

Children; Infants; Adolescents; Atopy; Respiratory health; Lung; Development; Disease; Environment; Asthma; Allergy; Cystic Fibrosis; SIDS (sudden infant death syndrome); Infection; Definition; Diagnosis; Treatment; Cohort studies; Indoor; Outdoor; Pollution; Tobacco; Genetics; Research; Policy; Integration

1. Introduction

In a European context the diseases of greatest interest affecting the child’s respiratory system are asthma and related allergies, pneumonia, viral bronchiolitis, measles, tuberculosis, HIV infection, sudden infant Death Syndrome (SIDS) and cystic fibrosis. With the exception of SIDS, these fall into three categories, allergic, infectious and genetic although all are strongly influenced by environmental exposures.

Environmental factors play an important role in altering host resistance to respiratory diseases in childhood. It is likely that the accession of a number of former Soviet Union countries to the European Union will be accompanied by changes in the patterns of disease among children in those countries. These are likely to include increases in asthma and allergic conditions and decreases in serious and life threatening infections. It is recommended that prospective research be targeted at such changes in order to establish likely causative factors and methods of intervention.

Many environmental factors thought to influence children's respiratory health remain unclear and somewhat controversial. This is especially the case with respect to asthma and allergies. Since it is likely that these conditions will increase in a number of European countries over the next decade, it is important to target research towards this area. Hence the recommendations to investigate the influence of the environmental and potentially modifiable factors while recognising that the risk factors may differ between the respiratory diseases and respiratory symptoms of childhood. Once these issues have been clarified, it is recommended that European-wide intervention trials be carried out. As the burden of childhood respiratory disease is greatest in the young and most asthma and related allergies first present in early life the most informative studies are likely to be prospective birth cohorts and support for their initiation and for aggregation of existing and prospective well designed studies is urgently

\textsuperscript{1} A syntheses of the baseline reports of the working groups established in frame of the EU Environment and Health Strategy can be found at the following URL: 
For the whole Baseline Report of the group see http://www.rome-conference.org/
required.

It is highly unlikely that there is any single measure that will reverse the rise in asthma and allergies in prosperous countries, since these diseases have multiple interacting causes. There is therefore a need to address all the identifiable risk factors and to establish the evidence base for whole population interventions by systematic reviews of existing evidence and by further research in the areas of uncertainty including the medium to long term outcomes of exposures in early life.

1.1 Allergy and asthma

Allergic diseases and asthma pose an important and increasing problem for populations and health care systems around the world. European research groups have been at the forefront of investigations into the causes and management of these conditions. The past 40 years have witnessed a dramatic increase in the prevalence of allergic diseases and asthma, which now represent a major and increasing global health problem. During the past 30 years the prevalence of allergic diseases and asthma has doubled in the EU countries and it is rapidly increasing in Central Europe. Over 50% of the population of Europe is likely to be allergic within the next 10-15 years. Asthma and allergies can be severe and life-threatening. In addition allergic diseases and asthma impose an important burden on society, affecting school children and their parents, affecting the ability to work, increasing health care costs and impairing the ability of a large part of the population to play a full role in society. The costs of allergic diseases and asthma to society are substantial and are increasing more than other health costs. The reasons for the rise in allergy and asthma remain unclear but epidemiological evidence indicates that this rise has been driven by changes in the social and physical environment.

1.2 Geographical variation

There are important differences in the prevalence of childhood respiratory diseases in different European countries; as a generalization, there is more asthma and allergy in the prosperous west and more infective disease in the poorer East. There are also North-South differences in the prevalence of asthma and allergies. These speak for important and perhaps correctable environmental factors either in their causation or in their triggering.

1.3 Multi causality

Many different and specific combinations of factors are responsible both for individual cases of disease and for particular fractions of total disease. It follows that there are many cause-effect combinations in differently configured causal chains.

Such multi-causality provides many obstacles to understanding the mechanisms and factors in the causal chain but it also provides many opportunities for removing links in the chain and thereby preventing harm, particularly where there are inter-dependencies between causal factors, such that removing even small links can reduce the impact of both those causal factors and others that may depend on them.

In other words: “the genes provide the bullets but the environment provides the triggers”; and “Biology is not necessarily destiny”.

1.4 Causes and triggers

Whereas some acute and chronic respiratory diseases and illnesses have clearly identifiable
causes, e.g. bacterial and viral pneumonias, others including asthma related respiratory allergies and bronchitis have a variety of potential causes and environmental stressors. In this context it is important to separate potential environmental causes or initiators of diseases such as asthma from environmental “triggers” of already existing disease.

1.5 Definitions

Definitions of childhood respiratory disease also need to be considered as they can distort what appear to be important regional differences in disease expression. In this regard childhood bronchitis and asthma are good examples. Asthma has been defined as intermittent episodes of airway obstruction that either resolves spontaneously or with treatment. This definition separates it from chronic progressive obstructive lung disease typically seen in middle to late adult life and which is less responsive to therapy. However, the term “bronchitis” is more widely used in Central and Eastern Europe than in Northern and Western European countries.

1.6 Genetics

Although pulmonary disease may accompany a number of genetic disorders in children and some pulmonary diseases have a genetic basis this is seldom based on simple Mendelian inheritance but rather on polygenic or multifactorial aetiology. A clear exception to this is cystic fibrosis, which results from a variety of mutations in a single gene located on chromosome 7q that encodes the CFTR protein.

Asthma on the other hand is a complex, polygenic disease that results from exposure of genetically susceptible individuals to environmental triggers, possibly at critical stages of development. There are already several hypotheses regarding interactions between genes and environment relevant to the programmes on nutrition, infection and environment. The variability of environmental exposure across Europe makes this an ideal environment in which to carry out these studies.

1.7 Fetal programming

There is growing evidence that fetal life and early childhood are critical periods of development during which many diseases that present during child and adult life may have their origins. In humans and other long-gestation species, the development of lung architecture occurs during fetal and early postnatal life.

1.8 Gender

Gender differences in the development, diagnosis and treatment of asthma and allergy have received little attention. Asthma is initiated in childhood with the majority of cases first presenting under 5 years. In early childhood there is a male excess of asthma cases with a male:female ratio of approximately 2:1. During adolescence this ratio reverses to a female predominance. Too little is known on the effect of hormones in both sexes as potential modifiers of environmental factors. Results currently suggest a greater effect of smoking and air pollution on respiratory consequences for women than for men. Too little is known in this area because analysis of data has generally considered gender only as a potential confounder and not as an effect modifier. A careful identification of the similarities and differences in health needs of men and women and their biological, environmental and socio-cultural determinants is a prerequisite for promoting gender equity. Further evidence for these sex patterns is apparent in hospital admissions with asthma. This characteristic pattern may be
informative in understanding the origins of this complex disease and in formulating novel therapies.

2. Ongoing research at European level

**PIAMA: Prevention and Incidence of Asthma and mite Allergy**
The PIAMA birth cohort study was started in 1996 to study the effects of the application of mite impermeable mattress and pillow covers on the incidence of allergy and asthma over an 8 year period especially in children at high risk to develop asthma or respiratory allergy. A second aim was to study the incidence of allergy and asthma in relation to various risk factors. The intervention measures have resulted in a significant reduction of mite allergen exposure. Clinical effects have not yet been observed, but were not expected to manifest themselves in the first few years of life. The study will be continued over the next years with yearly questionnaires, and with a medical investigation at age 8.

**PARSIFAL: Prevention of allergy – risk factors for sensitisation in children related to farming and anthroposophic life style**
The ultimate aim of the project is to strengthen the basis for effective prevention of allergy in children, which has reached epidemic proportions in Europe and elsewhere in recent decades. It focuses on farming and anthroposophic children, two groups with a low prevalence of atopic diseases and sensitisation, but for which specific protective factors have not yet been identified. Specific objectives include assessment of the role of certain environmental and lifestyle factors for the development of allergy in children, such as diet, vaccinations, infections and animal contact. In addition, the influence by indoor microbial contaminants and the intestinal microflora is studied. Initially, this project will identify children in farming and anthroposophic families in five European countries: Austria, Germany, Netherlands, Sweden and Switzerland. A total of around 6,000 children aged 6 to 12 years are investigated according to a common protocol among farmers, families with an anthroposophic life style and controls. A questionnaire survey is carried out among the children to assess certain exposures, such as diet, animal contact, and history of infections and vaccinations, as well as atopic manifestations. In addition, validations will be performed within the project of bronchial hyperreactivity and dietary history.

Determinations are made in a central laboratory of biological contaminants in stables and other indoor environments, allergen specific IgE-levels in serum and intestinal microflora, respectively. The overall analyses and evaluation is aimed at identification of environmental and lifestyle factors explaining the lower rate of allergy in children of farmers and in anthroposophic communities as well as to indicate effective strategies for prevention.

**AIRALLERG: Effects of outdoor and indoor air pollution on the development of allergic disease in children**
The proposed study will investigate the relationship between allergic sensitisation and disease and a number of specific indoor and outdoor pollutants. The study will be conducted in the framework of three ongoing birth cohort studies in Sweden, Germany and the Netherlands. Data on allergen exposure, traffic related air pollution (NO$_2$, PM$_{2.5}$, diesel soot) and allergic sensitisation and disease will be available. Data on indoor air pollution (nitrous acid, NO2 and Environmental Tobacco Smoke) and microbial contaminants in house dust (endotoxin mould components) will be collected. Four groups will be compared: children with sensitisation and symptoms, children with sensitisation without symptoms, children without sensitisation with symptoms, and children with neither. The study will provide important new insights into the combined role of indoor and outdoor pollutants in the development and expression of allergic disease in children.
**PDCAAE** Prevalence and determinants of childhood asthma and allergies across Europe

The PDCAAE project will use data and specimens from fieldwork in representative community random samples of 9-11 year old children in 15 study centres in 13 countries across Europe. The studies are conducted according to the Phase II protocol of the International Study of Asthma and Allergies in Childhood-ISAAC. In each centre at least 1,000 children are studied using parental questionnaires, skin examination for flexural dermatitis, skin prick tests, blood samples and bronchial challenge tests with hypertonic saline. Dust samples are collected from homes of stratified random samples of children (100 children of those with wheeze during the past 12 months and 100 without wheeze). Detailed information on known and suspected risk factors for asthma and allergies in children will be collected by parental questionnaires.

Indoor exposure of children will be assessed by measurements of allergen and endotoxin content in house dust samples which will be performed at the universities of Wageningen (endotoxins) and Linkoeping (allergens). Levels of total and allergen specific serum IgE will also be determined in Linkoeping. Analyses of gene polymorphisms reported to be associated with childhood asthma and allergy will be conducted at the University of Oxford. All data on fieldwork and laboratory analyses will be submitted for central data management and analysis to the coordinating and data centre at the University of Muenster. Statistical analyses will also be performed by the respective partners in Linkoeping, London, Oxford, Munich and Utrecht.

**RUPIOH:** Relationship between Ultrafine and Fine Particulate matter in Indoor and Outdoor air and respiratory Health

A panel study will be conducted in which 35 non-working, non-smoking patients with asthma, chronic obstructive pulmonary disease (COPD) or other chronic respiratory conditions will be followed for six months in four cities in Finland, the Netherlands and the United Kingdom.

This project will test the following hypotheses:

- The correlation between central site and indoor particle number counts is lower than the corresponding correlation for PM10 and PM2.5
- The ratio between indoor particle number counts and central site particle number counts is lower than the corresponding ratio for PM10 and PM2.5
- Spatial variation of outdoor particle number counts is larger than for PM2.5 and PM10 and this contributes to the lower correlation between central site and indoor measurements
- Health effects of particle number counts are underestimated by characterizing exposure though central site measurements
- The comparison of the health effects of indoor and outdoor particulate matter exposure will focus on the intensive measurement week. If a model linking indoor measurements with outdoor measurements and diary information is sufficiently precise, indoor exposures during the complete six months period can be generated. This would allow comparison of health effects of indoor and outdoor exposures in the full diary period as well.

**NLCS-AIR:** Long-term effects of traffic-related air pollution on respiratory and cardiovascular mortality

Long-term exposure to particulate matter air pollution has been associated with increased mortality in the US. However, it is unclear whether these results apply to Europe. An association between long-term exposure to traffic-related air pollution and mortality was found in a cohort of elderly adults. However, the findings need to be replicated in larger study
before causality can be accepted. The NLCS-AIR study investigates the association between long-term exposure to traffic-related air pollution and mortality and lung cancer incidence in the full NLCS cohort (N ~ 120,000). Exposure will be characterised as a function of a regional, urban and local component, with improvements compared to the exposure estimate method used in the pilot study.

**AIRNET: A thematic Network on air pollution and health**

The main objective of the Network on Air Pollution and Health is to create a widely supported basis for public health policy related to improving air quality in Europe and regulatory needs to achieve that goal. Furthermore this thematic network will develop an interpretation framework for the (final and intermediate) result of research supported by the FP4 and FP5 programmes, as well as nationally funded studies and collect, discuss and interpret the (final and intermediate) results of research supported by the FP4 and FP5 programmes, as well as nationally funded studies. The framework will focus on assessment of the public health impact potentially associated with the findings of the studies, on assessment of potential consequences of such impacts for the level of current air quality directives, and on assessment of potential further policy consequences. The findings of research on air pollution and health will be evaluated in the light of the framework developed.

**RAIAP: Respiratory Allergy and Inflammation Due to Ambient Particles**

The overall objective is to assess the role of ambient suspended particles in causing local inflammation in the respiratory tract and induction and elicitation of respiratory allergies, in order to understand the underlying mechanisms for an involvement of particles in the development of these diseases. Specific objectives are: to characterise representative particulate samples from a western, an eastern, a northern and a southern European city and a sea-side site by physical, chemical and immunological methods; to screen the samples for allergenic and inflammatory potential; to verify findings from the screens in in vivo inhalation models; and to study mechanisms underlying the allergic and inflammatory effects. The establishment of a role of ambient particulate matter in respiratory allergy and asthma is of clear public health importance, as on such a link preventive measures can be taken to improve the quality of life and health of European cities.

**HEPMEAP: Health effects of particles from motor engine exhaust and ambient air pollution**

The primary concept is the novel approach of combining 'state of the art' expertise from the fields of epidemiology, toxicology, antioxidant research, chemistry, physics, clinical respiratory medicine and allergy, to address particulate matter (PM) adverse effects. The foundation lies in correctly sampling ambient PM done in association to an established European epidemiological project, as well as freshly generated diesel and gasoline engine PM using state-of-art slit samplers. The physico-chemical characteristics of the particulates, including transition metals and hydrocarbons are to be determined and used in the later parts of the project to find explanations for variations of bioactive effects.

Following this first stage, PM samples will be screened for their bioactivity by in vitro methods including ELF and an array of representative airway cell types. Particles shown to have strong oxidant capacity will be further investigated to determine free radical activity the signalling mechanism between particles and pulmonary target cell, and the mediators of the inflammatory response. The generated information will be used to investigate in vivo toxicity of selected ambient and experimentally generated PM samples in laboratory animal models. Additional characterisation of the biomedical responses in man will be undertaken (using environmental chamber exposures with freshly generated PM from gasoline engines) in relation to diesel exhaust PM in healthy volunteers. Further provocations will be conducted in
local airway segments to selected ambient PM and diesel and gasoline PM. Asthmatics, COPD patients and controls will undergo challenges followed by induced sputum sampling to evaluate the usefulness and relevance of this less invasive method.

The final step will be for the epidemiologists and statisticians to relate the results of the physico-chemical PM characterisation and the in vitro, animal and experimental human studies to the epidemiological findings

**PAMCHAR:** Chemical and biological characterisation of ambient air coarse, fine and ultrafine particles for human health risk assessment in Europe

The PAMCHAR project has selected six urban traffic and industrial sites in different parts of Europe (Amsterdam, Athens, Barcelona, Duisburg, Helsinki, Prague) to represent contrasting ambient air PM pollution situations (e.g., fuel combustion in winter, resuspended and wind-blown dust in spring, photochemical smog in summer). In these sites coarse, fine and ultrafine particles will be collected. These collected samples in each city are pooled to form a large mass to be divided into multiple chemical analyses and biological in-vitro and in-vivo tests. The key cytotoxic and proinflammatory findings in these in-vitro studies will be investigated in primary cultures of human nasal cells, and in intratracheal instillation exposures of healthy mice and compromised rats by measuring response markers in the bronchoalveolar lavage fluid.

3. **Important gaps in knowledge**

- Constituents of the indoor environment that impact on the respiratory health of children. Focus on new building materials and agents used within the home.
- Interaction between external and internal (home) environments.
- European definitions of chronic childhood respiratory symptoms.
- Evidence based reviews of environmental hazards possibly relevant to childhood allergy and respiratory health.
- Role of protective environmental factors on the development of allergy and asthma.
- Influence of the anthroposophic life style on the prevention of allergy and asthma.
- Important gene/environmental interactions and identification of susceptible population sub groups.
- Medium to long term effects of exposures for allergy and respiratory health (Birth and child cohorts).
- Effects of exposure to indoor and outdoor air pollution at different stages of development.
- Synergistic effect of toxic agents in the development of asthma and allergy
- Why and when children respond differently to toxic agents as well the variation in human susceptibility to indoor and outdoor pollution

4. **General research needs**

- Development of appropriate biomarkers and methodologies for identification of individual susceptibility to allergy and asthma
- Development of and validation of systems for monitoring Environment and Health, by for example utilising existing School doctors, Nurses etc.
- Surrogate indicators such as proximity to main roads, tobacco sales, hospital admissions for respiratory exacerbations.
- Define the role of ambient particulate matter in childhood allergy and asthma
- Data collection on (children’s) medicine use;
- Improve data quality in the new EU countries
- Acquiring and disseminating the evidence for public health actions.
- Building research capacity in Child public and environmental health.
- Recommendation for CDC (Centre Disease Control) not only to monitor infectious diseases but also monitor the ‘environmental diseases’. (Or consider the establishment of other body/centre for environmental diseases.)
- Addressing challenges of aggregating and accessing relevant databases (Data protection legislation and its interpretation);
- Identification of genes accounting for regional and ethnic differences in the EU population. This set of indicators would help identify “intelligent” cost-effective strategies for prevention of the onset and exacerbation of children respiratory health disorders and allergies
- Medium to long term consequences of exposures in early life.
- Assess the protective effect of several agents (e.g. endotoxins) on allergy and asthma
- Assessment of the exposure – effect relationship
- Establish an internationally competitive network of European centres of excellence and European research projects including several established by the 5th Framework to enhance the quality and relevance of research in this area.
- Assist EU and national policy makers to make recommendations and directives from the knowledge of the interaction between the environment and susceptible genes in the onset and progression of allergy and asthma in order to reduce their burden in all regions of Europe.

5. Specific recommended actions and research needs.

5.1 Indoor environment

European children spend up to 90% of their time indoors and in many European countries. Of all indoor exposures the most clearly identifiable is environmental tobacco smoke and which has a wide range of clearly established adverse health effects, particularly on the developing respiratory system hence the emphasis on this particular exposure.

5.1.1 Environmental tobacco smoke

Exposing the fetus and children to environmental tobacco smoke (ETS) adversely affects the health of children and may have lifelong consequences. ETS is a major risk factor for sudden infant death, leads to a decrease in pulmonary function, increased lower respiratory symptoms in early life, increased bronchial hyper responsiveness, exacerbation of allergic symptoms and to the development of middle ear disease. It remains the most clearly defined environmental factor that adversely affects the health of children and has its greatest impact in young children who by nature of their dependence and immaturity cannot remove themselves from the exposure.

Smoking by adults living in the family home not only exposes children to the adverse effects described above but also increases the risk of children living in these environments taking up the habit themselves as adults.

**Main action:**
Banning smoking in public places and, in particular, in those environments where children and young people live, work and play.

**Research needs:**
Further work on genetic susceptibility is likely to identify sub-populations at higher risk of ETS exposure and is relevant to the JRC initiative on childhood asthma and envirogenomics (see separate section below).

In order to assess the impact of any intervention adequate disease surveillance would need to be established across the EU. This would require work on disease definitions and on networks of surveillance centres in collaboration with the relevant healthcare professionals and scientific community using networks such as those available with the Framework research programmes and/or the relevant professional European Organisations (European Respiratory Society and the European Academy of Allergy and Clinical Immunology).

Research on effective prevention and cessation strategies to reduce ETS exposure in pregnancy and early childhood.

5.1.2 Other indoor exposures

According to WHO everyone has a right to breathe healthy indoor air. Living in damp homes is associated with adverse, mostly respiratory, health outcomes and WHO has estimated that this is the single most frequent hazardous environmental exposure for the European population. So far, a satisfactory explanation has not been found and allergens from mites and moulds, cell wall components from bacteria and fungi, fungal toxins, and volatile organic components produced by fungi may all play some role.

There is a need for guidelines, recommendations and regulations for improvement of the indoor environment including ventilation, heating, exchange of air, avoidance of moisture and moulds, avoidance of allergens and allergen sources (especially mites), chemicals used and released within the home, adequate building management, maintenance and cleaning especially in children’s environments.

**Main actions:**
Monitoring of exposure within homes, kindergartens and schools. Risk assessment of environmental chemicals and particulate matter imported to the internal environment such as carpeting and furniture or released by activities such as renovation. The data should be fed into the chemical data, foreseen under REACH and under the general product safety directive.

**Research needs:**
1. Systematic reviews in order to identify the most effective interventions and to inform the development of European standards and regulations.
2. Measurement of indoor exposure to biological contaminants (from bacteria, moulds, mites, pets etc.) in suitable population studies and determining the exposure effect relationship
3. Joint analysis of suitable population studies for interactive effects of indoor and outdoor pollution on allergy and asthma.

5.2 Outdoor environment

Outdoor air pollution mainly from motor traffic and industry constitutes a major environmental health problem. It has been identified as the factor leading to the largest loss of quality adjusted life years in the European region. According to WHO, as many as one billion people, are regularly exposed to levels of outdoor air pollution exceeding WHO guidelines by up to 100 times. Children are of particular concern as they are especially vulnerable to high levels of air pollution and when exposed suffer a range of unpleasant and
adverse respiratory symptoms. Despite increasing knowledge about harmful health effects of air pollution, preventive action is often slow to follow. It is necessary to provide a sound environmental policy framework and actions applicable to different settings and to different socio-economic conditions. A proper strategy to eliminate avoidable air pollutants and thus reduce this disease burden in a cost-effective way is required. Exposure to high concentrations of outdoor air pollutants such as fine particles and ozone may exacerbate existing asthma and other allergic conditions, but it is less clear whether pollution affects the incidence of new cases of asthma and allergy. Experimental studies demonstrate that specific forms of air pollution such as diesel soot act as adjuvants in increasing formation of IgE against common allergens, and in eliciting increased symptoms among already sensitised subjects. Conflicting evidence obtained from epidemiological studies looking at one factor at a time may be caused by inadequate consideration of interactions with other exposures and perhaps host factors.

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<th>Main actions:</th>
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<tr>
<td>1 Development and application of European guidelines for outdoor air pollution standards and stronger enforcement of existing guidelines and legislation.</td>
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<tr>
<td>2 The existence of a series of birth cohort studies in Europe, devoted to studying the natural history of allergic disease, offers unique opportunities to study the effect of interacting environmental and host factors prospectively, with adequate statistical power.</td>
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<td>3 Focus on actions to assess and reduce exposure to children</td>
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<table>
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<th>Research needs:</th>
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<tr>
<td>1 Interactions between indoor and outdoor air pollution</td>
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<td>2 Development of biomarkers</td>
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<td>3 Physico-chemical characterisation of traffic exhaust</td>
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<tr>
<td>4 PM is at the moment the main investigation target but other PM (i.e. PM10, ultrafine) are also of interest.</td>
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<td>5 Research on the risk of PM2.5</td>
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<td>6 Explore integration of modelling and remote sensing</td>
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<td>7 Standardization of research methods to gain comparable data and avoid sample errors</td>
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<tr>
<td>8 New research on human exposure to traffic exhaust</td>
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<tr>
<td>9 Interaction among personal, indoor and outdoor exposure.</td>
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<tr>
<td>10 Epidemiological and toxicological studies of exposure and its consequences. Investigation of the role of air pollution on allergy and asthma in children</td>
</tr>
<tr>
<td>11 Study of susceptible groups (see also Gene/environment section below).</td>
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<tr>
<td>12 Interactions between air pollution and noise, sport, obesity. This will generate synergies and facilitate the sharing of data and methodologies.</td>
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5.3 Gene-environment interactions

While genetic factors predispose children to develop asthma and related allergies, convincing evidence demonstrates that a number of environmental factors – allergens, environmental tobacco smoke, poor indoor/outdoor climate– contribute to the onset of allergic disease. Once the disease is established, these factors may also trigger symptoms.

In other words: “the genes provide the bullets but the environment provides the triggers”; and “Biology is not necessarily destiny”. Identifying genes that predispose children to the expression of disease and/or make them particularly vulnerable to adverse environmental exposures may therefore contribute to risk identification and assessment.

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<th>Main actions</th>
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Identification of genes accounting for regional and ethnic differences in the EU population. This set of indicators would help identify “intelligent” cost-effective strategies for prevention of the onset and exacerbation of children respiratory health disorders.

Research needs
1. Establish the population prevalences of candidate genetic polymorphisms likely to contribute to response to the main environmental exposures and identify any trans-European gradients.
2. Establish the contribution of functional genetic polymorphisms to effects of the known adverse environmental exposures relevant to the expression of and severity of asthma-related allergy and respiratory illness in children.
3. As child age is strongly associated with the different allergy manifestations, asthma phenotypes, viral associated and ETS exposure in the under 5yr age group, allergy in older children and active smoking in adolescents (above 12 yrs) children across the whole age spectrum would have to be involved.

5.6 Infections

European research teams were the first to propose and then demonstrate that environmental exposures to microbial substances and parasites may protect the development of allergies. Several large epidemiological surveys in Germany, Austria and Switzerland clearly show that children living on farms had more protection than other children. The earlier the exposure, the more the children were protected. In a recent study researchers discovered the highest levels of bacterial DNA in areas with fewer cases of allergies and asthma. The highest levels of DNA were generally found in barns; the lowest levels were in urban homes. The study found that endotoxin is a marker for bacterial DNA, which is also higher in locations of lower asthma and allergy prevalence.

Main actions:
Environmental exposures to microbial substances like endotoxin and parasites confer protection from the development of allergies. This effect is consistent over different studies and strong, showing reductions in risk of more than 70 percent associated with exposure. The effects of the environmental exposures are modified by a subject’s genetic background thereby allowing individual risk assessments. These observations strongly suggest that by understanding how to imitate nature powerful tools for the individual prevention of allergies can be developed. Although the strong negative association between livestock and allergy, very little is known about other potential explanatory factors.

Research needs:
1. Identify populations over a broad range of exposure to a suspected risk factor or populations with a significant contrast in the prevalence of allergic diseases. These epidemiological studies should also focus on the timing of exposure since several studies indicate the importance of the first 3 years of life.
2. Development of novel tools to assess potentially immunomodulatory microbial-derived compounds in environmental samples.
3. Identification of protective compounds in large population-based studies taking an individual’s genetic susceptibility and the host’s immune response into account.
4. Testing of the immunomodulatory compounds in animal models.
5. Clinical testing of most promising compound.
5.7 Networking

Collaborative projects such as the European Community Respiratory Health Survey (ECRHS), the International Study of Asthma and Allergy in Childhood (ISAAC), and many others have been funded by the European Commission and have clearly demonstrated the ability and advantages of European groups working together. Europe has been in the forefront of developing birth cohorts for the study of early life influences on the causes of allergy and asthma. The cultural, clinical and environmental diversity of Europe gives it a natural advantage in studies of the development and prognosis of allergy and asthma.

Although research laboratories in Europe are characterised by a large individual expertise, only few are effectively integrating their knowledge and expertise. Furthermore the increasing complexity of the research questions in this field calls for better integration of studies, by standardisation of methods, health effect assessment and analysis, and by increasing sample sizes.

The collaborations between European groups so far:
- have often had a relatively narrow methodological focus
- have used methods that are not always well standardised between programmes
- have produced relatively short term collaborations over specific research programmes with no formal enduring structure
- have often been funded without mutual knowledge of each others’ objectives
- have not always fully exploited the potential links to wider aspects of allergy and asthma or to the wider social context of research in Europe.

**Main actions:**
1. create a European Network of Excellence to address allergy and asthma in their totality
2. create permanent structures that will maximise the scientific contribution of Europe to this area (GA²LEN, the Global Allergy and Asthma European Network, short listed for funding within the 6th Framework program)
3. create a clear link between the needs of patients and policy makers and the research agenda
4. accelerate the application of research results to policy development and clinical practice

**Research needs:**
1. establish a large European platform with integrated databanks and biobanks
2. standardisation of methods
3. health effect assessment and analysis
4. organisation of large scale epidemiological studies based on results of smaller pilot studies
5. improve and harmonise the effectiveness of prevention to environmental exposure (development and implementation of guidelines)
6. raise public awareness about allergy and asthma
7. assist EU and national policy makers to make recommendations and directives from the knowledge of the interaction between the environment and susceptible genes in the onset and progression of allergy and asthma using the following scheme
8. Propose tools and guidelines to policy makers.

6. Dissemination of results

One of the major aims of the future research in Europe is to improve and harmonise the effectiveness of prevention to environmental exposure in Europe. The development and
implementation of guidelines is therefore needed. Patients need simple information on environmental factors both indoors and outdoors and both primary and secondary prevention. A very large amount of information is available, especially in the Internet but the quality of the information may be questionable. In the future one of the major objectives of research in Europe is to assist EU and national policy makers to make recommendations and directives from the knowledge of the interaction between the environment and susceptible genes in the onset and progression of allergy and asthma in order to reduce their burden in all regions of Europe. The problem requires an integrated approach that proposes tools and guidelines to policy makers and help policy makers to formulate policies and directives, in particular on primary and secondary prevention strategies.

7. Relevance to policy

Guidelines are an important instrument in reducing the burden of diseases and for policy makers to propose cost-effective decisions. Evidence-based guidelines for asthma and allergy have already been produced. However, with the increased knowledge of the causes and mechanisms of disease and developments in therapeutics these guidelines need to be continuously updated and guidelines for many allergic diseases are not developed yet. One of the objectives is to assist EU and national policy makers to make recommendations and directives from the knowledge of the interaction between the environment and susceptible genes in the onset and progression of allergy and asthma in order to reduce their burden in all regions of Europe.

The problem requires an integrated approach that can best be proposed by the following scheme:

1. Propose tools and guidelines to policy makers.
2. Help policy makers for policies and directives, in particular on:
   a. primary and secondary prevention strategies
   b. school and work policies
   c. disease management outcomes
3. Rapidly provide expert opinion to policy makers (EU or national) on any question raised on allergy and asthma.

Moreover, when directives will be made at the EU level, they should be harmonised and implemented at the national level. Also research should not only be focussed on the current EU countries but also on the Accessing Countries.

There is also a need for more prevention and precaution and the identification of the risks for human health, taking account of particularly vulnerable groups such as children. Also the public awareness about allergy and asthma should be improved towards a public “right-to-know” about the impact of the environment on diseases like allergy and asthma.

8. Key References


- Friedman MS, Powell KE, Hutwagner L, Graham LM, Teague WG., (2001). Impact of...


Parnia S, Brown JL, Frew AJ. The role of pollutants in allergic sensitization and the

- Barnes KC, Marsh DG. The genetics and complexity of allergy and asthma. Immunol Today 1998;19:325-32
4.3 TWG childhood cancer

The baseline related to childhood cancer is described in detail in the baseline report of the corresponding technical working group\(^2\).

4.4 TWG biomonitoring of children

The baseline related to biomonitoring of children is described in detail in the baseline report of the corresponding technical working group\(^2\).

Lisbeth E. Knudsen

**Key words**

Children, biomonitoring, integration, harmonisation, survey, research, validity, susceptibility, power, toxicology, epidemiology, exposure

**Summary**

Surveys of children’s exposures to environmental exposures and the related health impact of e.g. heavy metals, dioxins, endocrine disrupters are ongoing in some European countries and several EU-funded and nationally funded research activities focus on environmental impacts on the health of children. Gaps in knowledge exist between environment and health linkages relative to children and appropriate policy responses. Biomonitoring that focus on environmental exposures, diseases and/or disorders and genetic susceptibility, and their potential relationships – may increase that knowledge and allow using this knowledge to develop national public health programs and policies for preventing disease.

A common European approach to monitoring needs sound and harmonised study design, availability of reliable tools for sampling and analysis, harmonised data treatment and adequate quality control. Collaboration of epidemiologists, toxicologists, exposure assessors and regulators, in order to develop and implement systematic biomonitoring systems to produce useful results for regulatory and/or policy decision-making is lacking in many of the activities reported. Adherence to existing collaborative and supporting administrative systems within the research structure in EU is suggested to initiate integration and interdisciplinarity.

Integration of monitoring activities into a European biomonitoring program raises the need for concerted actions and for more basic research

Concerted actions may relate to:

1. data sharing, necessitating common protocols regarding study design, analysis, data analysis, data management and protection, dissemination of results and ethical issues
2. elaboration of a European ethical standard in relation to studies with children
3. common design and protocols for e.g. mother/child cohorts with biological and prospective information collection

\(^2\) A syntheses of the baseline reports of the working groups established in frame of the EU Environment and Health Strategy can be found at the following URL: http://europa.eu.int/comm/environment/health/pdf/baseline_reports.pdf

For the whole Baseline Report of the childhood cancer group see http://www.rome-conference.org/
For the whole Baseline Report of the biomonitoring group see http://www.brussels-conference.org/
4. collection of information on biomonitoring activities in Europe starting from the preliminary information gathered in the baseline report and by collaboration with other initiatives (WHO, US)

More basic research concentrating on mechanistic research relates to:

1. Age differences in environmental exposures (e.g. including validation of biomarkers for children, taking into account differences between age groups)

2. Age differences in metabolism (and susceptibility) of environmental agents (e.g. including Specific Physiologically Based Pharmacokinetic (PBPK) models for children)

3. Age differences in DNA damage and repair of selected environmental agents

**Summary in bullet format**

- survey of children’s exposures to environmental exposures and the related health impact of eg heavy metals, dioxins, endocrine disrupters are ongoing in some European countries
- several EU-funded and nationally funded research activities focus on environmental impacts on the health of children
- a common European approach to monitoring needs sound and harmonised study design, availability of reliable tools for sampling and analysis, harmonised data treatment and adequate quality control
- collaboration of epidemiologists, toxicologists, exposure assessors and regulators, in order to develop and implement systematic biomonitoring systems to produce useful results for regulatory and/or policy decision-making is lacking in many of the activities reported.
- adherence to existing collaborative and supporting administrative systems within the research structure in EU is suggested to initiate integration and inter disciplinarity

**Background to the problem at an European level**

Prenatal and postnatal exposure to environmental pollutants may have large implications for children’s health and also determine morbidity occurring later in life including asthma and allergy, cancer, mental illnesses, delayed neurodevelopment, cardiovascular diseases. Recent studies (WHO/EEA 2002) indicate that gene-environment interactions are important in many diseases. Exposures at early life are important because children are often more susceptible than adults and because critical periods of exposure in early life condition later health effects.

Gaps in knowledge exist between environment and health linkages relative to children and appropriate policy responses. Biomonitoring that focus on environmental exposures, diseases and/or disorders and genetic susceptibility, and their potential relationships – may increase that knowledge and allow using this knowledge to develop national public health programs and policies for preventing disease.

Biomarkers are seen as indicators of the continuum of biological events that can occur between exposure to an external agent and disease. Within this continuum four classes of biomarkers have been identified: markers of internal dose, markers of biological effective dose, markers of early response and markers of altered structure and function. In addition susceptibility markers are measurable indicators of genetic and acquired factors that influence
the probability that a disease will result from external exposure.

The question is raised if coordination of these efforts could provide important additional value and if the development of a permanent harmonised European biomonitoring system built around ongoing monitoring in the Member States and the Accession Countries could allow better understanding of environment and health linkages and long-term health effects and could be used as a tool for the development of further environmental policy.

Current research activities in Europe and future research priorities

Biomonitoring activities are taking place in most European countries as part of surveys or research projects with measurement of eg.

- prenatal exposures by studies of placental transfer
- concentrations of various pollutants in breast milk
- heavy metal concentrations in blood and urine from children
- Chromosomal Aberrations or other genotoxic endpoints in blood from children
- Expiration of volatile compounds (Solvents etc.).
- Lung function measurements.

Several EU-funded research projects, nationally funded projects and surveys focus on environmental impacts on the health of children. Exposures of urban air pollution, pesticides and chemicals are associated with increased risks of respiratory diseases (asthma, bronchitis) allergies and cancers as well as damages to the reproductive system.

Recent observational birth cohorts that incorporate both questionnaire data and collection of biological samples have enrolled a total of more than 200,000 newborns in Belgium, Denmark, the Faroe islands, Finland, France, Germany, Italy, Norway, Spain, Sweden, the Netherlands, the UK. It is expected that in the next 2-3 years several hundred thousands newborns will be enrolled in ongoing studies. Such cohorts with collection of valuable information about prenatal exposures, biosamples and environmental sampling will enable valuable follow-up studies.

The extent and scope of ongoing activities is presently surveyed by the TWG-biomonitoring of children. The results will be available within months.

Several national and EU-projects financed by the European research programs have identified major health problems in children (cancer, asthma, neurodevelopmental disorders, reproductive disturbances) arising from exposure of children. Often biomonitoring is the tool used for detecting exposure since the sources may be diverse and routes of exposure several (inhalation, dermal ingestion).

Biomonitoring studies with children have been related to specific exposures (eg. Urban air pollution in Czech Republic and Poland) or specific adverse health effects like asthma (eg. Denmark, Germany much more countries : almost ¼ of the projects !!) or risk of cancer from exposure to genotoxic substances (eg. Croatia, Germany, Belgium).

Integration of these activities into a European biomonitoring program raise needs of validation of biomarkers at several levels, which may include testing of standardised protocols for
- Selection of study persons, including ethical approval
- Sample collection and processing
- Sample analysis
- Reporting and dissemination
- Data storage, protection and release.

Development of less- or non-invasive sampling techniques is suggested to be crucial for the succeeding of future large-scale biomonitoring studies.

Since children are developing organisms biomonitoring projects should also include considerations regarding which age groups to monitor.

Gaps in knowledge of differences between children and adults and within different age groups of children are also significant within areas of mechanistic actions, uptake, distribution, metabolism, storage and excretion of environmental pollutants:

- The exposure and the susceptibility of the fetus to transplacentally transported agents
- Mechanisms of actions of DNA damage and repair at different ages to be studied by toxicogenomics/proteonomics
- Molecular epidemiology studies of children and mothers enrolled in European mother/child cohorts studying eg the impact of genetic polymorphisms on birth outcomes (e.g. birth weight, intrauterine growth rate) and child morbidity

Also efforts studying the interpretation of biomonitoring studies, including molecular epidemiology studies for the risk assessment are important.

Relevance to policy

Information gaps exists in occurrence and severity of the most relevant adverse effects potentially induced in children’s health by a variety of environmental agents. An integrated effort of biomonitoring of children enables coupling of data on environmental pollutants to health data on a European level with the aim of harmonised sampling, analysing, dissemination and regulation.

Emerging issues (threats)

Increasing childhood morbidity and mortality from unregulated environmental exposures may result if exposures are not detected by use of a.o an integrated monitoring system.
Baseline reports from the TWG biomonitoring in children

The baseline report from the 1st stage includes the inventory describing app 100 European studies reported to the TWG Biomonitoring in the survey initiated in the group. The table shows the distribution by country. http://www.brussels-conference.org/biomonitoring.htm

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The numbers from the survey were:

1. total number of questionnaires received: 100
2. reported budget with 47 questionnaires: about 57 million euro
3. average budget per project 1,2 million euro
4. about 440 000 children are covered (basis 90 questionnaires)
5. average about 5200 children per project
6. average duration of a project 4.9 years
7. 15 projects covered dioxin/PCB exposure, 44 heavy metals, 5 endocrine disrupters
8. 27 projects examined asthma or allergies

Very few projects covering cytogenetic endpoints were recorded. However more than 200 studies have been identified in this area by the CHILDRENGENONETWORK, many of which do not meet criterias of control groups, sufficient size of study etc

Although the response to the call was encouraging, gaps in information clearly remained (no information from eg Hungary and very sparse information from eg UK) and no straightforward assessment or assumption could be made on the level of representativity of the data collected.

The baseline report from the 2nd stage includes the final conclusions from the TWG concerning future actions, including research needs and concerted actions described in several options under the following headings:

- Collection and analysis of available information within the European area concerning biomonitoring (including mother/child cohorts)
- Development of new methods for biomonitoring (e.g less invasive methods, use of genomics, proteonomics etc)
Establish relationships of biomarker outcome with emission and imission data by e.g. modelling

Ethical, social and legal issues related to biomonitoring

Information and communication strategies

Research in problems associated with use of cord blood (ethical, stem cells, disruption of the birth environment)

A number of options detailing research needs have been developed by the TWG and further described in the baseline report:

- Learn and proceed from existing experiences from occupational health with regard to analytical methodology (including quality control) and interpretation. Institutions already engaged in biomonitoring of exposure under occupational conditions can also be involved in biomonitoring of children.

- Establish a European Standard on how Social, Ethical and Legal Questions need to be taken into account in biomonitoring studies and surveys

- A comprehensive evaluation – by independent experts – of the levels of scientific evidence between exposure to pollutants and diseases or disorders that can be deduced from existing epidemiological, biomonitoring and food contamination studies including but not limited to those collected in Phase I of the TWGs work.

- Define procedures for sampling and analysis in surveillance programs that are focused on less invasive methods

- Develop Biomonitoring Programs based on integrated system and focused on mother-newborn pairs (by using, as much as possible, less invasive and cost effective methods), to characterise pre- and post-natal exposure to critical pollutants

- Lessons to be learned from previous and ongoing research programs within EU

- Research in breast milk as a widely used indicator

Key references


4.5 TWG heavy metals

The baseline related to heavy metals is described in detail in the baseline report of the corresponding technical working group.3

Argelia Castaño (castano@inia.es)

Keywords: Heavy Metals, Genetic susceptibility, chronic effects, low-level exposure, exposure modelling, health risk assessment models. Integrated monitoring, Environment and Health.

SUMMARY CONCLUSION

- Elevated environmental levels of some metals are known to pose a health risk and many Member States undertake routine environmental monitoring. The information collection process we have used, due to resource constraints, unavoidably set a priority on certain metals, environmental media, and exposure vectors. Air, water, soil and food appear to be well monitored in predominantly systematic monitoring programmes, while there is a lack of information on biomonitoring and in addition is quite difficult to obtain.

- The initial analysis of the information collected by the TWG-HM indicates problems and deficits with the establishment of an integrated environment and health programme. There is therefore a need to cut across traditional research boundaries in order to fill data gaps and avoid study bias.

- A large body of heavy metals monitoring related information has been collected by the TWG_HM. However, in most cases, it has not been possible to fill the data set matrix which would be necessary for integrated monitoring. Data gaps exist for substances, media, and exposure vectors between the data sets of various countries and within the data sets of individual countries. It is not clear whether methods for sampling, analysis and data reporting are good enough to allow fair comparison of apparently similar data sets relating to single components. It is not possible to determine the likely effects of metals other than the priority set (Hg, Cd, Pb, Ni, As), metal combinations, cumulative or synergetic effects.

- Research actions were initially identified for:
  
  a) Research into population exposure to metals, and exposure assessment modelling, with a special focus on children.
  b) Research to define dose-response relationships for low-level heavy metal exposures. These will require innovative work to increase the sensitivity and specificity of traditional methodologies.
  c) Research into increased risk due to genetic susceptibility.
  d) Research into development of non-invasive biomarkers (both exposure and effect)
  e) Harmonised pilot studies, in selected areas, to integrate environmental and biological monitoring.

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3 A syntheses of the baseline reports of the working groups established in frame of the EU Environment and Health Strategy can be found at the following URL: http://europa.eu.int/comm/environment/health/pdf/baseline_reports.pdf
For the whole Baseline Report of the group see http://www.environmentandhealth.org/
f) Research on metals, not included in traditional monitoring programs, for which significant population exposure is anticipated in the future and that may, as a result, cause health problems.

g) Research on the impact of chronic exposure and possible delayed effects, cumulative (time), and synergetic (exposure to complex) exposure.

These, in a second stage has been compiled in three fiches for action on research:

1. **Research Topics – Exposure**

2. **Research Topics – Effects**

3. **Research Topics- Identification of new risks**

This three actions are long term research initiatives cross linked with other immediate or short term seven options for action proposed for the members of the TWG-HM

**Brief Assessment of the State of Related Research in Europe**

The initial meeting of the TWG_HM at the Warsaw Regional Conference (6-7 October 2003) agreed a list of priority metals that should be covered in this programme. This selection was based on the quality/quantity of information available\(^4\) on the characteristics and health impact of three groups of metals: A)\(\text{Pb, Hg }\); B)\(\text{- Ni, As, Cd and C) Others}\)

1. A number of initial observations can be made from the information collected:
   a) A large proportion of Countries are likely to collect information on the metals and media identified by the TWG_HM as being of high priority,
   b) Some exposure vectors seem to be much better covered than others (food as opposed to soil/dust for example),
   c) Information appear to be missing:
      i. from some countries altogether,
      ii. for a number of media for most countries (i.e. necropsy material, sediments etc.),
      iii. for some metals in part of the media in some countries,
      iv. to link environmental concentrations to human health impacts
   d) There is lack of activities in the assessment of human exposure. Some elements necessary for this e.g. demographic structure and population density in monitored areas could be extracted from the general statistics, but this would require clear policy driver (also clarifying responsibilities and rules of data sharing). There are no systematic attempts to convert the measured HM concentrations in the environment (and associated exposure) into the measures of human health impact (e.g. the risk). Bio monitoring activities within the countries are generally not coordinated or harmonised

2. In order to represent exposure pathways relevant for children there is a need for links with other programs e.g. in food quality and safety. Similarly there is a need to develop or implement relevant health risk assessment models (for general populations as well as targeted at children) within the environmental monitoring practice\(^5\).

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\(^4\) This decision was based on the documents cited in the bibliography.

\(^5\) There exists certain expertise in this field represented e.g. by ECETOC or a number of individual research groups.
3. The data collected so far appears mainly focussed on national surveys or results that are representative of general populations, with some data able to be made relevant to particular age groups such as children by, for instance, using age related exposure information. A more targeted data collection exercise will be necessary to investigate the extent to which information is available to quantify exposures for particular population subgroups or to determine the upper levels of exposure and where/why they occur. The frequency of exposure - even at low level, the occurrence of complex exposure to a series of contaminants (metals or others) and of "windows of vulnerability" need attention as well. Then the suitability of bio monitoring and health effects screening for these groups in the population can be considered.

4. Randomised sampling strategies for metals in the air, water, soils, dust, and food to which children may be exposed are needed for the establishment of exposure baselines. The “residential environment” is likely to be a predominant determinant of childhood exposures to multiple metals but is seldom sampled. It is possible that randomised sampling strategies designed to detect unknown sources of contamination or calibrate dose/response models might be a means for exploring the influence of other metals and routes of childhood exposure.

5. Human exposure (particularly children’s) will be the sum total of that metal contained in different environmental media. Exposure assessment models are needed so as to enable the conversion of environmental monitoring data into estimates of total systemic exposure. Research for refinement of such exposure assessment models should be assigned high priority and must be validated with biological monitoring data. Implicit in this is better understanding of toxicokinetic factors that govern metal uptake from different media and in elucidation of individual child behaviours and activities that may serve to increase or decrease exposure. Significant inter-individual variability is to be anticipated in the exposure of children to metals from environmental sources as a function of geochemical, genetic, lifestyle and behavioural variables. Such requirements might be achieved through the evaluation of existing data that has been collected in the vicinity of point sources. Such data may also have applications in assessing the predictive capabilities of models that seek to relate information for the production and use of metals to environmental release estimates. However, point source emissions may result in elevated systemic exposure through environmental pathways not characteristic for the majority of the population. For example inhalation exposure may be a predominant source of systemic exposure in the vicinity of point sources whilst other sources may be important in urban areas.

6. Pilot efforts to integrate environmental and biological monitoring data may be possible based upon existing national strategies. For example, Germany’s GerES program monitors both paediatric exposures and selected environmental media. Belgium has an integrated, validated methodology applied in research programmes. Although these programmes do not encompass the full range of substances or environmental media of concern, the “lessons learned” from the GerES and Belgian efforts could be instrumental in the development of harmonised strategies of wider applicability throughout the EU.

7. Metals are persistent in the environment. Research findings reveal evidence of impairment in children with bio indicators of exposure lower than guideline value. The absence of

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6 EUSES and other models
7 One recent example in the case of lead is proposed by Canfield et al (see bibliography). WHO is developing a position paper on the theme of "Dealing of uncertainty: how can the Precautionary Principle help protect the future of our children?" (see bibliography).
threshold and effect of chronic - even low- exposure is an important issue for sustainable policy as a goal and SCALE as a strategy. At the levels of exposure anticipated to exist, effects upon the individual child will be subtler than can be detected by existing medical technology. The design and implementation of separate prospective research studies that accurately define dose-effect relationships for low level exposure impacts is likely the preferred means of both detecting potential adverse effects and setting environmental standards that are protective of paediatric health. In many cases the exposure concentrations and the availability of exposed individuals may not be sufficient for conducting meaningful traditional epidemiological investigations. Therefore, modifications have to be introduced to the traditional approaches to increase the sensitivity and specificity of epidemiological studies.

8. At the moment, although there is raising awareness in the last years, little information is available for the role of genetic susceptibility. It is becoming clear that polymorphisms and defects in many genes can have a key role on the possibility to develop adverse outcomes after certain environmental exposures. Some examples of different individual susceptibility to inorganic salts of heavy metals have been until now reported in few studies.

Conclusions

9. Requirements to combat the deficiencies noted relate to rationalising the reporting requirements of existing legal instruments to ensure that, wherever possible, they generate data compatible with the concept of integrated monitoring. A specific requirement is the adoption by the Commission and Member States of an Integrated Monitoring Programme able to generate new data and act as a lever on existing programmes. The programme should be resourced, self-sustaining, and capable of generating consistent time series data. Such a programme could act as the catalyst to bring about the establishment of the multi-functional resource teams needed to challenge existing barriers to multi-media and cross-disciplinary work.

Research actions are specifically required for:

2.- Research Topic: Exposure

A programme of work to determine the exposure to metals, metal compounds, and metal combinations from:

a) known sources - where they may be included in existing monitoring programs ,
b) new sources, or routes, of exposure i.e. catalysts and additives, etc

The research programme will develop new and/or strengthen existing exposure assessment modelling, with a special focus on children. The programme should aim to improve knowledge of emission sources and exposure routes, including indoor domestic exposure, forthree groups of metals:

- short term action Hg, Pb, Cd
- medium term As, Ni, speciatium.
- Long-term Sn, Sb, Cr, Tl, Pt, Pd, Rh, Se and the relationship with essential metals [Cu Zn, Fe]
Exposure models will, take into account bioavailability (for example bioavailability of seafood-Cd and soil-Cd in children) Furthermore interaction between different metals influences their bioavailability. Develop age-specific exposure factors. These factors should include behavioural aspects, such as mouthing in young children, time of playing indoors/outdoors, smoking in adolescents and passive smoking (parental smoking), but also the composition of the food-basket; the diets should be analysed for risk factors e.g. (low) iron and zinc content.

Pilot studies recommended under option 4 will inform research requirements

2.- Research Topic: Effects:

A programme of work:
- Which, for various media and exposure vectors, develops new effect assessment methodologies for metals, particularly soluble forms (i.e. arsenic, cadmium, nickel, platinum, chromium, palladium, antimony) metal compounds (organotin, nickel compounds, Cr$^{+3, +6}$, As$^{+3, +5}$) and combination of metals depending on the sources and different medium (for example platinum& rhodium& palladium in air; mercury &arsenic in fish)
- Innovative work to increase the sensitivity and specificity of traditional methodologies as an aid to the establishment of dose-response relationships for low-level heavy metal exposures.
- On the effects of chronic exposures.
- Determine the increased risk due to genetic susceptibility.
- Develop non-invasive Biomarkers for lead and for platinum, chromium, palladium, antimony

3.- Research Topics – Identification of new risks

A programme of work to develop risk assessment methodologies for metals, metal compounds, and metal combinations from previously unrecognised sources which are found in the exposure vectors for children. The action will be complementary to options 7a (exposure) and 7b (effects) and methodology validation may be undertaken as using pilots studies proposed in action 4.

BIBLIOGRAPHY

4.6 TWG endocrine disruption

The baseline related to endocrine disruption is described in detail in the baseline report of the corresponding technical working group.

Prof Poul Bjerregaard, Dr Andreas Kortenkamp; TWG Research Needs

Key words

Integrated exposure assessment, biomarkers, hormonal carcinogenesis, fecundity, precocious puberty, fetal origins of disorders, combination effects, dose-time relationships, exposure timing

Conclusions

In future years, European research in the area of endocrine disruption should pursue the following topics:

- Integrated exposure assessments of the full spectrum of endocrine active chemicals in human tissues and environmental media, including air, water and soil,
- Establishment of biobanks with suitable human reference material, covering European countries with marked differences in relevant human disorders,
- Research into biomarkers of effects and mechanisms underlying male and female disorders, strengthening links to fundamental research into mechanisms of hormonal carcinogenesis,
- Systematic explorations of the relationship between exposure time and dose and of mixture effects, with a view to underpin better risk assessment by defining chronic effects of both single chemicals and mixtures,
- Investigations of the link between exposure and health effects in males and females, building on better exposure information, differences in disease incidence between countries and taking account of combination effects, exposure timing and individual susceptibilities,
- Research into the impact of lifestyle/environment factors on fecundity, precocious puberty and on fetal origins of male and female reproductive disorders.

State of related research in Europe

European research has demonstrated that disorders associated with human male reproductive organs have increased in incidence in recent years. A rise in genital malformations has caused much concern. Several studies have shown decreasing trends for sperm concentrations, although obvious geographical differences are observed. There are associations between chemical exposures in adulthood and reduced sperm counts. Very recent data indicate that in parts of Europe sperm counts are approaching levels that will impair fertility. The incidence of hormone-dependent cancers, such as testis, breast and prostate cancer is increasing.

Recent investigations have suggested that many of the disorders of the male reproductive

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8 A syntheses of the baseline reports of the working groups established in frame of the EU Environment and Health Strategy can be found at the following URL:
For the whole Baseline Report of the group see http://www.environmentandhealth.org/
system may have a common aetiology and can be linked into a testicular dysgenesis syndrome. The frequency of testicular cancer varies widely geographically. Amongst the Nordic countries where the offspring of immigrants have moved from one country to another, they tend to adopt the testicular cancer frequency of the new country. This indicates that the general increase in the frequency of testicular cancer is not determined by genetic changes, but may be linked to factors in the environment, lifestyles, etc.

The outcome of studies of health risks affecting women, particularly in relation to breast cancer has been largely inconclusive and there is the need to better integrate European research into female disorders with efforts targeted at endocrine disrupters. There is good evidence to link breast cancer with endogenous and exogenous exposure to steroidal estrogens, but potential risks associated with other man-made chemicals are far from clear. Published studies have focused on narrowly defined groups of chemicals, without considering combined exposures, genetic polymorphisms, life style factors etc. The role of endocrine active chemicals in the aetiology of other female reproductive tract diseases (endometriosis, polycystic ovarian syndrome) has received comparatively little attention in Europe.

Ongoing European research focuses on building up data bases on male reproductive effects, and on exploring the mechanistic basis of male disorders, with a view of developing improved biomarkers and screening tools. The range of effects caused by specific classes of chemicals (e.g. flame-retardants, phthalates, UV-screens etc.) is being investigated and efforts to characterise human exposures to endocrine active chemicals are taking shape. Further work focuses on defining low-dose and mixture effects of endocrine disrupters.

Future research needs

Exposure assessments, cycle of pollutants

Integrated assessments of the spectrum of endocrine active chemicals and their metabolites in human tissues and body fluids should be made. To achieve this, there is an urgent need to build up suitable human reference material for monitoring (“biobanks”). It is crucial that this encompasses countries with differing incidences in endocrine related health disorders so that the importance of environmental factors can be assessed. Reference material should include blood, umbilical cord, placenta, adipose tissue etc. The establishment of mother-child cohorts should be pursued or, if appropriate, use should be made of established birth cohorts in which relevant tissue/blood samples have been recovered.

To allow assessments of combined exposures, a large number of relevant chemicals should be analysed in one and the same specimen. Analyses should not be restricted to chemicals with known endocrine activity. Systematic efforts should be made to search for new endocrine active chemicals by combining chemical analytical techniques with relevant biological screening tools (bioassay-directed fractionations). Although aspects of this topic are being addressed in ongoing EU-funded projects, with first results imminent in the next few years, definitive answers cannot be expected within this time frame. It is therefore important to pursue holistic exposure assessments.

Human exposure assessments should be integrated across environmental media and exposure pathways, including food basket analyses, analyses of consumer products such as cosmetics, soil, water and air. Recent demonstrations that fine particles in indoor and outdoor air contain endocrine active chemicals underline the importance of such research.

There is a dearth of data on the fate and behaviour of endocrine active chemicals in
environmental media and human tissues. This applies especially to chemicals with comparatively low lipophilicity such as phthalates, parabens, UV-screens etc.

**Biomarkers of effect, mechanistic pathways leading to human disorders**

Research into biomarkers of effects, relevant to human disorders in the male and female, especially after chronic exposure, should be intensified, with a focus on vulnerable periods early during development.

While a great deal of mechanistic research has focused on receptor-mediated events, horizontal integration with fundamental cancer research has been neglected in the past and should be developed in the future. Emerging issues are the effects of endocrine active compounds on genomic instability, on stromal/epithelial interactions, and on cellular mal-differentiation as a result of faulty programming early in fetal life. These topics need to be addressed to provide a better understanding of molecular mechanisms in hormonal carcinogenesis with a view to developing better screening tools for the identification of causative chemicals.

The potential afforded by DNA array and chip technologies is being exploited with enthusiasm in the field of endocrine disrupter research, but the interpretation of the emerging data in the context of the assessment of health risks often remains unclear. It is necessary to link genomics with physiological and phenotypic information relevant to disease processes in order to trace gene expression to gene function. This is particularly relevant in the context of hormonal carcinogenesis and the development of improved screening tools.

**Chronic effects of mixtures of endocrine disrupters, time-dose relationships**

Current risk assessment procedures for endocrine disrupters pursue the single chemical / single medium approach. Furthermore, effect data emanating from laboratory assays usually describe acute and subchronic effects, with a neglect of chronic effects. To underpin better risk assessment, studies should systematically explore the influence of prolonged exposure times on effects (dose-time relationships), both with individual chemicals and with mixtures. While there has been success in evaluating the effects of mixtures made up of pure chemicals in the laboratory, more research is needed to establish whether mixture assessment concepts can be applied to “real world” complex mixtures.

**Probing possible links between exposure and health effects in males and females**

Building on information about realistic exposure scenarios, knowledge about mechanisms in disease development and a better understanding of mixture effects, research should attempt to probe a possible link between exposure and negative health outcomes in the male and female.

However, before this can be achieved, a number of methodological issues need to be addressed and solved:

In the past, epidemiological studies have not taken account of combination effects of mixtures of endocrine active chemicals and on interactions with life-style factors and individual vulnerability. A lack of exposure information has severely limited the scope of these studies. An important task will be to develop concepts and methods that will allow epidemiology to incorporate knowledge about combination effects into study design, data gathering and interpretation.

Key to the success of such studies will be to build on ongoing European research into male
disorders that is utilising between-country differences in disease incidence as a heuristic principle. It is crucial to further develop this approach by extension to breast and prostate cancer and by integrating this research with knowledge about lifestyle/diet interactions, mixture effects, genetic polymorphisms in metabolising enzyme systems, vulnerable life stages. Issues of timing with respect to latency and periods of vulnerability, and individual differences in susceptibility require urgent attention.

**Impaired fecundity in Europe, and fetal origins of male and female reproductive disorders**

Because of its enormous economic implications, research into the impact of environment/lifestyle factors on fecundity is urgently needed. Birth rates have fallen significantly in Europe, and this may not be explained solely in terms of societal changes. There are very recent indications that male sperm counts are approaching crisis levels at which fertility is likely to be impaired.

There is growing evidence that male reproductive disorders and testis cancer have their origin in fetal life. Indications are that fetal effects in the female are of similar importance. For example, risk of polycystic ovarian disease, the most common reproductive disorder in adult women, may be altered in fetal life as a result of androgen exposure. More research assessing the importance of such factors in the development of testicular dysgenesis syndrome, insulin resistance, precocious puberty, and cancers is urgently needed. Such work needs to address the interaction between environmental exposure and lifestyle factors on the one hand with developmental types and genetic backgrounds on the other.
4.7 TWG dioxins

The baseline related to “Integrated Monitoring of dioxins & PCBs in the Baltic Region” is described in detail in the baseline report of the corresponding technical working group9.

Jouko Tuomisto

Research proposals, TWG on Integrated monitoring of dioxins and PCBs in the Baltic Region

- There is not much information on the dioxin and PCB situation in some accession countries. Research activities and an integrated monitoring program could help in assessing this in line with other European countries.

- There is still an incomplete understanding of the chain of events leading from industrial and other emissions to food, especially Baltic fish, and possibilities to clarify these steps should be emphasised. This would give better possibilities for emission abatement. A special problem is different congener spectrum in Baltic herring from the congeners in dominating sediments. Herring spectrum is rather close to the spectrum in dairy products and meat, and this raises the possibility that airborne recent pollution might be more important to plankton-feeding herring than the old storage in the sea and sediments. This should be investigated.

- Time series information is highly important for predicting future. This can be done indirectly by analysing sediment patterns or directly by analysing biota. Few time series are available for dioxins and dioxin-like PCBs in herring. To be able to conclude that levels in different fish species are going up or down, time series from different parts and species of the region has to be established within integrated projects.

- Basically the results indicate quite clearly that there are problems with Baltic herring and salmon. In herring the concentration is age-dependent. Site-dependence requires more work. Concentrations and congener spectra may be very different in different species of fish and vary even in the same fish from different parts of the Sea. It is important to recognise these differences because they can potentially be sources of error, but they can also be used for highly useful source analysis.

- Fish is identified as the most inhomogeneous group of foodstuff and require special attention since the contribution is significant. Meat, dairy products and other food groups will also need improved integration to fulfil the objective of reduced children exposure. To calculate daily intakes in children, food consumption data are needed. This would also require consumer behaviour studies.

- Influence of fish consumption on human exposure has been clearly demonstrated, especially in fishermen consuming high amounts of fish. This group is an obvious population for health effect studies.

- Despite significantly decreased levels in foodstuffs and subsequent intake, 8 to 12 % of populations in some member states are still estimated to exceed the tolerable intake of dioxins and dioxin-like PCBs. Because the risk assessment is based on developmental

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9 A syntheses of the baseline reports of the working groups established in frame of the EU Environment and Health Strategy can be found at the following URL: http://europa.eu.int/comm/environment/health/pdf/baseline_reports.pdf
For the whole baseline report of the group see http://www.environmentandhealth.org/
effects using maternal body burden as the exposure metric, it should be investigated what is the level of dioxin and PCB intake in the female population before the first pregnancy and the consequent body burdens.

- Risk assessment and risk management may result in unwanted outcomes, if certain principles are not followed. For instance, breast-feeding and fish consumption have clear health advantages, and if their use is discouraged, the total impact on health may be negative. It should be appreciated that any risk management without a careful cost-benefit assessment involves a risk of negative total impact on public health. Therefore research should be promoted in the EU to advance understanding in risk comparison and risk benefit assessment, in order to make more informed and better decisions possible in important environmental health issues. A thorough understanding of these considerations is important in applying the precautionary principle.

- New groups of chemicals are emerging, such as brominated diphenylethers and other brominated compounds. These compounds need some research effort to be included in dioxin and PCB monitoring programs. Simultaneous monitoring would be cost-effective, and integrated approach could help in early warning.
4.8 TWG indicators

The baseline related to “Environment and Health Indicators” is described in detail in the baseline report of the corresponding technical working group\(^ {10} \).

\(^{10}\) A syntheses of the baseline reports of the working groups established in frame of the EU Environment and Health Strategy can be found at the following URL: 

For the whole Baseline Report of the group see http://www.brussels-conference.org/
5 Research areas

5.1 Environment and health implications of electromagnetic field exposure

Paolo Ravazzani, prepared with the assistance of Gugliemo D’Inzeo, Jolanta Karpowicz, Norbert Leitgeb, Paolo Vecchia, Bernard Veygret

Additional keywords:
combined effects, children, regulations

Summary

Electromagnetic field (EMF) exposure from equipment such as power lines or mobile phone base stations and TV and radio transmitters are seen as a potential source of risk for the public health and the environment that present a difficult set of challenges for decision-makers. This document aims to provide overviews on: the state of the research on health and environmental implications of EMF exposure in Europe, the ongoing research activities, the possibilities to improve linkage to policy development, the future research needs, including also regulation issues and development of guidelines.

As to research priorities and non-priorities, a consensus has emerged over the recent years within the scientific community and the various sponsors and governments, on the use of research recommendations consisting of five priority lists covering epidemiology, human, animal, cellular studies, and dosimetry. Their main requisites span across three levels: (i) ongoing studies (now in progress and critical for future risk assessment), (ii) short-term or urgent needs (studies not yet begun but that should be initiated as soon as possible) and (iii) long-term or future needs. Such recommendations should be followed in future European research strategies. Overall, one of the major pending issue is that of the potential health risks related to the exposure of children: an association has been found between exposure to Extremely Low Frequency field (ELF) and leukaemia. It is of utmost importance to investigate whether this is a causal relationship and what are the mechanisms. This document, explores in details the research needs in: ELF, Radiofrequency Radiation (RFR), epidemiological studies, exposure of children, emerging technologies, combined exposure, long-term and occupational exposure, low- or non-priorities, regulations and guidelines.

Introduction

Among the environmentally related health issues and potential health hazards which are claimed to be related to new modified and combined exposures to environmental factors, exposure to electromagnetic fields (EMF) meets a significant growing public concern in some Member States. In view of the rapid growth in diffusion of applications based on these types of EMF, population exposure is almost universal and thus it is important to establish if an environmental hazard exists.

Research on the health implications of EMF exposure is a scientific area in which a significant number of studies are ongoing at many different levels (international and national, public institutes, industrial research, activities of normative and regulatory bodies). However, the large number of published studies creates a dramatic difficulty in providing relevant and timely input for policy development. This can result in misinterpretation or inappropriate extrapolation of scientific findings and hence in concerns of all stakeholders since health implications are not adequately addressed. Moreover, new and emerging technologies, which
continuously appear, may generate further health concerns and raise new questions that research must address. Based on these considerations and on the mandate of the Technical Working Group “Research Needs” in the framework of the EC SCALE project, the present document was developed to provide overviews on:

- the state of the research on health implications of EMF in Europe;
- ongoing activities and future needs on the possibilities to improve linkage to policy development, primarily in the field of the health implications of EMF exposure; this includes also the relative roles for national, regional and European research actions, on the health implication of EMF exposure;
- suggestions and recommendations for future research needs, priorities and opportunities on the topics related to EMF exposure and health.
- the future needs and priorities for regulation issues and development of guidelines, stemming from new emerging technologies, involving both the European Commission and other authorities at national level, and regulatory bodies.

Section 1. Research activity in Europe

Research on possible health implications of EMF exposure is being carried out by a number of industrial, national and international funding bodies, to investigate the biological effects and potential adverse health effects of EMF. Research related to EMF and health is currently active in Europe, as compared to other parts of the world. In the last ten years the level of research has decreased in North America and increased in Europe. The main reason for this change has been the change in public risk perception and the increased public concern in Europe about EMF in the environment, firstly with high-voltage power lines and now with mobile telephony handsets and base stations.

The various approaches that are needed to assess potential health risks (epidemiology, human, animal and cell studies) are all well represented in Europe. The critical mass has been reached in many laboratories where both physical and biological approaches can be combined. Epidemiology is also strong in Europe with several major ELF studies, in particular in the Nordic countries, and the large EC Interphone project on mobile phones and head-and-neck tumours, activated in the course of the 5th EC Framework Programme. Several major expert-committee reports have been published in recent years, in particular on mobile telephony and health.

National programmes have been set up in many European countries and several initiatives have helped foster and organise European research activity (COST actions 244, 244bis and the ongoing action 281, about 10 research projects in the 5th EC FP Framework Programme and one currently starting Coordination Action in the 6th EC FP), but there is still a lack of coordination in research objectives and means, in particular among the national programmes.

Section 2. Policy development, research perspective and relative roles for national, regional and European research actions

EMF exposures from equipment such as power lines or mobile phone base stations and radio and TV transmitters are seen as a potential source of risk that present a difficult set of challenges for decision-makers. These include: determining whether EMF exposure is a hazard and what is the potential health impact, i.e. risk assessment; recognizing the reasons why the general public may be concerned, i.e. risk perception; and implementing policies that protect public health and respond to public concerns, i.e. risk management. Responding to
these challenges requires the involvement of individuals and organizations with the right set of competencies, combining relevant scientific expertise, strong communication skills and good judgment in the management and regulatory areas. This will be true in any context, be it local, regional, national or trans-national such as the EU.

European research in this area is internationally acknowledged for the level of expertise, the quality of its research, the impact of its results at any level (scientific, technological, political, regulatory). Most of the research activity in Europe is funded by the European Commission (about 10 ongoing research initiatives) and also within the ongoing national programmes (e.g., in Finland, France, Germany, Italy, Norway, Poland, Slovenia, Sweden, UK, etc.), all of them with a European dimension, involving international partners. Moreover, European research in this area is in close contact with non-scientific stakeholders, such as European industry associations, customer associations, and regulatory bodies.

Ongoing research needs a dynamic infrastructure to help to develop, validate, maintain, and update a common knowledge database at the EU level on EMF health implications. This common basis for decision makers will increase the coherence of the approaches taken in the various Member States and help restore public confidence. This is one of the main priorities to be considered in order to provide timely and effective scientific inputs (priorities, gaps, prospects of on-going research and results) and relevant advice to the EU and Member States. Within the 6th FP, the European Commission has started to address this issue via a Coordination Action aimed to provide a framework for the coordination and dissemination of the results of the research activities in Europe. However, this initiative should be considered only as a first step for the improvement of the linkage to policy development primarily from the research perspective, on the health and environmental concern related to electromagnetic fields. To achieve this goal, future additional actions should be established to consolidate ongoing initiatives and achieved results.

Section 3. Research needs

A consensus has emerged over the recent years within the scientific community and the various sponsors and governments, on the use of the research recommendation agenda of the World Health Organization (WHO), within the framework of the International EMF project.

These recommendations cover the ELF and the RFR ranges, but neither static fields nor intermediate frequency ranges. They have been established by independent experts and revised recently for the RFR range. They consist of five priority lists covering epidemiology, human, animal, cellular studies, and dosimetry. Moreover, overarching issues are documented that help define the requisites for each approach. For each of these classes, they span across three levels: (i) ongoing studies (now in progress and critical for future risk assessment), (ii) short-term or urgent needs (studies not yet begun but that should be initiated as soon as possible) and (iii) long-term or future needs.

It is recommended that such recommendations should be followed in future European research strategies. There are gaps in the spectrum that, in particular in the light of new technologies, have not yet been sufficiently considered. Research projects should be initiated in these frequency ranges, as they are increasingly used in emerging applications (EAS11, RFID12, millimetre wave radars, etc.).

Overall, one of the major pending issue is that of the potential health risks related to the

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11 Electronic article surveillance  
12 Radiofrequency identification
exposure of children. Based on epidemiological studies, IARC has concluded that there is an association between exposure to ELF and leukaemia but this should be increasingly supported by experimental data. It is of utmost importance to investigate whether this is a causal relationship. Various approaches should be used in the laboratory to test the hypotheses. Of equal importance is the question related to the use of mobile telephones by children. More should be done to know whether they are more vulnerable than adults to this type of local exposure.

It is also urgent to learn more about potential health risks associated with the use of very high strength static magnetic fields such as those found in new MRI equipment (> 2 Tesla). Studies of bioeffects at high levels, i.e. close to the known critical effects as defined by the International Commission on Non Ionizing Radiation Protection (ICNIRP), are needed to decrease the uncertainties in the exposure guidelines.

In the following, these items will be described with some more details.

**Extremely Low Frequency fields**

ELF electric and magnetic fields are known to induce electric fields and currents in the body. No adverse health effects have been established below ICNIRP limits but some research suggests that biological effects exist below the limits. The current gaps in knowledge can be identified mainly in: i) study on the ELF magnetic fields in their “2B” classification by IARC; ii) investigation on the possible influence on epidemiological study results related to selection bias, transients and/or other mechanisms; iii) replication and extension of some in vitro studies; iv) studies on the role of duration and intermittency of exposure in the development of bioeffects; v) studies on the interaction at molecular and subcellular levels.

**Radiofrequency Radiation - RFR**

The current gaps of knowledge can be identified on topics in which some effects have been reported but not yet established and more research is needed, such as subjective effects (hypersensitivity), blood brain barrier, and heat shock proteins. Additional research and development are also needed in exposure assessment, development of personal dosimeters (for epidemiological studies, exposure assessment of populations for risk estimation) and improving exposure assessment specific of children.

As to the interaction mechanisms, although there are no novel relevant hypotheses to test, more work on micro-dosimetry at the cellular or sub-cellular levels might give new information about the targets of RF.

The main efforts in in-vivo and in-vitro studies should be provided on assessing effects on immune system, on the blood-brain-barrier and neural damage, on the test of new signals in large scale chronic studies, and on the stress and heat shock proteins induction, genotoxic effects, microdosimetry and molecular interaction.

The future epidemiological studies should mainly address prospective cohort studies of mobile phone users. Additional studies on potential long-term effects of whole-body exposure should be undertaken only after thorough investigations of the technical feasibility and performances of individual dosimeters capable of monitoring all components of the RF spectrum (e.g., TV, radio, base stations, mobile telephones, etc.).
Medical and health care applications and devices

The importance of the EMF exposure, also at occupational level, due to medical devices is due to the continuously diffusion and increase of such applications in the daily life of all Europeans. Future research needs in this area should address occupational exposure of health operators to EMF at any frequency and modulation and long-term exposure of patients to devices and/or treatments of various types. This includes exposure to EMF fields produced by imaging devices, prosthesis such as cochlear implants, and diagnostic and therapeutic treatments such as magnetic stimulation of the nervous system and bone reparation.

Research on emerging and future technologies

Research on EMF and health should consider the introduction of new technologies and devices using electromagnetic radiation and the need of performing new research. Emerging technologies with expected large-scale wide-spread use include telecommunication systems (UMTS, TETRA, Bluetooth, WLAN) with new smart applications; digital-broadcasting technology which are expected to replace present analogue techniques; electronic article surveillance systems together with smart labels applied for antitheft devices and product management with systems both for entrance and indoor placement; personal identification systems for access monitoring and/or limitation, new fee-charging solutions, health care applications, transport technologies such as magnetic levitation systems, anti-collision radar, vehicle piloting and surveillance, traffic control, road pricing, new industrial processing and manufacturing technologies; household and office applications such as inductive heating, wireless communication, power line communication, electronic power control, new medical technologies such as high field magnetic resonance imaging including spectroscopy for diagnostic and intrasurgical application, medical robotics, telemedicine, magneto-therapeutic applications, technologies used by authorities and military.

New and emerging EMF emitting technologies are associated with the following changes: existing frequency bands are used more intensively; the use of existing frequency bands is modified and allocated to new technologies; new frequency bands are used such as in the ultra-high frequency region; new signal structures are applied, e.g., for coded and multiplexed access; sources will become more and more mobile, numerous and omnipresent; both in the RFR and the ELF range, exposure will evolve to multiple frequencies and broadband frequency content; partial-body exposure from different sources at different sites of the body will become more and more common together with different public exposure pattern in terms of frequency and duration.

The rapid evolution of this ongoing dynamic technological process shortens the reaction time both for biological health-related research, technology assessment, and risk communication. This leads to an increased need for proactive measures. Therefore, a series of recommendations can be made, that can be summarised as follows:

- Existing reference limits for EMF-exposure, which are derived for whole-body exposure to homogenous fields, should be further developed to allow a practicable assessment of partial-body exposure to inhomogeneous fields.
- Product standards should leave as large as practicable an exposure margin to reserve space for new technologies and account for the increasing number of EMF contributions from mobile sources.
- There is a need for strategies for monitoring public exposure to EMF to become aware of unintended interference of EMF sources.
• Research funds should be allocated to investigate the possible health impact of new signal structures, including ultra wide-band pulses and new frequencies.

• Manufacturers should be encouraged to adopt a precautionary approach according to COM 2000(1) and make minimization of EMF emissions and body exposure a design criterion.

• Manufacturers should include EMF-related health issues in the risk management file of their products.

• Manufacturers should inform the user about relevant EMF emissions and possible restrictions concerning the associated conditions and/or requirements of use.

• A European radiation-protection committee should be installed to scientifically monitor the EMF related development and give advice to the commission.

• Specific attention should be given to adequate risk communication preparing and accompanying the introduction of new technologies rather than reacting to already arisen public concern.

• Health-risk assessment including EMF-related aspects should be made and communicated prior to large-scale introduction of new technologies.

**Occupational EMF exposure**

EMF occupational exposure is characterised by more complex frequency pattern than the exposure of general public. Different sources of ELF, RF as well as intermediate frequencies of EMF exist in occupational environment. EMF exposure dose of workers is generally much stronger than the one received by the general public from all kinds of electrical devices and even from power lines and mobile phone systems. Nowadays, occupational exposure to simultaneous multi-frequency fields comes very often from more than one emission sources as well as exposure to pulse or non-sinusoidal fields of single source exist. Moreover, modern industrial technologies are such that combined exposures between physical agents on one hand and between physical and chemical agents on the other are more likely to occur in industry than in daily life.

From those reasons, besides the above mentioned research needs for further EMF investigations, additionally specific research should be dedicated to workers prevention. More complex physical characteristics of exposure need specific assessment methods, for example when exposure assessment of non-sinusoidal fields is done according to the ICNIRP guidelines (multi-frequency exposure factor) an overestimation of exposure conditions can occur. There is specific need to study occupational exposure and outcome in groups of workers that have a high EMF exposure. Since the number of workers being in this category is small, it is necessary to perform a multinational study in order to get large enough samples to get meaningful results. There is need to pay more attention to workers with implants or chemical treatment, pregnant women and young workers exposure limits, exposure prevention methods and computer dosimetry of complex interaction between EMF sources, workers body and environment elements.

**Combined exposure**

The future of research on EMF and health will certainly encompass investigations of the synergies between EMF and other environmental factors since most health hazards are multifactorial in nature. It is thus recommended to design and use experimental models that include exposure to EMF and other physical, chemical or biological factors.
Low- or non-priorities

In this context of social concern and limited resources, there are some research axes that should not be continued or initiated. More epidemiological studies on ELF and childhood cancer are not considered of further value. In vitro experimenting on cultured cells is less informative than animal studies and should have a lower priority, except for the verification of specific interaction mechanisms. The new techniques of genomics and proteomics are very powerful but should be used with caution and aimed at improving the quality of animal investigations and not at determining the mechanisms of the action of the EMF.

Section 4. Regulation issues and development of guidelines

The regulation issues and development of guidelines in the field of the electromagnetic field devices and health and environmental effects of EMF are mainly related to both technical standards, that limit the EMF emissions from devices, and exposure standards, that limit EMF exposure to people and are scientifically-based. At the European level, the first task is performed by CENELEC, which has already issued several product standards. However, it is important that a continuous activity is maintained, in particular with regard to emerging technologies that require regulation of new sources of exposure. As regards exposure limits, there is a need for harmonisation, i.e. for national regulations based on a common approach. Important achievements have been gained by the European Union with a Recommendation issued by the Council in 1999 for the protection of the general public and with the development of a Directive for the protection of workers that is close to final approval. It is important that both are based on the guidelines of the International Commission on Non Ionizing Radiation Protection (ICNIRP), an international body formally recognised by the World Health Organization (WHO) and by the International Labour Office. ICNIRP periodically revises its guidelines in the light of new research findings and on reviews of the scientific literature carried out by ICNIRP itself as well as by WHO and the International Agency for Research on Cancer. It is of crucial importance that European recommendations and directives are revised accordingly. This task is best performed by establishing and maintaining tight liaisons with the above-mentioned organisations. Within the general context of harmonisation of national standards, there is special need to reconcile standards adopted in Western and Eastern European countries. Divergences exist, that are related on one side to different interpretation and evaluation of the scientific database, on the other side on different approaches to protection and to the development of safety standards. The harmonisation process is therefore tightly connected to the development of common research programmes and to the establishment of networks for the continuous exchange of data and experience. Finally, there is the absolute need that both workers and the general public trust that national and international standards are scientifically well founded, and adequate to protect human health. Therefore, the development of standards should be accompanied by continuous information to, and communication with the public.

Conclusions

The main conclusions on the future strategy and needs related to the environmental and health implications of electromagnetic field exposure can be summarised as follows:

- **State of the research:** research on possible health implications of EMF exposure is currently active in Europe, with research programmes at both national and European Commission level.

- **Linkage to policy development:** ongoing research needs a dynamic infrastructure to help to develop, validate, maintain, and update a common knowledge database. The
Coordination Action that the European Commission is starting in the 6th Framework Programme to this purpose is a first step and needs future continue actions to consolidate the achieved results.

- **Future EMF research priorities** can be summarised as:
  
  o **Extremely Low Frequency (ELF):** study on the effects of the magnetic fields in their “2B” classification by IARC, replication and extension of some in vitro studies, studies on the role of duration and intermittency of exposure in the development of bioeffects and on the interaction mechanisms.

  o **Radiofrequency Radiation (RFR):** studies on blood brain barrier, heat shock proteins, immune system, neural damage, subjective effects (hypersensitivity), test of new signals in large scale chronic studies, genotoxic effects and molecular interaction, studies on micro-dosimetry at the cellular or sub-cellular levels.

  o **Epidemiological studies:** prospective cohort studies of mobile phone users, studies on potential long-term effects of whole-body exposure to radio-frequency radiation that should be undertaken only after thorough investigations of the technical feasibility and performances of individual dosimeters capable of monitoring all components of the RF spectrum (e.g., TV, radio, base stations, mobile telephones, etc.), development of exposure and personal assessment, with particular attention to that one specific for children, studies on high level EMF exposed workers, influence of selection bias, transients and/or other mechanisms, particularly for ELF exposure.

  o **Exposure of children:** studies on the association found between exposure to ELF and leukaemia, to investigate whether that can be considered a causal relationship; studies on potential higher sensibility and vulnerability of children to exposure to EMF.

  o **Emerging technologies:** performing new, previously unexpected research, with an increased need for proactive measures due to the continuing introduction of new EMF technologies and devices at new frequency and modulation.

  o **Long-term and occupational exposure:** occupational exposure of workers to high levels of EMF, of health operators at any frequency and modulation and long-term exposure of patients to EMF produced by devices and/or treatments of various type.

  o **Combined exposure:** design and use experimental models that include combined exposure to EMF and other physical, chemical or biological factors, as well as personal conditions (e.g., health status, pregnancy).

- **Low- or non-priorities:** more epidemiological studies on ELF and childhood cancer are not considered of further value. In vitro experimentation on cultured cells should have a lower priority. Genomics and proteomics should be used with caution and aimed at improving the quality of animal investigations and not at determining the interaction mechanisms of EMF.

- **Regulations and guidelines:** monitoring of emerging technologies that require regulation of new sources of exposure and improving harmonisation of exposure regulations, particularly to reconcile the standards adopted in Western and Eastern European countries.
Key References


5.2 Traffic pollution, childhood allergy and asthma, and effects of long-term exposure on mortality

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Summary

Traffic is likely the largest source of exposure to outdoor air pollution in Europe today. Traffic not only is a major producer of hazardous air pollutants, but it also produces most of its pollution in places where human beings are concentrated. This is very different from pollution produced by power generation, which is nowadays usually away from population centres.

Traffic pollution has been implicated in many adverse effects on health in recent years, including in particular effects on children living close to busy roads. Although a series of measures to reduce traffic pollution are being implemented already, debate still surrounds these measures, and further information is needed to identify what more needs to be done.

New research is proposed to concentrate on:

- Assessment of human exposure to traffic exhaust
- Epidemiological and toxicological field studies of current exposures and of changes in exposure
- Health impact & risk assessment
- Toxicological evaluation of exhausts of different engine and fuel types
- Physico-chemical characterisation of traffic exhaust

This note is a further development of an ‘Expression of Interest’ that was submitted in June 2002 to the European Commission. This ‘Expression of Interest’ was supported by about 40 partners including all partners in the EU funded AIRNET Thematic Network on Air Pollution and Health (2002-2004) that is currently being coordinated by professor Brunekreef.

Key words: air pollution allergy asthma traffic mortality

Background

Of all environmental health risks, outdoor air pollution has been identified as the one currently leading to the largest loss of quality adjusted life years in the European region. At the same time, childhood allergic diseases and asthma have been increasing, and although a role of air pollution in this has been suggested, it is still very unclear what this role is. Especially air pollution in the form of fine particulate matter (FPM) has been shown to have many adverse effects including short-term and long term effects on mortality and increases in hospital admissions and in the prevalence of chronic respiratory disease. In recent years, traffic exhaust has been implicated as contributing significantly to exposure to FPM. It has been estimated that for Austria, France and Switzerland combined (population ~ 74,500,000), some 40,000 death per year can be attributed to air pollution, about half of which to air pollution from traffic specifically (Kuenzli N, Kaiser R, Medina S, et al. Public-health impact of outdoor and traffic-related air pollution: a European assessment. *Lancet* 2000; 356 : 795-801). Similarly high numbers have been estimated for respiratory and cardiovascular hospital
admissions, bronchitis episodes and restricted activity days. Cardiovascular diseases have also been associated with air pollution exposure in recent years.

Recent studies from Europe are also implicating traffic exhaust more and more in manifestations of childhood allergic disease. Two large studies, both conducted within the framework of the International Study on Asthma and Allergies in Childhood (ISAAC), are particularly worth mentioning because they used detailed characterisation of exposure to traffic exhaust, and objective measurements of allergic sensitisation. The study from Germany (Nicolai et al., European Respiratory Journal 2003; 21: 956-963) found that asthma, wheeze and cough were associated with traffic counts, and that among children with smoking parents, there was more allergic sensitisation associated with high exposure to traffic exhaust components. The Dutch study (Janssen et al., Environmental Health Perspectives 2003; 111: 1512-1518) found increases in respiratory symptoms in children living in areas with pollution from high truck traffic counts on the adjacent freeway. Exposed children also had more sensitisation to pollen, and children who were sensitised experienced more symptoms in areas with high exposure.

Traffic exhaust has also been implicated in premature mortality in the first European cohort study on air pollution and mortality that was published (Hoek et al., Lancet 2002; 360: 1203-1209). Living close to busy roads in cities, or to freeways, was found to be associated with an almost twofold increased risk of death due to cardiovascular or respiratory causes.

Petrol and diesel engines produce combustion particles and gases and contribute also to secondary formation of particles and ozone due to chemical reactions in the atmosphere. Although strenuous efforts are being made to reduce emissions, some of these reductions have been offset by strong increases in traffic volume, and real-world emissions may be higher than emissions measured in the laboratory as required by current EURO regulations. Also, off-road emissions have not been addressed with similar intensity as on-road emissions so that the relative contribution to air pollution of transport by rail, ships, and off-road combustion engines used in farming, building etc is expected to increase.

A research programme is needed that will systematically cover physico-chemical characterisation of traffic exhaust (including combustion engines used in off-road applications), toxicological evaluation of exhausts of old and new engine and fuel types, assessment of human exposure to traffic exhaust, and toxicological as well as epidemiological field research to investigate effects of current exposures as well as changes in health status related to exposure reductions in the real world. Most of past laboratory and epidemiological studies on diesel emissions have focused on lung cancer risk rather than on cardio respiratory effects attributed to ambient PM. Most available literature on non-cancer effects addresses old-technology engines, focusing on the particulate fraction. Changes in gasoline and spark-and compression-ignition engine control technologies have clearly reduced the total particulate mass emissions but whether changes in chemical composition are also occurring, and if so, in what direction of toxicity, is much less certain.

**Expected results**

The expected results of new research in this area are:

for public health and environmental policy makers: detailed insight in health effects of traffic
related pollutants; improved basis for standard setting; improved basis for making health impact assessments. Contribution to sustainable transport policies adequately protecting the health of the population including sensitive subgroups such as children with asthma.

for oil and automobile industry: guidance for technology development aimed at reducing the most harmful components of traffic-related air pollution.

for patient organisations and other NGOs: improved insight in distribution of susceptibility to traffic-related air pollutants in the population; improved insight in policy options at local and (intern)national scale to reduce population exposure to traffic-related air pollution.

for the European scientific community: new insights of a basic as well as applied nature, publishable in the highest-ranked journals; training and manpower development of young researchers needed to develop the involved fields of science further in the future; strengthening of research collaboration and infrastructure in Europe.

Suggested research priorities

Assessment of human exposure to traffic exhaust

Traffic exhaust almost by definition has a high intake fraction, i.e. a relatively small dilution from source to human receptor. Because there are very large numbers of mobile sources in Europe, the spatial variability of exposure to traffic exhaust is relatively large over small distances. The temporal variability of exposure to primary traffic exhaust is also large when considering daytime vs. night time traffic and rush-hour peaks. In addition, exposure and thus health impacts inside buildings are significantly modified by the ventilation and air conditioning techniques. As a result, there can be large differences in exposure to traffic exhaust within the population depending on location of home, school and workplace. Depending on the route and method of commuting, the intake fraction is higher still in the midst of traffic, where the ‘sources’ (= motor vehicles) and ‘receptors’ (= human beings) move within just metres from each other. In order to support quantitative risk assessment, a large effort is needed to characterise exposure to traffic exhaust in the population, and to specifically link the exposures to cars with diesel and petrol engines, with and without catalytic converters, busses, trucks, scooters and motor bikes. This is especially true when considering potentially important exhaust characteristics such as particle number, composition and presence of semi-volatile components. Special attention needs to be paid to assessing exposure at the very local scale using advanced Geographic Information System tools that have recently been successfully implemented in environmental health research and risk assessment, in combination with detailed air quality models. Validation of exposure estimated by GIS techniques by personal monitoring is also of crucial importance.

Epidemiological and toxicological field studies of current exposures and of changes in exposure

There is emerging evidence that exposure to traffic-related air pollution is associated with a variety of adverse health effects including premature mortality due to lung cancer and cardiopulmonary causes; childhood allergy and respiratory disease; childhood cancers and adverse pregnancy outcomes. Many of these associations are still tentative, requiring substantiation in studies using objective measures of exposure and health. Integration of toxicological and epidemiological approaches is in particular promising as this will significantly increase credibility of study findings. A variety of endpoints is proposed, with emphasis on premature mortality due to lung cancer and cardiopulmonary causes, childhood
allergy and respiratory disease, and incidence of cardiovascular disease. Premature mortality has been associated with air pollution exposure in studies conducted in the US and recently also in Europe, the latter study pointing to traffic-related air pollution specifically (Hoek G et al.. The association between mortality and indicators of traffic-related air pollution in a Dutch cohort study. Lancet 2002; 360: 1203-9). Childhood allergic disease has been increasing steadily in Europe, and although air pollution in general is not thought to play a major role in the increase, there is mounting evidence of interactions between traffic exhaust and allergen exposure in stimulating the process of allergic sensitisation as well as aggravation of existing allergic disease. As the technology to conduct on-site toxicological studies with real-life exposures has been significantly developed in recent years, it is now also possible to combine the epidemiological and toxicological approaches in truly integrated studies.

As traffic exhaust is an extremely complex and variable air pollution mixture, traditional toxicology studying one component or simple mixtures at a time in laboratory settings is unlikely to produce a complete answer to questions with respect to which components or attributes of the mixture are primarily responsible for effects on health.

A powerful approach to support a causal role of specific mixtures or sources is to systematically study changes in exposure as they occur in the real world. There are many changes taking place in exposure to traffic exhaust in relation to road openings and closings, traffic rerouting measures etc. Few if any attempts have been made to systematically study changes in exposure related to, and possible health consequences of such changes.

**Health impact & risk assessment**

Integration of knowledge from exposure and effects research is needed to qualitatively and quantitatively model the risk from sources to health effects; to assess health impact and risk to specific population groups and assess uncertainty. Health impact and risk assessments are very important to disseminate to, and discuss with, stakeholders from various sectors in society. New research should link source-emission-exposure-health oriented research groups, stakeholders, national governments (and their environmental action plans) and international agencies and bodies involved in transport, emission and health control.

**Toxicological evaluation of exhausts of different engine and fuel types**

In order to evaluate new technologies as they are being developed for the market, toxicological studies utilizing in vitro and inhalant in vivo techniques are needed. Predictive toxicology is needed to assess which of various new technologies are most promising to reduce toxic emissions. In the absence of such knowledge, the health risks associated with new technologies can only be evaluated after they have been introduced by health effect screening and epidemiological studies. Research needs to be targeted at technologies which are likely to have the highest market penetration in the next ten years such as direct injection gasoline engines, high pressure common rail injection diesels, pressurised natural gas powered city vehicles, gas-electric hybrid automobiles and new catalytic converters and diesel particle traps.

**Physico-chemical characterisation of traffic exhaust**

Although not directly related to health, physico-chemical characterisation of traffic exhaust is also needed. The emphasis here needs to be on on-road characterisation of traffic exhaust using a standardised methodology in real-world situations representative of high exposures. These include roadway tunnels and street canyons with detailed characterisation of traffic
composition. In parallel, emission studies are needed using dynamometer facilities to measure how the particulate composition relates to engine type and driving conditions. Studies need to be conducted in a number of different European areas to systematically evaluate differences relating to differences in fleet composition (in particular engine types), maintenance, climate, and the like. Existing models need to be improved to be able to generalise the emission and air quality data. This will provide detailed insight in determinants of traffic exhaust concentrations and compositions in different European areas. In addition to on-road studies, a specific attention is needed for characterisation of air quality near shipping lanes, off-road equipment and railroads used by diesel locomotives to assess the impact of these as yet poorly characterised sources on air quality.
5.3 Climate change and climate variability

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Summary conclusions

The climate in Europe is changing, and the intensity and frequency of extreme weather events, such as floods and heat waves are likely to change in the future. Rapid climate change is anticipated to have a range of impact on health population health. Within Europe, research is needed to:

- Develop appropriate methods for quantifying and understanding the potential impact of climate change on human health, including assessment of effect modification in weather-health relationships and health impact assessment including scenario development, and evaluation on uncertainties.
- Improve our quantitative evidence on the effects of heat waves and hot weather in order to understand the underlying mechanisms and how heat-related illness and premature mortality can be prevented.
- Improve our quantitative evidence on flood-related health impacts and how they can be prevented.
- Improve projections of the impact of climate on air quality, particularly tropospheric ozone.
- Clarify the relationship between changing climate, allergens and allergic disorders to improve forecasting accuracy.
- Assess the potential effect of climate change on current and emerging vector-borne diseases in Europe, improve surveillance, and develop risk management strategies.
- Clarify the mechanisms by which changes in temperature and rainfall may increase the risk of infectious diseases in the water supply and in food.
- Evaluate the health benefits and costs of measures for adaptation and mitigation, and improve assessment of the short-, medium-, and long-term health effects of the different methods of energy production, including fossil fuel combustion and renewable technologies, and energy efficiency policies.
- Improve understanding of individuals' perceptions of, and responses to, climatic changes and resulting health impacts.

Climate change

The European Science Foundation Report in 1999 made recommendations regarding research tasks for the health impacts of climate change and stratospheric ozone depletion:

Improve the epidemiological and mechanistic science base and develop predictive methods for assessing the future health risks of human induced climate change and increased UV radiation.

This research need still stands. The need to develop appropriate strategies and interventions to reduce impacts on health is also becoming urgent. Climate change is already beginning and extreme events have had a demonstrable effect on human health (e.g. August 2003 heat wave in western Europe). [The ESF report addressed health effects of stratospheric ozone depletion but these are not addressed here]
The climate in Europe is changing. The global average land and sea surface temperature has increased by 0.6 ±0.2 °C since the mid-19th century (IPCC, 2001). Warming has been observed in all continents, with the greatest temperature changes occurring at middle and high latitudes in the Northern Hemisphere. Minimum temperatures are rising faster than maximum temperatures. Patterns of precipitation have also changed. There has been a disproportionate increase in the frequency of the heaviest precipitation events. The region stretching from the Mediterranean through central Europe into European Russia and Ukraine has experienced decreases in precipitation by as much as 20% in some areas. The current projections from the IPCC suggest an increase in global mean temperature in the range of +1.4 to +5.8°C by 2100 for the full set of plausible emission scenarios (IPCC, 2001). In Europe, it is projected that there will be less precipitation in the southern areas and a risk of desertification, and an increased risk of riverine flooding is indicated in many northern and central regions (Palmer and Raisanen, 2002). However, uncertainties are considerable with regard to projections at the local or national level.

State of research on topic in Europe.

Mitigation is used to describe any policy intervention to reduce the sources or enhance the sinks of greenhouse gases. “Adaptation” is used to describe strategies, policies and measures undertaken now and in the future to reduce potential adverse impacts of climate change. The ultimate objective of the United Nations Framework Convention on Climate Change (UNFCCC) is to achieve:

... stabilization of greenhouse gas concentrations in the atmosphere at a level that would prevent dangerous anthropogenic interference with the climate system. Such a level should be achieved within a time-frame sufficient to allow ecosystems to adapt naturally to climate change, to ensure that food production is not threatened and to enable economic development to proceed in a sustainable manner.

The Parties to the UNFCCC must periodically communicate information related to its implementation to the Conference of the Parties. National Communications should address population vulnerability to the potential effects of climate change. Only two European countries have undertaken comprehensive national assessments of the health impacts of climate change: Portugal (Casimiro and Calheiros, 2002) and United Kingdom (Department of Health, 2002).

The Intergovernmental Panel on Climate Change (IPCC) is responsible for providing assessments on the science of climate change and its potential impacts. Although there have been chapters devoted to human health in both the Second and Third Assessment Reports, these have been limited by a lack of published research. The main policy questions have been characterised by the IPCC for the forthcoming Fourth Assessment Report, and these represent the current research challenges:

1. What is the evidence for the effects of regional climate change? What is observable now?
2. What are the likely impacts of future unmitigated climate change?
3. How much can the projected effects be reduced by adaptation?
4. What would be the effects under different levels of mitigation (including stabilisation)?

The first question needs to be answered by empirical assessment, including epidemiological studies (Kovats et al. 1999). Research in this area is currently limited by lack of long term health data series and the, as yet, small climate change signal. The second and fourth questions require information to be derived from scenario and sensitivity analyses from
integrated assessment (predictive) modelling. The third question requires assessment of current and potential practice, including the effectiveness of public health and related interventions. The development of predictive models, as recognised by the ESF (1999) is a research priority. Health impact models have been developed for a limited range of climate-sensitive outcomes. Scenarios of climate change, population growth and other non-climate factors need to be developed in order undertake sensitivity analyses. An additional important research component is describing and quantifying the uncertainty in the assessment.

Within the EC Fifth Framework programme, CCASHH (Climate change and adaptation strategies for human health) has undertaken impact and adaptation assessment for a range of health outcomes in Europe, and the PHEWE project is addressing the current impact of high temperatures in European cities. Several proposals are currently being reviewed under the 6th Framework Programme, and one Integrated Project that includes regional quantitative health risk assessment has been funded (ENSEMBLES). The Global Change Unit at the WHO European Centre for Environment and Health, Rome, has played an important role in coordinating research and policy in this area. Climate change is now one of the environmental risk factors in the WHO Global and Regional Burden of Disease Comparative Risk Assessment 2002 (McMichael et al. 2004).

Research needs

Climate change is anticipated to affect a range of health outcomes, by a variety of mechanisms:

- **Climate change and air quality**: Research is needed on the potential effects of climate change on air quality, including the effects on daily levels, seasonal patterns and changes in geographical distribution. During winter in temperate countries, air pollution episodes are often caused by stagnant weather conditions, and these are projected to decrease in frequency under climate change (UK Department of Health 2002). Summer ozone episodes affect a larger region, and may increase due to climate change.

- **Pollen and allergic diseases**: The onset of spring in Europe has moved forward by 7-10 days since the 1950s. Climate warming is likely to cause an earlier onset and may extend the duration of flowering and pollen season for some late-flowering species (grasses and weeds) that produce important allergens (WHO et al. 2003). Climate change may also facilitate the geographical spread of allergenic plant species (e.g. ragweed and mugwort). There is a need for multidisciplinary collaboration to further clarify the relationship between changing climate, allergens and allergic disorders and to improve forecasting accuracy and effectiveness.

- **Vector borne diseases in Europe**: The ecology and transmission dynamics of infectious diseases that depend on transmission via an intermediate "vector" organism (mosquito, flea, tick, etc.) is complex. Under climate change, some vector-borne diseases are anticipated to expand their range north within Europe (e.g. leishmaniasis), whilst some may contract their range within central Europe (e.g. tick-borne encephalitis) (UK Department of Health 2002; Maier, 2003). There is some limited evidence that the northern limit of the distribution of ticks in Sweden has changed between 1980 and 1994 (Lindgren et al., 2000). Research is needed to assessment whether climate change will increase the transmission season of tick-borne diseases (such as Lyme Disease) and entail changes in human behaviour that lead to increased contact with the tick vectors, and whether such changes increase the total burden of the disease in the population (UK Dept of Health, 2002).
Emerging vector borne diseases: It is very unlikely that “tropical” diseases such as malaria or dengue would become re-established within Western Europe if current control measures are maintained. However, climate change may increase the small risk of localised outbreaks of malaria (Kuhn et al., 2003). In eastern Europe, health resources are scarce and thus imported infections are less likely to be treated quickly, creating a potentially larger natural reservoir of malaria parasites. The importance of considering other factors in relation to future disease transmission can therefore not be underestimated and these factors, in turn, can only be identified by examining historical patterns of disease. Research is needed on the historical patterns of vector-borne diseases and improved models for climate-related risk assessment, in conjunction with improved surveillance of pathogens and vectors.

Foodborne diseases: Environmental temperature is considered an important factor in the transmission of bacterial agents causing enteritis. Pathogens such as salmonella multiply at room temperature, and cases of salmonellosis populations have an approximately linear relationship between temperature, above a threshold (Kovats et al. 2004). Higher temperatures in the week before illness are most strongly indicated as contributing to infection. The mechanisms by which weather factors facilitate infection need to be further investigated.

Waterborne diseases are usually understood to be those diseases that are spread via water that is contaminated with faecal material. There is some epidemiological evidence that heavy rainfall events or extreme run-off are associated with outbreaks of waterborne disease (Curriero et al. 2001). Research is need in Europe to determine the role of weather and specifically wet-weather events in the transport of water borne pathogens in surface and ground water. Research is needed on the effect of changes in rainfall regimes on water supply and sanitation systems in Europe, and the consequent risks of water-borne disease.

Climate variability and extreme weather events (heat waves, floods, etc)

The intensity and frequency of extreme weather events, such as floods, heat waves, and cold spells, is likely to change in the future, and populations are becoming increasingly vulnerable due to population growth in coastal and flood plain areas, and population ageing. Extreme weather events have caused recent problems in Europe, particularly in urban areas. These events will continue to pose additional challenges to health risk management, and to the reliability of the power supply and other infrastructure. The development of effective strategies and interventions to reduce the effects on health of the increased frequency of extreme weather events requires:

1. Quantitative studies to assess individual and group risk factors and vulnerabilities
2. Development of weather based quantitative risk assessment models and warning systems.
3. Establishment of surveillance systems to provide timely information on the health impacts of extreme weather events, in order to improve responses.
4. Qualitative studies on the links between weather, health impacts and socio-cultural characteristics regarding acceptance, behaviour and reaction.
5. Qualitative research to better understand risk, trust and perception in institutions providing health related information, underlying education and knowledge.

Heat waves and hot weather: Europe has experienced an unprecedented rate of warming in recent decades during 1976-1999 the annual number of warm extremes increased two times faster than expected from the corresponding decrease in the number of cold
extremes (European Climate Assessment, 2003; Hulme et al., 2002). Climate change will cause summer conditions in large towns and cities to become more stressful as the number of hot days increase, exacerbated by the urban heat island effect. There will be pressure to increase the use of domestic air conditioning which has implications for health, energy use and greenhouse gas emissions. Heat waves have a significant impact on human health. Preliminary reports estimate more than 14000 excess deaths in France during the heat wave of August 2003 (IdVS, 2003). Little is known about the factors that determine the risk of heat-related mortality, especially in the elderly and those with pre-existing cardiovascular disease (see section 5.10). Research is also needed on the mechanisms by which hot weather increases morbidity in children, from respiratory and bacterial diseases. There is need to undertake studies in Europe to determine the risk factors for heat-related mortality in relation to social networks, housing type and for residents in institutions. Research is needed to improve our quantitative evidence on the effects of heat waves and hot weather in order to understand the underlying mechanisms and how heat-related illness and premature mortality can be prevented.

- **Heat waves and air pollution.** Research is need to address co-exposures to, and possible interactions with air pollutants during periods of high temperatures. Recent work suggests that the 2003 summer heat wave effects on mortality in the UK and the Netherlands were in part due to air pollution (ozone and to a lesser extent fine particles) which were also increased during the heat wave (Stedman 2004 Fischer et al. 2004). A study from Taiwan found that air pollution was associated with the incidence of stroke on hot days but not on cool days (Tsai et al., 2003).

- **Flood events:** In Europe, floods are the most common natural disaster. In recent years, major flood events have occurred in the Rhine, Meuse, Po, Danube, Elbe and Oder rivers. The adverse human health consequences of flooding include deaths and injuries, gastrointestinal and respiratory infections, and an increase in common mental disorders (Hajat et al., 2003; Bennet, 1970). Given the consistently high correlation between physical and psychiatric morbidity, increased rates of CMD may contribute to both higher rates of medical consultation following a flood and to increased mortality. Qualitative research studies have pointed towards disproportionate impacts on women, the elderly, and children (Ohl and Tapsell, 2000). The limited evidence on children's health and behaviour suggests that they appear more prone to mental disorders in the longer-term. Research is needed to undertake systematic analysis of flood-related health impacts using data from multiple flood events in order to provide evidence needed for planning health service and emergency responses to flooding and the longer-term support for flood victims. Specific research is needed to (WHO, 2001): 1) formally assess the effectiveness of flood forecasting and warning systems, including the targeting of warnings to vulnerable groups; 2) develop methods for environment and health impact assessment of flooding; 3) assess communities’ capacity to respond to and manage flooding and its effects on health; and 4) develop monitoring tools for the health impact of all categories of flooding.

*Energy and health*

There is a need to evaluate the health benefits and costs of measures for adaptation and mitigation. Different forms of power production are associated with varying health impacts to industry workers and the general population. While some health impacts occur with very short time lags, others (e.g. those associated with chronic exposure to airborne pollutants) may occur after a time lag of some years. In the case of climate change, the impacts are predicted to build over a period of decades and centuries. Trans-boundary transport of pollutants and
the processes of climate change mean that populations distant from the original site of power generation can be adversely affected.

Actions taken to reduce greenhouse gas emissions are very likely to benefit population health (Barker and Srivastava, 2001; Cifuentes et al., 2001). Fossil fuel combustion releases both local hazardous air pollutants (especially particulates, ozone, nitrogen oxides and sulphur dioxide) and greenhouse gases. Hence, policies to reduce greenhouse gas emissions via a reduction in vehicle exhausts or other traffic policy measures could yield benefits to health. Controlling road traffic could also benefit health through reductions in road traffic accidents and a possibly a decrease in sedentary lifestyles. From a health perspective, it is therefore very desirable that greenhouse gas emissions from all sources, including power generation, are reduced, so that the rate of climate change is slowed. There is a need to develop methods to quantify the health benefits of climate policies, and specific mitigation strategies.

The European Commission ExternE project assessed selected fuel cycle impact pathways, and estimated the impacts in terms of costs (see section 5.7 on Health Impact Assessment and Cost Benefit Analysis). The impacts on human health in the power sector are greatest from coal cycles, followed by oil and gas cycles. There has been a shift in the types of fuels used, away from coal and towards the relatively cleaner ones, such as gas, in several Central and East European countries. Studies show that the health and the environmental benefits easily make up for the higher costs associated with renewable energy use. Many of the health impacts of energy are related to energy poverty and the increased use of indoor biomass burning which is responsible for a considerable burden of respiratory disease in women and children (Menne and Markandya, 2003). Research is needed to evaluate the health benefits and costs of measures for adaptation and mitigation, and improve assessment of the short-, medium-, and long-term health effects of the different methods of energy production, including fossil fuel combustion and renewable technologies, and energy efficiency policies.

References


European Climate Assessment 2003.


Fischer et al. 2004 Atmos. Env. In press.

Hulme,M, et al., 2002, Climate Change Scenarios for the United Kingdom: The UKCIP02 Scientific Report, Norwich, Tyndall Centre for Climate Change Research.


Kuhn,K, D Campbell-Lendrum, B Armstrong, C R Davies, 2003, Malaria in Britain: past, present, and future. PNAS , 100: 9997-10001.


Maier,W. Possible effects of climatic changes on the distribution of arthropod (vector-) borne infectious diseases and human parasites in Germany. 2003. Berlin.


Stedman J 2004 Atmos. Env. In press.

WHO. 2001. Floods: Climate Change and Adaptation Strategies for Human Health. EUR/01/503 6813.. Copenhagen, WHO.

5.4 **Environmental health genomics and biomarkers**

The topic is closely related to chapter 4.4 on biomonitoring in children.

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*Summary and conclusions*

A concerted and sustained effort is required to develop a European-wide effort in the area of Environmental Health Genomics and Biomarkers which is expected to impart a major boost to our understanding of the basis of environmental disease. This effort should be based on the co-ordination and integration of multi-disciplinary activities, including

- the discovery and characterisation of environmental response-relevant genes,
- the charting of genetic variation in human populations,
- the assessment of the functional impact of genetic variants on environmentally relevant genes,
- environmental exposure assessment, and
- the development, validation and exploitation of molecular biomarkers.

*Environmental Health Research in the post-genomic era*

The recent completion of the sequencing of the human genome, in combination with technological advances in high-throughput characterisation of DNA sequences as well as RNA and protein expression, are revolutionizing biological research. By permitting a global view of cellular processes, these advances, which are covered by the areas of genomics, transcriptomics, proteomics, metabolomics ("-omics") are driving a novel, systems-biology approach to the understanding of the working of the cell and how it responds to environmental stresses. The opportunities provided by these advances to environmental health research are immense and there is an urgent need for the European Union to formulate a concrete strategy for their development and application on a continent-wide scale. Such strategy offers unique opportunities to disentangle the etiological basis of multi-factorial chronic diseases, to understand the basis of individual susceptibility and to understand environment and gene interaction, thus opening the way to effective prevention strategies.

During the previous decade, the discovery of genetic variation in genes of relevance to cellular response to environmental agents led to increased emphasis being given to genetics as a determinant of disease. However, the experience accumulated has shown that only a small fraction of the overall disease burden can account for by relatively rare kinds of genetic variation which by themselves impact high disease risk on their carriers (high-penetrance genes). On the other hand, most genetic variations so far discovered (no doubt making up only a small fraction of the total human genetic variation) have only small effects on individual risk by modifying the effect of the environmental exposure.

In addition to genetics, environmental exposure plays a major role as a disease determinant, as indicated, for example, by recent twin studies which suggest a contribution of 50-90% to risk variance for most cancers (Lichtenstein et al., 2000). Thus, it is clear that in order to properly analyse the influence of genetic variation on disease risk, relevant environmental exposures need also to be taken into account.
The study of gene-environment interactions in the post-genomic era

Although the importance of the interactions between genetics and exposure in the causation of environmental disease is well recognised and has received great attention during recent years, the approach employed up to now has focussed on studies of the interaction of one, or at most a very small number of genes, with a single environmental agent and a single response pathway. It is clear that to comprehend the way in which genetic variation causes significant changes in risks it will be necessary to a) understand the functional significance of the various DNA sequence variations, b) look at the effects of combinations of variant sequences on disease risk and c) place the effects of genetic variation within the context of specific exposures. Furthermore, the regulation of genes may also be influenced by environmental factors, making the systems even more complex. Achieving these tasks requires enormous efforts and resources, and, while current theoretical and technological advances in the "-omics" area greatly facilitate progress, the required effort remains truly immense and will require a well co-ordinated, continent-wide multidisciplinary approach involving studies in molecular biology, biochemistry, structural biology, xenobiotic metabolism, analytical chemistry, bioinformatics, biomarker research and population studies (classical and molecular epidemiology). The relevance of the scientific areas just mentioned, is briefly outlined below:

1) Discovery and characterisation of environmental response-relevant genes:

A key question concerns understanding which genes, or gene circuits, are important in the cellular response to environmental stresses, and how they operate to provide defense or contribute to the development of adverse effects. This requires studies of fundamental mechanisms, and is greatly facilitated, on a theoretical as well as a practical level, by current advances in the analysis of genome-wide changes in gene expression (transcriptomics and proteomics).

2) Charting genetic variation in human populations:

Current evidence suggests that sequence variation in the human genome is common, with a single-nucleotide polymorphism (SNP) occurring on average every 2-3 thousand nucleotides. Already many polymorphisms are known in a large number of genes of relevance to environmental influences, including genes involved in xenobiotic metabolism, cellular response to environmental stress, repair of DNA damage, regulation of cell cycle, apoptosis etc. A systematic search of genetic variation, in genes of relevance to environmental disease, in individuals covering the likely range genetic variation in Europe would lay the foundations for further studies aimed at the identification of susceptible individuals and populations.

3) Assessment of the functional impact of genetic variants on environmentally relevant genes, e.g. primary defense and cellular signal transduction pathways:

A sequence variation in a gene may have a greater or lesser impact on the function or on the level of expression of the corresponding gene product, or it may have no effect at all. Understanding the functional consequences of the multitude of SNPs, currently known or likely to be discovered, in environmentally-relevant genes is a major task, which could be approached by utilising a range of methodologies, ranging from computer modelling of protein structures, protein structure elucidation using crystallography or NMR methodologies, expression of the mutant proteins and assessment of their activity using biochemical techniques, to the construction of transgenic animals bearing the variant genes. In view of the large number of possible structural variations that would need to be assessed by such methodologies, a rational step-wise utilisation of techniques of increasing technical and
budgetary demands would need to be adopted.

Most biological processes depend not on a single gene product but on large number of gene products operating in the context of complex pathways. Consequently a functional variation in a single gene product may have only a minor effect on the overall efficiency of the complete pathway, while a specific combination of variant products simultaneously acting in the same individual may impact significantly on pathway efficiency. For example, it is currently recognised that, for some complex pathways of DNA repair, involving tens of genes, the frequency of natural sequence variation means that many hundreds of variants may occur throughout the pathway, and that any given individual is likely to carry a combination of 10 or more variant genes (Mohrenweiser et al., 2003). Elucidation, as described in the previous paragraph, of the functional significance of the different polymorphisms in each component gene would facilitate selection of the combination(s) of variants most likely to have a significant impact on overall pathway efficiency.

4) Environmental exposure assessment:

As already noted, examination of the role of genetic variation should ideally be carried out in connection with knowledge of environmental exposure. Modern analytical methodologies based on high-resolution NMR, liquid chromatography and mass spectrometry, have made great strides in facilitating the analysis of xenobiotic chemicals, or their metabolites, in body fluids (blood, urine) with great sensitivity and efficiency, thus facilitating the assessment of individual exposure to xenobiotics.

5) Development, validation and exploitation of molecular biomarkers:

Biomarkers have been defined as "indicators signalling events in biological systems or samples”, representing both the environmental agent and the adverse effect i. Biomarkers of relevance to environmental health include biomarkers of exposure, usually xenobiotics or their metabolites in human fluids or tissues, or their complexes with cellular components (e.g. proteins or DNA), or biomarkers of early effect, which vary widely depending on the type of effect or disease concerned – in the case of cancer they usually refer to permanent genetic damage, such as gene or chromosome mutations, or early changes in cellular structure of function related to neoplastic development. The use of biomarkers of exposure and early effect in population studies can help to increase the accuracy of exposure assessment at the individual level and reduce the time intervening between exposure and recognition of disease-related events, and greatly facilitate the investigation of the environmental and genetic etiology of disease as well as the assessment of the effectiveness of trials of preventive intervention and remediation policies.

During the past decade great strides have been made in the development and application of biomarkers, especially in the area of environmental carcinogenesis (Groopman and Kensler, 1999). This progress has helped to establish the usefulness of such biomarkers in exposure assessment, an achievement which should prove fruitful in the future if combined with genetic variation analysis as described above. However, biomarkers reflecting chronic or long-term exposure are still lacking, and there is need for further research in this area.

Significant progress has also been made in the development of biomarkers of early effects and their assessment as risk predictors, with results which are clearly positive in some cases [chromosome aberrations and cancer; Bonassi et al., 2000]) or, currently, suggestive in others [bulky DNA adducts; Tang et al., 2001). These findings hold great promise and need to be backed by further research, especially focussed on the assessment of the risk-predictive ability
of additional biomarkers.

The use of the –omics in biomarker development offers new advantages at more relevant markers of biological effects may be discovered, and that the effect markers or clusters thereof may be more specific for the exposure and dose of exposure - toxicogenomics.

Although most of the newer biomarker work has been focused on cancer, the same approached can be used for other chronic diseases.

Organisation and implementing a European effort in environmental health genomics

For most of the areas described above, there exist high-calibre research groups spread throughout the European Union. In view of the complexity and the multidisciplinary nature of the research activities covering these areas, a concerted and sustained effort is required in order to achieve the degree of continent-wide interaction and integration needed to maximise the corresponding benefits, and to develop an activity of the scale and ambition to compete with the American "Environmental Genome Project". Among other priorities, this effort would need to aim at

a) the co-ordination of diverse specialities,

b) the creation of large-scale facilities,

c) the promotion of maximal exploitation of existing tissue banks as well the creation of new, including banks related to mother-child cohorts in order to study impact of environmental factors in utero and early life on the development of environmentally related diseases or altered behaviour, and

d) the training of scientists in the new and technologically rapidly developing fields.

References


Groopman JD, Kensler TW. The light at the end of the tunnel for chemical-specific biomarkers: daylight or headlight? Carcinogenesis 20 (1999), 1-11


Mohrenweiser HW, Wilson DM 3rd, Jones IM. Challenges and complexities in estimating both the functional impact and the disease risk associated with the extensive genetic variation in human DNA repair genes. Mutat Res. 526 (2003) 93-125

5.5 Water

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Keywords
Health, research, water, environment

1. Introductory comments (state of the related research)

Water research in relation with health and the environment must be undertaken in an integrated way, considering all parts of the water cycles (natural and anthropic). Nevertheless, for the definition of the actual state-of-the-art, we need to divide water research into several items. For each of them, we will describe the relationships with health and environment.

a) Water resources
b) Water supply
c) Wastewater
d) Water for other uses (bathing, air conditioning…)
e) Analytical tools
f) Risk related research
g) Information and socio-economic aspects
h) Technologies
i) Rules and regulations
j) Other.

Although this presentation is related only to water research, emphasis must be made in the fact that water acts relying all environmental matrices (plants, soil, atmosphere…). In this way, water is a component of the whole ecosystem and cannot be considered in a separate way.

a) Water resources

Several regions of the European Union are experiencing water resources scarcity, either temporal or structural. As lack of water quantity is strongly related to bad water quality, it is necessary to ensure a sufficient amount of water to any EU place in order to maintain quality of water resources.

The classical way to solve water scarcity problems has been an increase of the offer, instead of working on the demand side. Following both items, research on new, non-conventional, water resources is being undertaken, but also research on the reduction of demand is also barely needed. Reclaimed wastewater is one of the possible solutions in this sense, with the related risks being considered (Salgot et al., 2003).

It does not to be forgotten that water is an integrant of aquatic ecosystems, and that the geographic distribution of water has direct implications in mosquito born diseases (malaria and yellow fever); rodent born diseases (hantavirus and plague); water borne diarrheas and...
skin diseases (Epstein, 1998). The relationship of parasites with water is widely known. Nevertheless, the extremely complication of life-cycle of such parasites and the fact that the preferred area for its development is in the developing world “hot” waters, leads to a not absolute knowledge of the health influence of such animals.

b) Water supply

Water supply is to be considered, in relation to health and environment, as a potential carrier for contaminants/pollutants to human beings (direct threat to health) or to agricultural crops (indirect – food related way).

Water for domestic supply is analyzed carefully, for natural contaminants but also for contaminants derived from the potabilization practices, especially disinfection by-products (Oxenford, 1995). Nevertheless, water used for irrigation of agricultural crops is not at all controlled; in this case, for example, vegetables eaten raw are a cause of health concern.

Water distribution is also a research matter, in which concerns the quality changes that water can suffer when being stored or through its pipelines passage. The changes happening to water inside the houses must also be considered, especially in old residences. Although lead pipes were banned and its change suggested, few initiatives are described until now in this sense. Also in the distribution systems, it is to consider that there is a bacterial growth, or regrowth, in the pipes and other elements, caused by the presence of even minute amounts of biodegradable organic matter (Künnis, 2003). Summarizing, the quality of drinking water at the consumers’ tap depends on several, combined, factors (Hoekstra et al., 2003): presence of chemicals and microorganisms in the water, effectiveness of the raw water treatment process, physical status of the distribution system, and materials used in the system. All these mentioned circumstances can pose health threats.

It is to note that in some cases, drinking water is not clean enough for use in hospitals, because patients have a reduced resistance and are more susceptible to infections caused by microorganisms in drinking water for which normally humans are resistant. Other aspects to be considered are that vulnerable groups such as babies drink water in which they bath; and that consumers inhale drinking water during showering and may become ill due to the presence of e.g. *Legionella* (Hoekstra et al., 2003).

Nitrates are also a cause of health concern, because of the illnesses related to this contaminant. Research is being undertaken on the relationships of groundwater with the nitrate sources. Although it seemed until now that the main nitrate generator is agricultural practice, it happens that other sources are to be considered; among them wastewater disposal into rivers (then the relation with the aquifers is quite immediate) or soil based algae.

From the chemical/biological point of view, the widespread and non-sense use of antibiotics in humans and animals (including cattle and fish) is generating the spread of antibiotic resistance genes and pathogenicity determinants (Bernasconi et al., 2003; Künnis, 2003). Water cycle is acting as a way of dispersion for this type of contaminants.

Desalination and membrane technologies (Schippers, 2003) are nowadays being studied, especially in which relates to new membrane compositions and energy needed. The improvement of water quality (salinity reduction) due the use of these techniques could have a positive impact on human health, but this statement needs to be fully demonstrated through research.

Other sources of water supply must also be considered in relation with environment and
health, as water used in foodstuffs production, water supplied by tankers, and water put into bottles to be sold (Hoekstra et al., 2003).

Mineral water commercialization is not sustainable in many aspects such as energy consumption for transport and recycling of bottles compared to tap water, but some problems of odor, taste and users/public perception of safety are influencing the decision on which water use for drinking purposes (Hoekstra et al., 2003). In this case, it seems important to determine the long-term consequences of the change of drinking water source for the consumer’s health.

Asano (1998) is indicating in several publications (e.g. 1998) that directly or indirectly, reclaimed wastewater should be used in the future for drinking purposes. Specifically, the risk-related considerations are paramount for this case.

c) Wastewater

As the final destination of domestic and cattle wastewater is usually the environment, this is the classical way of pathogen dissemination, as well as chemical contaminants entrance into the environment. Direct point disposal could be improved although the possibility of transforming this type of disposal is seldom considered. Wastewater disposed of into rivers or lakes becomes a resource, being collected, sometimes immediately, for water supply; thus, establishing a link between pathogens and human beings. This “transport” needs also further research.

The dispersion of treated wastewater into several points (non-point/diffuse disposal) could improve the impacts on the environment and of course in the human health, because of the self-purification capacity of natural waters. This is also a possible matter of research.

There is a classical way to treat domestic wastewater, based in huge facilities, energy-consuming and scarcely integrated in the environment. Decentralization and the use of more natural systems are nowadays studied and implemented (R+D). When disposal is being done in sensible areas, further nutrients elimination is required. For wastewater reuse and disposal in bathing areas, disinfection is under study: the main related problem is the generation of disinfection by-products, being nowadays a matter of important health and water related research.

Wastewater treatment using natural systems is also being studied for small communities, and for advanced and tertiary treatments. Those systems are, if properly managed, efficient enough to dispose water safely, because they are capable to eliminate the need for chemical disinfectants. At the same time, natural systems can also eliminate from water an important amount on xenobiotics and refractory organic matter. The consequence is an important reduction of the possibility of THM formation in the water cycle.

Industrial and cattle wastewater are nowadays a matter of concern, once the domestic wastewater treatment systems are completed or nearly. The health impact of some industrial wastewaters (containing hazardous chemicals) and cattle wastewater (pathogens, but also chemicals) is to be dealt with.

It is to consider also the health impact of chemicals (drugs, xenobiotics) released into the environment without being eliminated in the classical wastewater treatment systems.

Membranes for wastewater treatment and reclamation are also being developed (Oron and Bick, 2001). Membranes and natural systems reduce the presence of natural and synthetic
organic microcontaminants (antibiotics and other). Nevertheless, there is still a lack of useful data to be obtained by applied research (not cheap at all in this case).

d) Water for other uses

Water is used for other purposes than domestic supply or agriculture. Bathing and other recreational uses can also generate health problems. Actual research is being done on bathing water quality and risks related to it and leisure uses, as golf or landscaping irrigation practices.

Legionella related problems are a matter of concern, because of the difficulties to detect preventively the problem and how to manage it once detected (Pascual et al., 2002).

Natural waters where shellfish is grown are being monitored, and the influence into health problems of wastewater disposed into shellfish growing areas is to be established.

The impact of wastewater discharges into seawater is to be addressed, especially in which respects to the coastline relationships with shellfish, fish and other products from the sea used by mankind. In bathing and sailing areas is especially important, from the health point of view, to consider seawater quality.

In this same sense, often, stresses to water ecosystems are multiple, as such influencing the formation of harmful algal blooms in marine, estuarine, or freshwaters; which encompass often combined effects of excessive nutrient loading leading to eutrophication, reduction of wetlands, overfishing, chemical pollution and warming (Epstein, 1993). The man menace to ecosystems related with water can be expressed as Cardoso et al. (2003) do: At one end of a continuum of human influence on biological condition, there is severe disturbance that eliminates all life. At the other end of the gradient are pristine, or minimal disturbed, living systems. These systems possess biological integrity. A gradient from integrity to nothing alive passes through healthy, or sustainable, conditions or activities. Health, in this case, can be relied to water quality. Research is needed to establish the relationships among water bearing ecosystems and human health (when water resources are obtained from these systems).

e) Analytical tools

Because quite all water analysis are in some way historical, research is being done on how to obtain tools capable of generate data in real or near-real time. As analytical tools improve, the spectrum of contaminants increase, as also happens with the limits of detection. It seems evident that real time analytical results will provide more room to undertake preventive, health related, measures.

Microbiology and chemistry are subjects of research in two aspects (improvement of time until the results are obtained and analytical capabilities in which respects to precision). Then, actions can be taken in shorter times than now, allowing a better defense of health in such a way.

Genetically related analytical tools (PCR and other) are one of the main features of actual research on microbiology and parasitology. Indicators are needed to determine virus incidence on health: in this moment, research is being done in bacteriophage as virus indicators (Maux, M., 2003). The implementation of a virus control in water and water supplies will allow a further knowledge on virus related diseases transmitted by water.

In microbiology is usual to find what is called in bacteria VNBC (Viable but non-culturable) cells. Similar forms can be found for protozoa cysts and oocysts, and nematode eggs. The real
sanitary incidence of such organisms in human health is to be established through comprehensive research.

The use of biological indicators (e.g. invertebrate) is also being developed (Benito and Puig, 1999). As this type of indicator is fully comprehensive of the water quality all around the year and in any condition, and because of the basin-specific invertebrates or other bioindicators, the development must be case by case (basin by basin). It is also necessary to correlate bioindicators with other health/water indicator parameters, like bacterial ones (Faecal coliforms or E. coli).

The toxicology-related analytical techniques are intended to evaluate toxicity at the mechanistic level, essential in order to understand and prevent adverse environmental exposure. Environmental toxicogenomic allows the identification and characterization of genomic signatures of environmental toxicants as gene protein expression profiles. The techniques used are based on molecular post-genomic knowledge (Lettieri and Eisenreich, 2003). Up to now, many microorganisms have been sequenced and information is already available (pathogenicity, genomic DNA, microarray) but more research is imperative, especially in relation to epidemiology.

Toxicogenomic (Lettieri and Eisenreich, 2003) is boosting its application in aquatic environment to deal with the toxic effects of chemical compounds (e.g. heavy metals, organic compounds, pesticides and complex mixtures).

f) Risk related research

The risk concept is being nowadays introduced in the water health related research, both for drinking water and wastewater reuse (and for other uses). Risk-related research focuses on risk assessment and management (RAM). Up to now, water microbiology Risk Assessment knowledge is poor due to lack of information on prevalence of microorganisms, their pathogenicity and their genetic code (Bernasconi et al., 2003). There, a new matter for health related research appears.

Tools developed previously for foodstuff and pharmaceutical industries are being applied to RAM in the water field: e.g. HACCP (Hazard Analysis and Critical Control Points) and Good Practices are being implemented.

In which respects on microbiology, new (emergent) and old (re-emergent) pathogen caused diseases are being described as increasing.

One of the main reasons of risk related to water and health increase is the capability acquired for human beings to move from one region to another quite without limitation, pushed by the conflicts and facilitated by the availability of transportation. Then, the number of people at risk, such as children, immunocompromised, transplanted and elderly is dramatically increasing (Bernasconi et al, 2003).

g) Information and socio-economic aspects

One of the policies of the EU is to provide information to the user. It is now important to planning how to provide this information: current research is being undertaken on how to supply information without creating unnecessary alarms and concerns.

It is also mandatory in the EU to include all costs in water bills for all users, including agricultural and industrial ones. It is not easy to implement this policy without previous work on the education of all water stakeholders and users. Up to now, quite all the anthropic water
cycle has been strongly subsidised by the Governments. This change of policy will be
difficult to implement without further consideration of all economic aspects of water supply
and treatment, including health-related aspects. Better communication ways are to be found.

Economic aspects of water use are not only related to the price of water to be paid, but also on
the technologies and controls needed to ensure good water quality and to deal safely with
health concerns. Then economic applied research seems necessary in this field.

h) Technologies

Although considered previously, techniques and technologies to be employed in the
water/environment research field are important enough to be considered alone.

Existing technologies for water treatment (supply) are well developed, but research for further
health improvement is still necessary. Research needs to be focused into:

- The membrane technology improvement: reduction of energy, better membranes,
  applications…
- Disinfection procedures: reduction of chlorine use, combination with other disinfectants
  (UV, Ozone, chlorine dioxide…). Thus organic microcontaminants will be reduced.
- Reduction of the by-products generated which enter the end-product (water supplied).
- Odor and taste control (reduction).

In the field of wastewater, the research needs are:

- Using more friendly technologies (cheaper, less energy-consuming…).
- Returning to the wastewater health-related concept (pathogen reduction
  instead/complementarily to the SS and Organic Matter reduction) but also maintaining
  the technological concept.
- Implementing new technologies specifically developed for wastewater treatment,
  instead/complementarily to the use of water-related technologies.
- Implementing membranes and natural systems.
- Developing technologies adapted to wastewater reclamation and reuse.
- Introducing the water reuse concept in the planning step.
- Improving the disposal of wastewater into the environment

i) Rules and regulations

The “legal field” in water is represented mainly by the Directives. At the present moment (end
of 2003) are in force (Künnis, 2003; Hoekstra et al, 2003):

- Drinking Water Directive CD 98/83/EC
- Natural Mineral Water Directive CD 98/83/EC
- Surface Water intended for the abstraction of drinking water Directive CD 77/795/EEC.
- Bathing Water Directive CD 76/160/EEC.
There is a movement to incorporate two main new ideas transversally in the water field, as in other environmental fields:

- The precautionary principle.
- The information to the citizens’ principle.
- The “health-related” concept needs to be implemented as a transversal policy. In this way, the precautionary principle and the information policies will be improved.

j) Other

As the field of water research is extremely important for the improvement of health conditions, a lot of considerations can be done, apart from the stated ones. We can introduce (without being exhaustive) the following ones:

- Considering and introducing the precautionary principle in all water/health related activities.
- Increase the interdisciplinariety in the field of water research, especially when dealing with health purposes (lawyers, economists… even psychologists, can play a role into the environment, health and water research).
- Implementing the concept of consumer protection for all cases of water use.

2. Future research needs.

The same division used before will be employed here. The rationale for research has been explained in the point 1. Accordingly, health and environment related research is needed on:

a) Water resources

- How to obtain new water resources or improve the use of the existing ones without compromising the state of the environment and consequently the health.
- Desalting technologies, mainly related to membrane uses.
- Real development of wastewater reuse: in agriculture, other irrigation uses, groundwater recharge, urban uses and other. This is to be done considering always the risk.
- Studying the relationship between quantity and quality of water, especially for the health related items. In this sense, it is to note the need of more information about the persistence of pathogens and indicators in nature.
- Redefinition of the relationship/balance water demand/water offer and how to manage both, reducing the demand side. Then, an improvement of water quality can be obtained, with a direct incidence on health.

b) Water supply

- Relation of water supply with raw water source, treatment processes and materials.
- Alternative ways to plumbing substitution are needed at least temporarily; i.e. passivation using chemicals.
- Information about the total amount of microorganisms and their diversity in water facilities for drinking purposes, the causes for it and the ways to cope with such presence.
- Changing quality inside the houses: direct relationship with the consumer’s health.
- In relation to the three precedent items: biofilm developments in the piping systems, and its capacity to trap particles, detritus and hygienically relevant bacteria.
- Reduction of water losses.
- Further and comprehensive studies of the nitrate problem: sources, reality and extension of the problem, solutions...
- Further studies in relation with agricultural water quality: foodstuff end-quality.
- Taste and odor related problems.
- Tap water consumption versus bottled water consumption for drinking purposes in terms of Life Cycle Analysis and health.
- Determination of the health problems associated with products after the tap: filters, domestic devices for treating water, ice-machines, ice-cubes sold out of the foodstuffs chain...

c) Wastewater
- Centralization/decentralization of facilities: a major dispersion of effluents can improve self-purification.
- Natural treatment systems.
- On-site systems for wastewater treatment.
- Disinfection systems and by-products.
- Nutrient elimination using less energy: reduction of nitrate release.
- Use of membranes for wastewater secondary and advanced treatment.
- Disposal impacts and implementation of non-point/diffuse disposal.
- Treatment and disposal of wastewater generated by cattle.
- Characterization, quantification, and possible treatments of chemicals released into the environment (drugs/pharmaceuticals, endocrine disruptors and the like).
- Reclamation and reuse of wastewater for old and new purposes: agriculture, groundwater recharge, urban uses...
- Odor related-problems.

d) Water for other uses (bathing, air conditioning…)
- Water quality standards for bathing and recreational waters.
- *Legionella* in conditioning and other water including systems: identification and treatment of *Legionella* containing facilities.
- Shellfish/water related problems, especially reduction of pathogen disposal into the environment and protection of growing areas.

e) Analytical tools
Three types of tools need to be separated: biology, chemistry and general.

**Biology- related**
- Real time (< 4 hours) microbiological and parasitological analysis.
- Further development of molecular genetic, similar, and related methods for pathogen determination.
- Appropriateness of existing indicators for the statement of faecal pollution.
- Good indicators and analytical methods for virus and parasites in water and wastewater.
- More is to know on the viable but non-culturale (VBNC) bacteria cells, oocysts, cysts and nematode eggs and analytical tools to determine its presence.
- In all cases, emergent and re-emergent pathogens are to be included in the analytical methods development.
- Transmission of antibiotic and pathogenicity resistance.
- Biological indicators for water and wastewater treatments efficiency determination, and for the real full-time quality of natural waters.

Chemistry/toxicology related
- Toxicological studies in relation to water pollutants appearing after water and wastewater treatments.
- Toxicogenomic is to be developed as a tool to assess the molecular mechanisms of toxicity. By this way, chronic effects should be determined.
- Improvement of analytical tools to increase the sensitivity, and in this way the capability to determine the low dose exposure effects.
- Endocrine disrupting chemicals; once clearly established that this is a need, and not an analytical a la mode caprice.

General
- Good sampling procedures.
- Comprehensive indicators of the state on natural water environments.
- Real cost of the control of water/environment/health concept.

f) Risk related research
- Comprehensive risk assessment and management studies for water (domestic and agricultural supply) and wastewater to be reused.
- In the specific Risk Assessment research, the following gaps are to be filled: hazard identification, dose-response relationships, exposure assessment and risk characterization and calculation.
- Filling the gap of stakeholders’ knowledge on the risk concept/precautionary principle.
- HACCP and Good Reuse Practices development.
- Problems related with emergent and re-emergent pathogens.
- Synergistic effects of chemical mixtures and different pathogens need to be considered.
- Economic aspects of the implementation of the risk management concept.

g) Information and socio-economic aspects
- The techniques for obtaining public opinion and in order to improve the participation of public in all steps of water planning and uses, especially in the concept of acceptable risk.
- The communication techniques and aspects, including also the education of public to understand technical and technological aspects related to water, environment and health.
- Evaluation of the costs related to the implementation of the information policy.
h) Technologies
- Further development of membrane technologies.
- Nitrogen (especially nitrate) reduction.
- Reduction of by-products generated during water and wastewater treatment.
- Membrane research.
- Natural systems development.
- Disinfection systems (for both water supply and wastewater treatment).
- Odor and taste reduction technologies.

i) Rules and regulations
- Enter the precautionary principle into all rules and regulations, especially in relation with risks to health and water environment.
- Rules and regulations for wastewater reclamation and reuse.

j) Other
- Stakeholders compromise with the environment/health water related problems.
- How to implement interdisciplinarity in the field of environment/health water research.
- Legal aspects, especially in which respects to the precautionary principles (see previous point).
- Implement the concept of consumer protection.

3. General aspects

The different characteristics, concepts and concerns in the Northern countries of the EU compared with the Southern countries must be considered and studied carefully, before implementing any global solution for the whole Union.

In any case, the integrated management of all waters must be taken into consideration. In this sense, non-conventional water resources (including reclaimed wastewater) must imperatively by used for any purpose, including perhaps drinking. Research on this type of resource is paramount in the areas of the world where water is scarce and not easily available. A direct relation with health arises from this concept.

Health problems related to the coexistence of several water contaminants (chemical and biological) are to be considered, especially when new members enter the EU. The concept is called multi-causality.

The increased hygienic practices, and the subsequent reduction of acquired immunity to several water-related diseases, could be a cause of concern in the near future. At the same time, it seems that the continuous exposure of chemicals is gaining momentum as a cause of long-term illnesses. Common sense tells us that both aspects (immunity reduction, increase of effects derived from exposure to chemicals) does not correlate at all with the increase of life-span in developed countries: some explanation is needed in what relates to water quality and human health.

Full epidemiological studies must be undertaken, especially considering the existing ones on water-related diseases have not been planned carefully. Epidemiological data existing have
been obtained mainly after illnesses appeared, not as planned studies.

One of the heading technologies which needs to be fully considered in view of its potential are the analytical procedures related to genomics. Its utility is related to both biology/microbiology and chemistry. Short effects (illnesses, acute toxicity) and long effects (chronic illnesses) will be easily and reliably determined as it is contemplated nowadays.

The technologies for water and wastewater treatment need to be implemented after carefully planning and considering the concept of Best Available Technology.

Additional attention must be paid to the collaboration among all research bodies, including universities, Government research entities, private firms, and other. It is especially necessary to consider what the stakeholders have to indicate as priority research items.

There is an imperative need to allow the participation of all types of professionals into the research related to the environment and health aspects, in relation with waters but also on all the other items dealt with in this TWG.

Comprehensive tools (LCA, DSS, GIS, and other) are to be implemented in the health and environment-related management of water.

The water cycle must be considered as a whole; what is called global or integrated management of basins and water resources.

Sustainability has to be the basis for all research in relation with environment, water and health.

4. Research proposals

Although in the field of water the research possibilities in relation with environment and health are enormous, it is our feeling that perhaps the more important research items are:

- Risk related items (due both to chemicals and pathogenic organisms; algal toxins and other could also be included here).
- Emergent and re-emergent pathogens and derived illnesses.
- Health hazards derived from water treatment (potabilization and wastewater treatment) and reuse. Short and long term results (pathogens and toxicology considerations).
- Relationships among water quantity and water quality, in terms of integrated water management.
- Water and food relationships in which respects to health problems

References


Künnis, K. (2003). Report for the TWG Environment and Health: research needs in Microbiology II.


5.6 Noise

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It is considered that new residential areas should have an outdoor noise level better than 55dBA and that urban “grey areas” would have levels between 55-65dBA whilst areas above 65dBA would be considered “black spots” and those exceeding 75dBA would be unfit for Human habitation.

In Europe 450million people (65%) are exposed to levels above 55dBA, of which 113million (17%) are exposed to levels above 65dBA and 9.7million (1.4%) are exposed to levels above 75dBA.

Around 30 million people in Europe work in noise environments hazardous to hearing and a further 113 million live in community noise levels above 65dBA, which is thought in most people to cause annoyance and lead to sleep disturbance. Other adverse health effects include interference with communication, performance and learning as well as cardiovascular and immunological problems. Furthermore, leisure time activities can also produce noise levels potentially damaging to hearing.

Environmental noise has a major impact on the quality of life of those exposed and may in time lead to other health effects. A number of health effects related to noise exposure are summarised below. The health effects of a combination of exposures, for example air and noise pollution from road traffic or poor housing conditions and noise, environmental exposure to chemicals and noise need to be studied in detail as combined exposures may be more detrimental to health than each acting alone and particularly in vulnerable groups such as children and the elderly.

Annoyance: Environmental noise leads to annoyance. It is possible to produce a dose/response relationship for noise and annoyance although it is acknowledged that there are a considerable number of non-acoustical factors, which affect annoyance. The dose/response curves primarily related aircraft noise and road traffic noise to annoyance. It was also agreed that annoyance affects quality of life. In the EU, it is recognised that 22% (77 million) of the population is considered annoyed by environmental noise. It is recognised that there are a lot of data sets available relating noise to annoyance (Schultz, 1978; Kryter 1982; Fiddel 1991; Fields 1994; Miedema 1998; Miedema 2001).

There were discussions relating Ldn and Lden measures and about the various models for combining sources of noise, for example energy summation, dominance source model or annoyance equivalent levels from a reference noise source. Furthermore, it was acknowledged that annoyance dose/response relations applied to steady state conditions but if changes at airports were taking place then there may be greater annoyance.

Annoyance is regarded as the most important adverse effect of environmental noise. Dose-response curves have been presented relating the percent of people highly annoyed increasing with the Ldn measure of noise level. From these curves, it is apparent that aircraft noise is more annoying than road traffic noise followed by rail. The individual noise annoyance can be predicted to maximal 33% by acoustic parameters but a number of effect modifiers influence the effect. Night and evening noise as well as weekend noise is more annoying when quietness is expected. The individual noise sensitivity is the most important personal parameter of influence. The other parameters of consideration are
1. General appraisal of noise source

2. Confidence in people responsible for noise and noise abatement

3. History of noise exposure

The importance of annoyance also lies in the extent to which this may lead to stress and further physiological changes consequent upon this.

**Sleep disturbance:** It is widely accepted that noise from aircraft, road and rail noise may disturb sleep. Numerous studies over the last 30 years in both the laboratory and in home settings have sometimes provided conflicting results with large discrepancies between studies. It has been difficult therefore to reach any firm conclusions as an understanding of the reasons for the discrepancies between studies is necessary to determine the true extent and nature of the problem. The discrepancies may be arising due to different noise exposure measures and different sleep parameters considered in various studies. The situation is further compounded by the fact that certain studies indicate habituation whereas others indicate physiological stress effects which do not habituate. In addition the next-day-effects of a lack of sleep or disturbed sleep also need to considered.

The most obvious effect of noise exposure during the night is the disturbance of sleep with possible effect on efficiency of work next day and long-term health effects.

Intermittent noise causes fragmentation of sleep progression or in the case of continuous noise shallow sleep. Both have the effect of shortening duration of deep sleep and rapid eye movement sleep. The alarm function of the sense of hearing may lead to awakening if the noise contains information perceived to be of relevance even if the level of noise is low. Arousal during sleep is a short-term noise induced activation. Frequent occurrence of arousals leads to a deformation of the circadian rhythms. Long-term disturbance of circadian rhythms has consequences for health impairment. These have been shown to have an impact on the neuro-endocrine regulation, which has an effect on the physical and psychological well being of an individual.

**Endocrine Effects:** Among the multitude of physiological systems which response to acute and chronic stress with high sensitivity, the hypothalamus-pituitary –adrenal axis (HPA) has a prominent position. Physical and psychological stress rapidly induces HPA activation, which is well characterised by discrete increases of cortisol levels. Ambulatory assessment of cortisol levels in saliva has facilitated the detection of stress responses in various populations of healthy individuals and patients. Following recent methodological advances, salivary cortisol levels are now measured in large groups of subjects in cross-sectional and longitudinal studies. Among other parameters, the repeated assessments of the early morning cortisol rise and circadian cortisol rhythm are most promising indices to be investigated in studies on the effects of environmental stressors on health.

**Mental Health Effects:** Studies suggest that exposure to aircraft and road traffic noise may cause symptoms such as headaches and tension but there is little direct evidence that environmental exposure is related to clinically defined psychiatric disorder measured by screening questionnaires in community studies. The analyses associating aircraft noise exposure and admissions to psychiatric hospitals have shown inconsistent results but have been largely negative. There is some evidence for higher tranquillisers and hypnotic consumption in noisy areas. Recent studies associating noise exposure and health functioning have also been negative. It may be that environmental noise exposure levels in the UK are not
high enough to find effects but there is some suggestive evidence from Japanese studies that higher levels of aircraft noise exposure may be related to impairment of mental health. Many of these studies are limited by methodological problems such as poor characterisation of noise exposure, selection of biased samples of subjects, lack of measurement and adjustment for appropriate confounding factors and lack of standardised measures of mental ill-health outcomes. Further research is needed to address these methodological problems but nevertheless, current evidence suggests that the effects of environmental noise on mental health are likely to be small.

- **Sufficient evidence** is given if a positive relationship is observed between exposure to the agent and the health outcome (cancer), in studies in which chance, bias and confounding can be ruled out with reasonable confidence.

- **Limited evidence** is given if a positive association is observed between exposure to the agent and the health outcome (cancer), for which a causal interpretation is considered by a Working Group (experts) to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

- **Inadequate evidence** is given if the available studies are insufficient in quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association.

The authors and expert groups of the reviews mentioned above, made the following statements from the evidence:

**Health Council of the Netherlands, 1994 and Passchier-Vermeer & Passchier, 2000:**

- “Limited” evidence for the relationship between noise (including occupational noise) and biochemical effects.

- “Sufficient” evidence for the relationship between noise (including occupational noise) and hypertension.

- “Sufficient” evidence for a relationship between noise and ischaemic heart disease. Institute for Environment and Health, 1997 and Porter et al., 1998:

- “Inconclusive” evidence for a causal link between noise exposure and hypertension.

- “Sufficient” evidence for a causal association between noise exposure and ischaemic heart disease.

**Health Council of the Netherlands, 1999:**

- “Limited” evidence for the relationship between noise (including occupational noise) and biochemical effects.

- “Sufficient” evidence for an association between ambient noise and hypertension.

- “Sufficient” evidence for an association between ambient noise and ischaemic heart disease (observation threshold: Leq,6-22 h: 70 dB(A)).

**Babisch, 2000:**
• “No” scientific evidence for association between transportation noise and mean blood pressure readings (exception: in children consistently higher readings were found in the exposed groups).

• “Little” evidence regarding the association between transportation noise and hypertension.

• “Some” evidence regarding the association between transportation noise and ischaemic heart disease. The latter was viewed as being “sufficient” for action. Neus and Boikat, 2000:

• “Limited” evidence regarding the association between traffic noise and ischaemic heart disease.

The various evidence ratings of a correlation between traffic noise and cardiovascular disease can be summarised as follows:

• Biochemical changes of risk factors: "Limited" evidence,
• Hypertension: "Inadequate/limited" evidence,
• Ischaemic heart diseases: "Limited/sufficient" evidence.

Recently, a systematic review was published which used the meta-analytic approach to assess quantitative estimation of the relationship between community noise and occupational noise on blood pressure, hypertension and ischaemic heart disease (IHD) [Kempen et al, 2002]. The authors concluded that the epidemiological evidence on noise exposure, blood pressure and ischaemic heart disease is still limited. With respect to blood pressure and hypertension, results were contradictory and for IHD only a few studies were available. Inconclusive findings may be due to limitations in exposure characterization, adjustment for important confounders, and the occurrence of publication bias.

Some new epidemiological studies are on its way focusing on IHD, high blood pressure and IHD risk factors.

Conclusion:

As pointed out in earlier statements, 65-70 dB(A) outdoor sound level during day and 55-60 dB(A) during night (LAeq) may be quality targets for environmental policy regarding cardiovascular diseases based on current knowledge from research carried out in this area.

2) Blood pressure in children

Epidemiological studies carried out in adults suggest long-term health risks in chronically exposed adult populations. High blood pressure and myocardial infarction have been the primary focus of noise effects’ research. Also in noise-exposed children, cardiovascular (blood pressure) and endocrine (stress hormones) markers of enhanced physiological arousal have been studied on an epidemiological basis. The results can be summarised as follows:

• Weak data-base
• No systematic increase in mean BP readings in higher noise exposed children
• The better control for confounding factors, the smaller the noise effect
• BP increases in new studies are within normal physiological range
• Dose-response relationship rarely studied
• Acute or chronic noise effects?
• Age range: 8-11 (16), no age*noise effect
• No sex differences (except MLAF noise: girls)
• No differences regarding the noise source (evidence and magnitude of effect)
• Noise at school was the primary source of interest. Additional noise at home increased the effect.

Depending on the to study design, effects were seen at Leq > 60 dB(A) (road), Leq > 65 dB(A) (air). These figures may serve as quality targets although the evidence is weak. The statements given by Evans and Lepore, 1993 are still true: “We know essentially nothing about the long-term consequences of early noise exposure on developing cardiovascular systems.” “The degree of blood pressure elevations is small. The clinical significance of such changes in childhood blood pressure is difficult to determine. The ranges of blood pressure among noise-exposed children are within the normal levels and do not suggest hypertension.”

"The extent of BP elevations found from chronic exposure are probably not significant for children during their youth, but could portend elevations later in life that might be health damaging." This is in line with other researchers, e.g. Maschke, 2000, who stated: “Children – with the exception of newborns – usually show a smaller reactivity to acute noise than adults. Children are less likely to wake up by noise. Regarding blood pressure, studies do not suggest lower limits values than for adults. Nevertheless, Maschke suggests 5 dB lower limit values for children from a preventive point of view, given the US EPA Agenda for Child Environmental Health, 2000: “Ensure that all standards set are protective of the potentially heightened risk faced by children…” Babisch stated at the NOPHER-Meeting 2002 in Berlin:

A quantitative health risk assessment for children cannot be given at the moment. The impact of body size was not adequately considered in studies. The available database on cardiovascular effects of noise in children is poor. Based on the available data, children do not appear to be a particular risk group with respect to cardiovascular outcomes, with the exception that they may simply be longer exposed to noise throughout their lifetime than adults that have been studied, and who grew up when motorization was not as widely spread. This, too, justifies the 5 dB(A) safety margin suggested by Maschke.

Conclusions:

We do not see sufficient evidence for health effects in children exposed to community noise, however the current data base does not allow to conclude that effects may not occur in susceptible children or in a susceptible contexts (socio-cultural, environmental.).

3) Stress hormones

In recent years, the measurement of stress hormones including epinephrine, norepinephrine and cortisol has been widely used to study the possible increase in cardiovascular risk of noise exposed subjects. Since endocrine changes manifesting in physiological disorders come first
in the chain of cause-effect for perceived noise stress, noise effects in stress hormones may therefore be detected in populations after relatively short periods of noise exposure. This makes stress hormones a useful stress indicator, but regarding a risk assessment, the interpretation of endocrine noise effects is often a qualitative one rather than a quantitative one. Stress hormones can be used in noise studies to study mechanisms of physiological reactions to noise and to identify vulnerable groups.

Although not being a risk factor as such (in epidemiological terms), stress hormones like epinephrine, norepinephrine and cortisol can be viewed as reliable stress indicators. Stress hormones are easy to measure non-invasively, and appear to be an attractive outcome for epidemiological studies. They are particularly useful for investigating biological mechanisms, and play a crucial role in the metabolism of the organism, where they act as bio-messengers and neuro-transmitters in the regulation of autonomic and other physiological functions. They are part of a complicated system of positive and negative feedback mechanisms affecting: the activity of the heart, blood pressure, blood lipids, blood glucose, blood clotting and blood viscosity. All these are established biological risk factors for hypertension, arteriosclerosis or myocardial infarction, when considering the cause-effect chain, i.e.: sound - annoyance (noise) - physiological arousal (stress indicators) – changes in biological risk factors – morbidity – mortality. Long-term effects on the cardiovascular system are specifically focused in this respect.

In studies, free catecholamines have been analysed in plasma and urine using standard biochemical and electrochemical methods. Regarding corticosteroids, different procedures and derivates have been used to determine adrenal-cortical activity (total or free cortisol, hydroxycorticosteroids, ketosteroids). New studies have tended to focus on free cortisol in plasma or urine including certain metabolites such as 20α-dehydro-cortisol; a few have considered saliva. However, due to strong circadian and weekly rhythms of hormone excretion, epidemiological studies may suffer from methodological problems when only certain parts of the day/night are considered for sampling. Problems may also arise from too short observation periods in experiments regarding the longer half-life time constants (cortisol: about 70 minutes) of the hormone metabolism.

Conclusions:

- Stress hormones can be useful stress indicators in field and laboratory noise studies
- Their clinical relevance in noise studies is not clear compared to classical risk factors

Chronic stress induced changes resulting in neuro-endocrine dysregulation means that the individual may not habituate to the nightly disturbance and suffer consequences in term of health without being aware of the cause. From the results of the studies it may be concluded that long-term environmental noise exposure lasting for years may in a number of exposed people lead to chronic dysregulation of their endocrine system.

**Performance and Learning:** A general finding in studies of noise on human performance is that noise levels have to be high to produce a reliable effect on performance or the task has to be complex or cognitively demanding. Repetitive and simple tasks are unaffected by noise. There is insufficient data to generate any dose/response type of relationship for performance and learning. There is some evidence from studies in children living around airports that they have some reading or comprehension deficits as a result of noise exposure. In the Munich study children improved their long-term recall memory by approximately 25% when the old airport closed and at the new airport there was decline in performance of a similar extent. The
scores were similar for reading tasks. The change in noise levels before and after was about 14dBA at the old airport and 9dBA at the new airport. There are no field studies on adults reading and memory effects in relation to noise exposure. Several studies have shown that performance is impaired if speech material is played back while the subjects are reading and memorising verbal material.

**Cardiovascular Risks:** Review of epidemiological studies of cardiovascular effects of occupational noise have been published regularly. Most studies have been concerned with arterial blood pressure. In the earlier studies it was concluded that prolonged exposure increases the risk of hypertension further studies with improved methodology were unable to shed further light on the association between high levels of noise exposure and elevated blood pressure. Most recent studies show an increased risk of ischaemic heart disease in higher traffic noise exposed subjects as compared to less exposed subjects while associations regarding hypertension were not as convincing. It was concluded that more research is needed particularly on establishing a dose-response relationship. At present day time (6-22h) Leq values of 66-70dBA were considered as threshold of adverse effects. The impact of night disturbance requires special attention. The results of epidemiological studies show weak but significant negative correlations between noise annoyance and blood pressure. Methodological issues are important in establishing any relationship between noise exposure and cardiovascular risk.

4) General

In principle, the noise/stress hypothesis is well understood. Noise activates the pituitary-adrenal-cortical axis and the sympathetic-adrenal-medullary axis. Changes in stress hormones including epinephrine, norepinephrine and cortisol are frequently found in acute and chronic noise experiments. The catecholamines and steroid hormones influence the organism’s metabolism, thus increasing the risk for certain diseases. Cardiovascular disorders are especially in focus for epidemiological studies on adverse noise effects. However, not all biologically notifiable effects are of clinical relevance. The relative importance and significance of health outcomes to be assessed in epidemiological noise studies follow a hierarchical order, i.e. changes in physiological stress indicators, increase in biological risk factors, increase of the prevalence or incidence of diseases, premature death. Decision-making and risk management rely on quantitative risk assessment. Due to ethical aspects regarding the exposure in the laboratory and the fact that toxicological methods cannot be applied in noise research, epidemiological methods are the primary tool for providing the necessary information. However, the statistical evidence of findings from individual studies is often weak. Magnitude of effect, dose-response relationship, biological plausibility and consistency of findings among studies are issues of epidemiological reasoning. Similarly with other environmental issues, noise policy largely depends on considerations about cost-effectiveness, which may vary between populations. Limit or guideline values have to be set within the range between social and physical well-being, between nuisance and health. Following the precautionary principle it was estimated from epidemiological traffic noise studies that the threshold for a relevant increase of cardiovascular risk may be 65 dB(A) for the daytime outdoors average A-weighted sound pressure level. Because typical observational epidemiological research is hardly able to distinguish relative risks between 1 (zero risk) and 1.2 (20% increase in risk) there is an appreciable uncertainty left for populations with more than 10-15 % of people with noise exposure above 65 dB(A). Because the burden of noise differs substantially from country to country - the proportion of people at risk is an important factor in estimating the population impact.

In contrast, the findings from social surveys consider a lower figure, i.e. 55 dB(A), as a
threshold value regarding serious annoyance during the daytime. Whereas nuisance-related criteria may vary within populations, dependent on the type of area, (physical) health-related noise criteria should apply equivocally to all subjects within populations for ethical reasons. The cardiovascular risk is a key-outcome in non-auditory noise effects’ research because of the high prevalence of related diseases in our communities.

Specific studies regarding critical groups – including children, different noise-sources, day/evening/night comparisons, coping styles and other effect-modifying factors, and the role of annoyance as a mediator of effect are issues for future research in this field.

Exposure-Effect Indicators:

This work package sought to develop methodological issues including quantification of noise and health effects measures. Meetings of leading exponents in the field discussed the inadequacies or otherwise of the measures currently in use to quantify noise and health effects and indicate whether associations based on these measures were valid considering the large number of possible variables present.
The following contribution is a noise relevant contribution provided by EUROCITIES; comment made by John Hinton, from Birmingham, on 13th November 2003

1. Propose a project to identify the benefits (health and quality of life) of maintaining/creating quiet areas in agglomerations for the population to use for the purposes of quiet relaxation. This study should also consider the benefits of quiet facades at residential properties. Many people say that quiet areas and facades are beneficial and consequently they have been included in the so-called Environmental Noise Directive (END) 2002/49/EC. However, there currently appears, to me, to be no conclusive scientific evidence on what these benefits may be.

The project could also attempt set quality objectives for such areas/facades. Such a process should include public consultation to establish what are people’s expectations for such areas.

Work on the definition, identification and preservation of quiet areas has already started though a relatively small study contract let by DG-Environment. However, more fundamental research still needs to be carried out.

The final report on the above study has been produced and is currently being evaluated by EC Working Group Assessment of Exposure to Noise. I hope that the report will soon be made available on an appropriate web site.

2. Propose a project on the synergies and conflicts that may arise between actions to reduce air pollution in cities (such actions are currently being developed) and actions to manage and where necessary reduce environmental noise (such actions will have to be published in 2008 – END requirement). By way of a simple example an action to reduce noise from road traffic may be to slow the traffic down. This may produce an increase in air pollution (but would probably reduce the number of serious accidents as well as noise!).

Finally, when considering making any proposals for research on environmental noise issues the TWG should be cognisant of work carried out to date by the CALM Network Project (visit www.calm-network.com). This 3-year project is in its last year and is designed to identify, primarily for the EC, a research strategy and plan to support the transposition of the END. In addition this strategy and plan will focus on the further development of European noise policy covering noise assessment and abatement, new technologies and systems approaches for improved noise control at source and the further development of legislative standards.
5.7 Cost benefit analysis (CBA) + Health impact assessment (HIA)

by Fintan Hurley and Marta Schuhmacher

KEYWORDS:

policy tools; air pollution; extend; metals; dioxins; EMFs; uncertainty; indicators

SUMMARY: Bullet points

- Cost-Benefit Analysis (CBA) and Health Impact Assessment (HIA) are linked methodologies for assessing the costs and benefits of past, current and future policies.
- Within the EU they are now very widely applied at the level of the EU as a whole, of national Governments, of regional and local authorities. Often, their use is a requirement.
- To date, research in and applications of HIA and CBA have focussed on outdoor air pollution, especially the ‘classical’ air pollutants, and on policies that affect them. There has been work on some other areas (e.g. metals, dioxins, noise).
- We see two kinds of research priorities. Firstly, there is a need to expand and include HIA of many other kinds of environmental issue. We give some examples of how this might be done.
  - The four priority areas of SCALE refer to diseases/ health outcomes, not to causal factors. HIA and CBA refer to causal factors. However, the SCALE documents (e.g. Executive Summary) identify the priority links – ‘indoor and outdoor air, dioxins, heavy metals, endocrine disrupters, electromagnetic fields and the urban environment’ – though wider application of HIA and CBA in other contexts also is desirable (e.g. environmental noise).
  - The most important limiting factor is scientific knowledge in these particular fields; specifically, knowledge about (i) the fate of pollutants from emission to human exposure and dose; and (ii) the relationships between exposure (dose) and health, including the time-lag from exposure to health outcome.
  - Specific research needs on heavy metals, dioxins, EMFs etc. are identified not here, but in the appropriate chapters of this Report.
  - A benefit of HIA is that it can help identify what areas of research will most affect the answers of a HIA and so have a crucial bearing on policy.
- Secondly, the work to date has highlighted a number of general methodological needs, specific to HIA and CBA, which will apply across all applications. These include:
  - Better characterisation of background rates of morbidity and health service usage across the EU and its accession countries (plus development of indicators);
  - Improved methods for assessing uncertainty reliably and representing it accessibly;
  - Better monetary valuation and other methods of assessing health impacts (e.g. QALYs);
  - Identifying, for various kinds of applications, what are the key drivers of the final results, so that high-quality HIAs and CBAs can be done at affordable prices;
  - Improvement of application tools and software;
  - Maintaining close working links (i) among the various groups who are developing tools and methods; and (ii) between those groups and wider stakeholders (policy makers; NGOs, industry; ‘the public’; practitioners). HIA is quite a new methodology and those links are crucial.
- Because of the intrinsic links between HIA, CBA and policy development, research to improve methods and applications of HIA and CBA will have immediate policy benefits.

WHAT IS HIA/ CBA? WHAT IS ITS ROLE AND IMPORTANCE?

Cost-Benefit Analysis (CBA) and Health Impact Assessment (HIA) are linked methodologies for assessing the costs and benefits of past, current and future policies. Within the EU they are...
now very widely applied in the development of policy on environment and health at the level of the EU as a whole, of national Governments, of regional and local authorities, and of the development of local facilities (e.g. power stations; traffic plans). Increasingly, their use is not just desirable, it is a requirement.

In the present context, HIA is a methodology that assesses the impacts on health of any of a wide variety of measures that may affect the environment and so also affect human health. CBA goes further, by putting monetary values on those health impacts, and comparing the benefits of policies that reduce pollution with the costs of achieving those benefits. (Where policies increase pollution, e.g. growth in traffic, a new motorway, coal-fired power station, then HIA and CBA apply also, but the role of costs and benefits is reversed.)

Thus, HIA is a part of CBA. A full CBA includes within its benefits the impact of policies on animals, plants, ecosystems and on non-living materials such as buildings. We will focus only on health, where research on HIA and CBA in the EU (and world-wide) has focussed principally on the effects of outdoor air pollution and health, and so on policies that affect air pollution. These policies include assessing the health impacts of:

a. The general pollution mixture (irrespective of source) as found in a given country/ area/ Region e.g. the work of EU projects such as APHEIS and GARP; or WHO’s work on Transboundary pollutants. These projects assess the overall size of the air pollution problem on health.
b. The specific pollution mixtures associated with pollution from particular sources; e.g. the EU ExternE studies assessing health effects from electricity generation, traffic and waste disposal; and the work of Kuenzli and colleagues on effects of traffic.
c. The health effects (in a given population) associated with a given, named, pollutant (e.g. PM, ozone, benzene). This is usually in the context of proposed local/ national/ EU-wide standards to control specific pollutants.

The policy applications now are very widespread. For example, applications in the EU context, from one team (AEA Technology, using ExternE methodologies) include:

- PVC disposal (2000 – 2001)
- BeTa (Benefits Table database) (2002)

Thus, the links with policy are clear and fundamental; improvements to HIA and CBA methodology will have a direct benefit in improving the reliability of policy development.

**CURRENT STATE OF EU RESEARCH ON HIA AND CBA**

HIA and CBA are relatively new methodologies. Their systematic application to air pollution and health in Europe has been championed by a small number of multi-disciplinary teams,
who have benefited from EU funding to do this work. These include:

- The ExternE team, active since the early 1990s, estimating the external costs of energy (electricity, traffic, energy from waste) and extending these methodologies more widely into ‘green accounting’ (e.g. GARP I and GARP II) see, e.g., http://www.externe.info/

In addition, there are many groups applying the methods locally. Many of these are now working together, e.g. within the HIA Working Group of AIRNET (http://airnet.iras.uu.nl/)

The use of HIA in the context of air pollution and health could not have been successful except for the extensive European and international research on air pollution and health. Likewise, many of the limiting factors in applying HIA to air pollution and health depend on unknowns in the area of air pollution and health: what aspects of particulate matter (PM) most affect toxicity; in particular, the toxicity of sulphate and nitrate particles; whether E-R relationships in SO2 and NO2 reflect causal effects of these gases; the time-lag between changes in PM exposure and associated changes in death rates; etc. These issues are addressed under air pollution priorities.

There are, however, other issues which transcend the applications to air pollution. We will focus on these, in particular. Some, such as studies of monetary valuation of the health effects of ambient air pollution, have also received substantial EU research funding in the past years.

**FIRST RESEARCH PRIORITY IS EXTENDING HIA/ CBA METHODS AND APPLICATIONS TO COVER**

- **THE SCALE PRIORITY AREAS;**
- **THEIR UNDERLYING ENVIRONMENTAL CAUSES**
- **POLICIES THAT AFFECT THOSE CAUSES**

The four priority areas of the 1st cycle of SCALE (2004-2010) refer to diseases/ health outcomes:

- Childhood respiratory diseases, asthma, allergies;
- Neurodevelopment disorders;
- Childhood cancer;
- Endocrine disrupting effects.

These should therefore be priority issues for HIA and CBA also. In particular:

*Topic 1.1: These health endpoints should be priority endpoints for monetary valuation studies.*

However, HIA and CBA as a whole refer better to the underlying causal factors, or to policies which affect those causal factors, than they do to endpoints. Fortunately, these research priorities have been selected not only because they are important to public health, but also
because already they are active areas of research in Europe. This means that there is already a base of knowledge about topics which are crucial to the applications of HIA and CBA methods, including:

**Topic 1.2:** What are the health impact pathways linking environmental causes with these priority outcomes?

Indeed, the SCALE documents (e.g. Executive Summary) identify the priority environmental causes as including

- indoor and outdoor air,
- dioxins
- heavy metals
- endocrine disrupters
- electromagnetic fields and
- the urban environment.

*These environmental factors, and the policies that affect them, therefore become priority topics for HIA/ CBA and so we suggest that*

- the systematic extension of HIA/ CBA methods and applications to these topics is the 1st strategic priority of the next several years;
- applications of the methods consider all the adverse health effects of these environmental causes, and not only the priority endpoints; i.e. that while their links with priority endpoints may be the motive for focusing on these endpoints, evaluations should be of the health effect of the factors – or underlying policies – as a whole. Indeed, any wider application of HIA and CBA to other contexts (e.g. environmental noise) is desirable and valuable – because other pathways link environment and children’s health, and because wider applications increase methodological understanding.

As noted earlier, there is already some HIA/ CBA work in these areas – e.g. the ExternE team has considered various heavy metals, dioxins, noise; and some further studies are already funded under EU FP6.

The most important limiting factor is scientific knowledge in these particular fields; specifically, knowledge about:

**Topic 1.3:** What are the sources of emissions? What factors or policies best reduce these emissions?

**Topic 1.4:** What are the pathways linking emission to human exposure and dose? What developments in modeling are needed to make these pathways and linkages explicit and quantifiable?

**Topic 1.5:** What are the most important E-R relationships linking environmental factors with the priority endpoints?

NB: Specific research needs on heavy metals, dioxins, EMFs etc. are identified not here, but in the appropriate chapters of this Report. (We note however that a benefit of HIA is that it can help identify what issues and uncertainties have greatest impact on public health, and so
contribute to identifying policy-related research priorities.)

SECOND RESEARCH PRIORITY: RESEARCH THAT SUPPORTS HIA AND CBA METHODOLOGY, WITH A VIEW TO ITS WIDER APPLICATION

As well as the pathway-specific research needs (exposure modelling, E-R relationships) considered elsewhere, there are several underlying methodological affecting HIA and CBA work issues that transcend particular applications. We propose therefore that research on these generic or underlying methodological issues be the 2nd strategic priority of HIA/ CBA research in the coming years.

These include, but are not restricted to:

Topic 2.1 Better characterisation of background rates of morbidity and health service usage across the EU and its accession countries (plus development of indicators);

Topic 2.2 Improved methods for assessing uncertainty reliably and representing it accessibly;

Topic 2.3 Better monetary valuation and other methods of assessing health impacts (e.g. QALYs);

Topic 2.4 Identifying, for various kinds of applications, what are the key drivers of the final results, so that high-quality HIAs and CBAs can be done at affordable prices;

Topic 2.5 Improvement of application tools and software;

Topic 2.6 Maintaining close working links (i) among the various groups who are developing tools and methods; and (ii) between those groups and wider stakeholders (policy makers; NGOs, industry; ‘the public’; practitioners). HIA is quite a new methodology and those links are crucial.

We consider the position, and research needs, in more detail, according to the various stages of a HIA or CBA (see Figure).

- The main goal is to elaborate a methodology that analyzes all the impact pathways from emissions to damage and that could be expressed in terms of cost (days of illness, or in concept of money invest by the state).
- The methodology has to be useful for all the pollutants, emissions and effects.
- On the other hand, the methodology has to be transparent (easy to read and do), with good result and cheaply. Also the methodology has to show the uncertainty of each step, and the total uncertainty.
- This methodology will be developed to assess and protect children against risks to health produced by emission of pollutants. However, applications will consider people of all ages, because the public health benefits are not age-restricted.

Impact pathway analysis

1. Emissions

During the life cycle of a product there are several processes such as extraction of materials, transformation, manufacture, transport, use and end of life (incineration, land field), that could generate emissions to air, water or soil. Emissions during use are also important for
health effects in children. For example, brominated flame retardants are used in plastics; also rubbers and insulation materials used in rubber cables; plastic components of consumer electronics (brown products); particularly external parts of TV sets; interior-decorating textiles, etc. These compounds are released during use, producing indoor-air contamination. It is estimated that around 0.2 g PBDEs will be emitted during the service-life of the TV. There is a need to cross-link with information on product safety.

With respect to industrial activities, emission rates for many chemicals are known, however there are uncertainties associated with (i) the technology used; (ii) lack of information about different parameters (for example production) that are necessary for good data; (iii) emissions from new substances; and (iv) substances whose production has been banned but that are included in products that are currently used (lead in paints, PCP in wood treated, PCBs in condensers).

**Needs:**

- To elaborate a rigorous working method for a database of industrial emission rates of various pollutants, and an associated inventory of industrial emission rates.
- To investigate emissions of products during their use and also produced by accidents (combustion of wood treated with PCP, fire of furniture treated with fire retardant).
- To do an inventory of substances in products that, despite manufacture being banned, are still present nowadays in products or in the environment (like asbestos, PCP,..).
- To investigate indoor emissions.

2. Fate and transport.

Once the chemical is emitted it is transported and distributed in the different mediums. The partition of each pollutant in the different mediums depends on its physico-chemical properties (volatility, half-life, etc.) in interaction with the environment. Depending on these properties, the fate and transport will affect local, regional or intercontinental areas. Nowadays, simple-compartment and multi-compartment models exist. Most of then (included those developed for the EU commission; EUSES) are ‘black boxes’, very complicated, often difficult to use, and with many areas of uncertainty.

**Needs:**

- To develop more comprehensible and transparent models.
- To improve models for persistent and long range transport compounds (like PCDD/Fs, PCBs..).
- To evaluate the uncertainty of the models.
- To develop sensitivity analysis of models.

**Exposition and bio-concentretation**

HIA and CBA of the classical air pollutants (PM, NO2, SO2, ozone…) deal with two types of time-related effects on health:

- The more-or-less immediate effects of acute exposure;
- The delayed effects of longer-term (chronic) exposure.

Chemical emissions such as heavy metals, persistent organic pollutants (POPs), volatile organic compounds (VOCs) and others, may lead to direct human exposure (inhalation or drinking water), or to indirect exposure (food consumption). These substances, apart from
their toxicity, have as a common characteristic their persistence (low degradability in the environment and ability to bioaccumulate) and so will principally affect health through cumulative rather than acute exposures. This can lead to uncertainties in extrapolation from one population to another because different habits and lifestyles can affect exposures.

**Needs:**

- Estimate contaminant concentrations in environmental media (soil, air, water) that are protective over a lifetime of children.
- Improve knowledge of the factors that modify the absorption and accumulation of pollutants especially during the development period.

**Exposure (Dose)- Response Relationships**

These functions relate an increase in pollutant concentration level (exposure) to an anticipated damage or negative effect (response) on a particular receptor (anything which is affected adversely by an increase in exposure), in our case humans, especially children.

Many laboratory and epidemiological studies have been carried out in order to establish relationships between exposure and response. Laboratory studies of longer-term (chronic) exposure are possible only for animals, not humans; there is an issue of cross-species transferability of relationships. Also, human epidemiological studies often refer to highly exposed occupational populations. Environmental applications require low-dose extrapolation, and extrapolation to more susceptible groups, including children. An understanding of mechanisms of damage greatly assists in extrapolation.

These issues are well-known in epidemiology and risk assessment, even if there are no easy answers. Principally, they are issues for the specific subject-matter experts; the basic studies needed fall within the research needs for those areas. However, there are some general themes.

**Needs:**

- One of the primary things to be resolve is to evaluate the time that passes between exposure and identification of health effect.
- The reliability of the various extrapolations necessary: from high to low exposure; from workers to susceptible humans; extrapolation across species.
- Sometimes D-R relationships are expressed in relation to biological indices of does, such as lead in blood; or manganese in blood or urine. There is a need to ensure that the assessment of dose endpoint of exposure assessment links up suitably with the dose start-point of the D-R relationships.

**Characteristics of the population-at-risk**

**Extent in space and time**

This depends on the pollutant being investigated and the parameters of the study. It is easy to under-estimate the scope and scale of the analysis needed to capture the majority of the adverse health effects.

**Background exposure levels**

For substances with non-linear D-R (or E-R) relationships (including thresholds), it is
necessary to characterise not only the incremental exposure, but also the background levels in the population. The information needed will vary by pollutant. It may be difficult to obtain this information reliably.

Background levels of morbidity
E-R functions expressed in terms of % change (in health effect, per unit exposure or dose) can be implemented only if there is also sufficient information on background levels of disease prevalence or incidence of health endpoint (disease; clinical change; use of health services). Again, there is often an information gap. Steps to address this in the context of air pollution HIA can be extended to other health end-points.

Needs

- The over-riding need is to ensure that the various components of a HIA analysis link up properly so that an integrated analysis can be done. This requires integration of information across sources with which even an expert multi-disciplinary team may not be familiar. Integration will be assisted by good inventories and ‘clearing-houses’ of research, not only on HIA studies in various contexts, but also on the background data necessary for carrying them out.

Issues in integrated implementation; tools
The impacts are estimated by integration of the E-R function, the level of exposure, the accumulation of the population (considering the entire exposure pathway), the population size, and the background rates of morbidity or mortality in the population at risk. Complexity, and reliability, vary according to the level of detail at which integration is carried out; the detail needed for an effective analysis is an issue of ongoing research.

Geographic Information Systems (GIS) and related mapping techniques are now widely used in implementation. Some integrated implementation tools have been and are being developed in the context of ambient air pollution. There is need and scope to extend these. As noted above, integration (whether mathematical, or via software) needs proper link-up between component parts; in particular, it needs common metrics of exposure, dose, effect (e.g. between epidemiological studies and background rates of morbidity). This may involve expert judgment based on limited evidence; it is important that assumptions be clearly stated and processes described clearly.

Another aspect of integration concerns the full life cycle of a product, considering all the damaged associated with it. For example children are spending more and more time with computers. It is known that its use can produce different damages as: loss of sight, loss of hearing due to the high volume, damage to shoulder due to bad ergonomics position, but also exposure to dangerous agents as polychlorinated bromide compounds presumed carcinogenic as PCDD/Fs. Integration across all pathways is needed for a full HIA. An initial scoping study would identify which pathways have the greatest potential for damage at the population level, and so guide the efficiency of the overall analysis.

Needs:

- To improve the use of Geographic Information System (GIS) maps and other tolls for implementation of HIA in various contexts.
- Because we have relatively little experience in combining different types of risk, a key issue is the need for methods development in this area:
  - Calculating cumulative risks associated with multiple pollutants and particular effects.
  - Calculating cumulative risks associated with multiple pathways.
• Calculating cumulative risks associated with multiple effects.

• Guidelines for conducting HIA/ CBA so that analyses are reliable, transparent and at the same time, not overly expensive. (For example, an iterative approach helps identify the key issues.)

**Damage Indicators**

Some attempts have been made to quantify diverse risk in a common metric. For example, cumulative risk may be expressed as margin of exposure (MOE) defined as the no observed adverse effect level (NOAEL) divided by estimated exposure. Much like a hazard index, they provide perspective, but without providing a statement of the probability of effects occurring in the exposure is greater than the NOAEL. MOEs can be used as an indication of possible risk, and can be mathematically combined across routes of exposure. The advantage of using MOEs for expressing risk is that one can preserve the route-specific nature of the different exposures and then add them to generate a total MOE. The inverse of the different pathway MOEs are added together and then the inverse of that sum is taken as the total MOE.

It has been also suggested the time as the unit of measure for the burden of disease; whether the disease results in disability or premature mortality (Murray, 1994). Based in this premise, economic analyses of the cost and benefits of disease intervention strategies have used Quality Adjusted Life Years (QALYs) and Disability Adjusted Life Years (DALYs) as the metrics for the adverse effects of disease. These metrics are intended to reflect the years of life spent in disease states and the years of life lost due to premature mortality resulting from disease as a surrogate measure of risk from a variety of different types of effect.

Adverse effects on health can also be monetised. There is an ongoing programme of EU research on valuation studies, prompted especially by CBA of the health effects of air pollution. This can and should be extended to cover the SCALE priority endpoints which are not relevant to air pollution HIAs.

**Needs:**

• Further methods development work is needed to improve the utility of QALYs and DALYs for environmental risk assessment, especially with respect to the incorporation of uncertainty.

• There is a need to extend reliable valuation to other endpoints.

• Also work can be done looking for new unit of measure for the burden of disease.

**Assessing and representing uncertainty**

The assessment and representation of uncertainty is a key need across all implementations of HIA. Poor assessment of uncertainty (deficient, or over complex) is a major barrier to the wider use of HIA and CBA for policy purposes. There is a suspicion, sometimes justified, that the quantification necessary for HIA/ CBA can be used to give spurious accuracy to the results. On the other hand, some uncertainty is unavoidable; and policy implies decision-making in the context of that uncertainty. The point is to ensure that the uncertainty is assessed fairly and represented understandably.

**Needs:**

• More research and experience-sharing on methods to assess and represent uncertainty in a way that is reliable and understandable.

**The social processes of HIA/ CBA**
There are two needs. First, there is a need for continued communication, experience-sharing and co-operation among the community of those who are involved in developing and implementing HIA and CBA. This is necessary in any area of methodology. It is particularly necessary for HIA/ CBA because (i) this area in intrinsically multi-disciplinary, and so communication and integration of judgments across disciplines is essential; and (ii) because HIA is a relatively new methodology, in its current developed form; most practitioners originally had (and sometimes still have) their primary research base in one of those disciplines, e.g. epidemiology; and, until recently, there has not been a basis for different teams to come together as practitioners of HIA. (This lack has been to an extent met in recent years by initiatives of WHO; of specific EU projects such as DIEM; and by the HIA Working Group of AIRNET).

Secondly, as HIA gets extended to other areas of application, there is a need for effective communication and co-operation between HIA developers and the subject-matter specialists (exposure, epidemiology, toxicology) in these new fields of application.

Thirdly, there is a need for ongoing contact and dialogue between, on the one hand, developers and practitioners, and on the other hand, other stakeholders (e.g. policy makers at all levels; industry; NGOs; ‘the public’). Again, current work within AIRNET and, e.g. DIEM, is helping to address these needs.

**Needs**

To develop, support and maintain good structures of communication and experience-sharing between

- developers and practitioners of HIA/ CBA as a methodological community;
- HIA developers and subject-matter specialists in new areas of application; and
- HIA developers/ practitioners and the diverse stakeholders who have a legitimate interest in the results of HIA/ CBA, as these impact on policy.

**RELEVANCE TO POLICY**

As stated at the outset, the whole purpose of HIA/ CBA is as a tool for better policy through better evaluation of possible scenarios.

The various research priorities identified above are intended to improve:

- The scope of effective application of HIA/ CBA;
- Its reliability; and

Its ease of use, both for practitioners and other stakeholders.
### Cumulative Risk Assessment

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<th>Pathways</th>
<th>Receptors</th>
<th>Endpoints</th>
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<td>Human Health</td>
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5.8 Indoor air

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The following text is widely inspired from the EnVIE FP6 project proposal and benefits also from specific inputs provided by members* of the Steering Committee of the European Collaborative Action on Urban Environment and human exposure. Nevertheless, at the present stage, this paper has not been formally reviewed neither by EnVIE or ECA members and must be considered as a working document not to be quoted.

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Key words

Indoor air pollutants, exposure, health effects, source control, research needs, policy

Summary and conclusions

Exposure to indoor air pollutants is now recognised as participating significantly to a wide range of environmentally related diseases including allergies, short term and long term respiratory pathologies. Numerous chemical, physical and biological contaminants have been found indoors. They result from various sources including outdoor air, building materials and systems, indoor activities, etc… for many of them the concentrations found indoors are higher than outdoor. Several projects at European level have been conducted in this field during the last two decades. Among those, exposure surveys to air pollutants have underlined the prominent contribution of indoor spaces to the global exposure for most pollutants even for those being already regulated outdoors like benzene, particles, NO2, CO, etc.

Research needs should consider to what extent indoor air pollution is affecting health of the European citizens and in particular what is its contribution to acute and chronic health impacts (including asthma and respiratory allergy) and what are exposure patterns, determinants and implications for safety thresholds.

Future research should address indoor air exposure surveys, exposure measurements, health effects measurements, risk assessments, networking Indoor exposure data bases, modeling of exposures and effects in buildings, standardization and harmonization and facilitate cross fertilization across Europe and multidisciplinary approaches.

Few emerging issues in direct or indirect connections either with general scientific progress or with buildings construction and management changes are also to be considered.

Background

Among the causes of disease in the population, three major factors can be identified: the genetic predisposition of the individuals, the life-style (including dietary and behavioural habits, use of tobacco, alcohol and other toxins), and the environmental conditions, including housing, quality of the living and working environments, and exposure to natural or man-made pollutants. For many pollutants, especially the more volatile ones, air exposure is the dominant pathway. Exposure via the air occurs both outdoors and indoors including
different additional compartments; home, workplace, transit. Air pollutants – both in ambient air and indoor air – have been demonstrated to represent a major contributor to the total burden of disease of the population. Knowing the relative contribution of these compartments is essential for effective control measures and use of financial resource.

Indoor pollutants include chemical and biological agents.

As regards chemical pollutants which are mostly represented by complex mixtures of substances, major sources are:

- Ambient air pollution due to traffic and urban and industrial activities, which come into the building through the ventilation system or by infiltration (building envelope permeability).
- Water and soil (air pollutants coming through water supply, radon, methane and contaminated soils).
- Building materials (wall and floor coverings, paints, insulation materials...)
- Processes that occur within buildings (combustion, heating, ventilation and air conditioning systems, paper processing such photocopying
- Occupants themselves and their activities (tobacco smoking, use of cleaning products, cooking, pets, plants etc.).

The number of pollutants present in the indoor environment and their diversity is immense and probably only a small number of these have been properly characterised.

WHO (2000) classified the compounds into organic air pollutants, such as some VVOC (vinyl chloride), VOC (benzene styrene, trichloroethylene) and SVOC (polycyclic aromatic hydrocarbons (PAH), polychlorinated biphenyls (PCB), polychlorinated dibenzodioxins and dibenzofurans (PCDD/PCDF) and formaldehyde, acrylonitrile, carbon disulfide, carbon monoxide; inorganic air pollutants (lead, hydrogen sulphide, asbestos), classical air pollutants (nitrogen dioxide, ozone and other photochemical oxidants, particulate matter and sulphur dioxide), and specific indoor air pollutants (environmental tobacco smoke (ETS), man-made mineral fibres and radon).

The concentrations of chemical pollutants indoors are usually low although, for many of them higher than outdoors; however, they are in a range where they may induce toxic effects or significantly interfere with the comfort of the occupants. As regards VOCs for example, so far more than 900 different compounds have been detected in indoor air of buildings; 250 of them have been measured at concentrations higher than 1 ppm. Generally, a single air sample collected in a building shows 30-50 VOC, the concentrations of which very rarely exceed 50 µg/m3 individually, the total concentration of VOC being usually lower than 1-3 mg/m3.

Indoor air biological contaminants are airborne particles composed of vital or dead microorganisms, spores, viruses, pollen, mites, or organic substances released by insects, pets and man. The main sources of biological agents in buildings are represented by man, domestic animals and some components of the building itself. Of particular importance are water reservoirs and materials wet by water leakage, humidity or water condensation, where micro-organisms like moulds may grow and replicate. Allergens in buildings are released from pet animals (cats and dogs), dust mites, cockroaches, moulds and humans (hair and dander). Pollen is introduced with outdoor air. Outdoor allergens such as pollens and moulds may penetrate into the indoor environment through open windows, doors or ventilation systems. Contaminated humidifiers in homes, industrial and non-industrial buildings, and cars have
been associated with allergic asthma, humidifier fever and extrinsic allergic alveolitis. The contaminated humidifiers generate aerosols containing microorganisms and debris of microorganisms. A wide spectrum of microorganisms, including thermophilic actinomycetes, moulds, bacteria, amoebae and nematodes, have been described as sources of offending allergens from humidifiers.

The sources contributing to indoor air pollution are responsible for either continuous emissions (long-term emission with constant sources strength such as material emissions) or discontinuous emissions (short term emissions with variable source strength such as human activities). Spatial and temporal variations can occur, depending on movement of the air, infiltrations between rooms in a building, etc. In conclusion, it may be stated that all ventilation aspects are of extreme importance in the concentrations levels obtained in a building.

The main diseases and health adverse effects caused by indoor air pollutants have been discussed in several reports (see ECA n° 10 and other references). The available knowledge is summarised below.

Indoor air pollutants are responsible for an increased occurrence of cancer, chronic and acute pulmonary diseases, upper airways inflammatory diseases, allergic diseases such as asthma and ocular and mucosal reactions, infectious diseases, and intoxications. Moreover, they can increase the occurrence of frequent and severe diseases such as myocardial infection and other cardiovascular diseases responsible for a great part of mortality and disability of the population.

Less severe, but socially very relevant adverse health effects, include sensorial discomfort, odour, sensorial irritation and annoyance and the so-called Sick Building Syndrome, an illness of epidemic nature affecting the majority of the occupants of a building and appearing with unspecific symptoms related to nose, eye, respiration, skin, and the nervous system.

A poor indoor environment at home may contribute to the development of allergies, particularly to house-dust mites, and respiratory infections and exacerbate certain hypersensitivity reactions. Damp-related indications in buildings may be of great significance to health. Combination effects have been shown between passive smoking, exposure to house-dust mites and furred animals with regard to the development of asthma among children.

Annoyance due to air pollutants outdoors and indoors is common. In Sweden, around one in ten inhabitants report annoyance from vehicle exhausts and smoke from wood-burning stoves. Among those with bedroom windows overlooking a busy street, main road or industrial premises, vehicle exhausts annoy more than one in five. Around 18% of the adult Swedish population) report symptoms that they consider to be due to the indoor environment (in the home, at school or at work). The symptoms include irritated, runny or stuffed-up nose (4%), tiredness (3%), itching and irritation in the eyes (2%), and headache (1%). Persons reporting asthma or allergic complaints affecting the eyes or nose (in Sweden almost one third of the adult population) more often report annoyance due to air pollutants than others. Almost two-thirds of those reporting asthma experience discomfort in dusty or smoky environments (The Swedish Environmental Health Report 2001).

In addition, there is no reason to assume that the range of health issues and the nature of the health burden from indoor and outdoor exposures are very different (Mauderly, Indoor Air
Conference 2002), and there may be good reason to give greater attention to the contribution of indoor exposures to health burdens that have then traditionally been attributed to outdoor exposures. The broad range of adverse health impacts of outdoor air pollution for which some evidence currently exists is listed in the following table.

Table 1. Health effects thought to be caused or enhanced by outdoor air pollutants (from Mauderly, 2002)

<table>
<thead>
<tr>
<th>Mortality (total, respiratory, and cardiovascular)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic increases in mortality related to short-term exposure</td>
</tr>
<tr>
<td>Shortened life span from long-term exposure</td>
</tr>
<tr>
<td>Increased infant mortality</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature birth</td>
</tr>
<tr>
<td>Reduced lung growth rates</td>
</tr>
<tr>
<td>Altered lung anatomical development</td>
</tr>
<tr>
<td>Reduced resistance to respiratory infection (viral, bacterial)</td>
</tr>
<tr>
<td>Eye and airway irritation</td>
</tr>
<tr>
<td>Enhancement of development of allergic sensitization (adjuvant effect)</td>
</tr>
<tr>
<td>Exacerbation of allergic responses among those already sensitised</td>
</tr>
<tr>
<td>Respiratory tract inflammation</td>
</tr>
<tr>
<td>Reduced lung function (volumes and flow rates)</td>
</tr>
<tr>
<td>Reduced gas exchange</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td>Emphysema</td>
</tr>
<tr>
<td>Lung cancer</td>
</tr>
<tr>
<td>Vasodilatation and increased vascular resistance</td>
</tr>
<tr>
<td>Altered heart rate and reduced heart rate variability</td>
</tr>
<tr>
<td>Altered cardiac electrophysiology</td>
</tr>
<tr>
<td>Inflammation outside lung, by circulating mediators and particles</td>
</tr>
</tbody>
</table>

Research activity in Europe

Research activities in the indoor air field in Europe started to develop significantly in the mid 80’s, the first “Indoor Air” international conference being organised in 1987 in Berlin. A good idea of the topics which were addressed and their evolution during the last two decades is given through list of reports which were issued by the European Collaborative action “indoor air quality and its impacts on man (nowadays “Urban Air, Indoor Environment and Human Exposure”)” presented in the following table.

Table 2 : List of European Collaborative Action (JRC-ECA) reports

- Report No. 11, Guidelines for ventilation requirements in buildings. EUR 14449 1992, EN.
Several national/international projects and studies focused on the importance of the population exposure to indoor pollutants. Examples of national studies are the French permanent survey on indoor air quality survey design in dwellings and schools, the German Environmental Survey (GerES) and the study Indoor air quality in English homes. In the EXPOLIS study (Air Pollution Exposure Distributions of Adult Urban Populations in Europe) personal exposures and micro-environmental concentrations (home and workplace) of selected air pollutants were measured in six European cities: Athens, Basel, Grenoble, Helsinki, Milan and Prague. The MaNaPI project has developed model for calculation of indoor air pollution.

Some protocols to measure the health and energy efficiency status have been developed, such as the protocols developed within the European IAQ-Audit and the TOBUS and EPIQR projects developed in the Vth RTD framework programme.

The ongoing HOPE project “Health optimisation protocol for energy-efficient buildings: pre-normative and socio-economic research to create healthy and energy-efficient buildings (2001-2004)” has the final goal to provide the means to increase the number of energy-efficient buildings that are at the same time healthy.

European thematic network concerning IAQ are PEBBU “Performance based building” aimed to improve the implementation of research information, practical tools and guidance available for the purpose of achieving a more sustainable built environment and EUROVEN “European multidisciplinary scientific network on indoor environment and health concerning associations between ventilation and health” devoted to create a multidisciplinary forum between different disciplines concerning associations between ventilation and health. The EFA Project “Indoor air quality in European schools “to collect

- information on indoor air quality (IAQ) in European schools, to review the related policies
- and preventive programs and to formulate recommendations aimed at providing a healthy school environment. At last, the ongoing “INDEX project: critical appraisal of the setting and implementation of indoor exposure limits in the EU” is focusing on priority indoor chemicals as candidates to indoor air thresholds or guidelines in future policies. The following table is presenting the list of recent and on-going European Projects having connection with indoor air preoccupations.

<table>
<thead>
<tr>
<th>Report No.</th>
<th>Title</th>
<th>EUR Code</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Radon in indoor air</td>
<td>16123 EN</td>
<td>1995</td>
</tr>
<tr>
<td>16</td>
<td>Determination of VOCs emitted from indoor materials and products: Second interlaboratory comparison of small chamber measurements</td>
<td>16284 EN</td>
<td>1995</td>
</tr>
<tr>
<td>17</td>
<td>Indoor air quality and the use of energy in buildings</td>
<td>16367 EN</td>
<td>1996</td>
</tr>
<tr>
<td>18</td>
<td>Evaluation of VOC emissions from building products – solid flooring materials</td>
<td>17334 EN</td>
<td>1997</td>
</tr>
<tr>
<td>19</td>
<td>Total Volatile Organic Compounds (TVOC) in indoor air quality investigations</td>
<td>17675 EN</td>
<td>1997</td>
</tr>
<tr>
<td>20</td>
<td>Sensory evaluation of indoor air quality</td>
<td>18676/EN</td>
<td>1999</td>
</tr>
<tr>
<td>21</td>
<td>European Interlaboratory Comparison on VOCs emitted from building materials and products</td>
<td>18698/EN</td>
<td>1999</td>
</tr>
<tr>
<td>22</td>
<td>Risk assessment in relation to indoor air quality</td>
<td>19529/EN</td>
<td>2000</td>
</tr>
<tr>
<td>23</td>
<td>Ventilation, good indoor air quality and rational use of energy</td>
<td>20741 EN</td>
<td>2003</td>
</tr>
</tbody>
</table>

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Table 3 : List of European research projects with connections to Indoor Air Quality (Paolo Carrer, 2003)

<table>
<thead>
<tr>
<th>PROJECT No</th>
<th>TITLE</th>
<th>STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EN4-CT96-0202</td>
<td>EXPOLIS: Air Pollution Exposure Distributions of Adult Urban Populations in Europe</td>
<td>Completed 1998</td>
</tr>
<tr>
<td>JOU2-CT92-002</td>
<td>European Audit to optimise indoor air quality and energy consumption in office buildings</td>
<td>Completed 1996</td>
</tr>
<tr>
<td>JOR3-CT97-0076</td>
<td>Development and Test of Modern Control Techniques Applied to Solar Energy Buildings</td>
<td>Completed 1999</td>
</tr>
<tr>
<td>JOR3-CT98-0235</td>
<td>TOBUS – A Decision making tool for selecting office building upgrading solutions</td>
<td>Completed 2000</td>
</tr>
<tr>
<td>JOR3-CT97-0171</td>
<td>AIRLESS – Design, operation and maintenance criteria for air handling systems and components for better Indoor Air Quality and Lower Energy Consumption, pre-normative research</td>
<td>Final reporting</td>
</tr>
<tr>
<td>JOR3-CT97-0194</td>
<td>MATHIS – Materials for healthy indoor spaces and more energy efficient buildings</td>
<td>Final reporting</td>
</tr>
<tr>
<td>EN4-CT96-0202</td>
<td>EXPOLIS: Air Pollution Exposure Distributions of Adult Urban Populations in Europe</td>
<td>Completed 1998</td>
</tr>
<tr>
<td>DG SANCO N. S12.130758 (99CVF2-602)</td>
<td>MaNaPI Managing Natural Pollutants Indoors</td>
<td>Completed 2001</td>
</tr>
<tr>
<td>EVK4-CT99-20002</td>
<td>SURERUO: Sustainable Refurbishment in Europe</td>
<td>On-going</td>
</tr>
<tr>
<td>EVK4-CT99-20008</td>
<td>CRISP: Construction and City Related Sustainability Indicators</td>
<td>On-going</td>
</tr>
<tr>
<td>IEA Annex 36</td>
<td>Retrofitting in educational buildings. New annex dealing with the development and demonstration of energy-efficient techniques applicable in the refurbishment of educational buildings.</td>
<td>On-going</td>
</tr>
<tr>
<td>DG SANCO N. S12.291168 (2000CVG2-604)</td>
<td>EUROVEN - European Multidisciplinary Scientific Network on Indoor Environment and Health concerning associations between ventilation and health</td>
<td>On-going</td>
</tr>
<tr>
<td>Thematic Network PeBBu - Performance Based Building</td>
<td></td>
<td>On-going</td>
</tr>
<tr>
<td>DG SANCO</td>
<td>INDEX: Critical Appraisal of the Setting and Implementation of Indoor Exposure Limits in the EU</td>
<td>On-going</td>
</tr>
</tbody>
</table>

Relevance to policy development

Among the most important challenges for tomorrow, European citizens want to live longer, healthier, in a precautionary world and at an affordable cost. It is therefore essential to take into account health determinants as upstream as possible in the various decision processes aiming at designing our tomorrow’s cities, improve environmental quality as well as quality of life of occupants.

Up to now national and European air quality policies have devoted most of their efforts towards the limitation of outdoor environmental concentrations for some specific pollutants resulting from industrial activities and automobile traffic. Although there is no reason to relax the society preoccupation towards these issues, it is now recognised that indoor exposures to air pollution must certainly be given a better attention in policy making in such a way

- to better understand and assess the contribution of indoor spaces to environmental diseases,
- to set up coherent policies as regards the reduction of exposures.

One well-known example is benzene for which target limits set for outdoors in close future might be systematically over passed indoors (the indoor/outdoor ratio is found around 1,5 in concentrations in various surveys). And if exposure instead of concentration is considered, it is clear that any effort undertaken to limit the burden of benzene related disease in the population should not ignore the way to reduce benzene concentration indoors.
Other typical examples of indoor environment exposures and health effects are environmental allergies affecting sensitive groups, especially children. The sources of many allergens, such as pollen, may be outdoors. Buildings usually reduce such exposures, and this reduction can be significantly enhanced by ventilation technology, indoor space cleaning (including air cleaners) and personal behaviour. Although the allergic reactions can be quite abrupt, development of the allergies often takes years of persistent low doses. These exposures occur almost exclusively indoors, and also their sources, other than pollen, are often inside the buildings, which are occupied by the affected individuals.

- It should be therefore the objective of the European research policy this project to increase the understanding of health impacts of indoor air quality and to provide grounds for health risks assessment and management. It should especially focus on the assessment of policy relevance of research into the health effects of isolated agents and mixtures, and consider the implications for thresholds and safety margins for the general population and for people at work. It should address in particular how indoor air quality contributes to the observed rise in asthma and respiratory allergy as well as in other acute and chronic health impacts.

- It is also essential to evaluate the various scenarios for policy making, such as
  - Sources control,
  - Building regulations,
  - Set up of indoor air quality thresholds,
  - People education and information,
  - Professional trainings,
  - Etc.

Research needs

Research needs in the field of Indoor Air address a wide range of disciplines. They should aim at bringing answers to the following main questions:

- To what extent indoor air pollution is affecting health of the European citizens, being at home, at the workplace or in any indoor space? And in particular what is its contribution to acute and chronic health impacts (including asthma and respiratory allergy)

- How and how much the European citizens are exposed to this pollution?

- What is the respective contribution of the various determinants (outdoor pollution, indoor sources, building spaces characteristics, people’s behaviour, etc.) on indoor air pollution?

- And what are the implications in terms of implications for safety thresholds

In this context, future research works should address the following research area:

- **Indoor air exposure surveys**: Identify sources and agents in indoor environments which are responsible for the increase of allergy and other disease. Elaborate guidelines contributing to improve the design of indoor exposure surveys in member states according to the various objectives of risk assessment.
- **Exposure measurements**: elaborate measurements and sampling techniques, chemical and analytical procedures, experimental design and statistical terms. Facilitate emergence of European SME companies oriented to indoor environment sampling, measurement and control.

- **Health effects measurements**: Effects: Health and perceptions, comfort, productivity and effects measurements.

  **Risk assessments**: assess the contribution of indoor environments to the combined exposures to harmful agents and health risks. Provide guidance and means for managing these risks in indoor environments.

- **Networking Indoor Exposure data bases**: identify and elaborate links between existing data bases dealing with indoor exposures in the various type of spaces (public, dwellings, office buildings, schools, …);

- **Modeling of exposures and effects in buildings**: Modeling: Exposure modeling, survey design, time budget, and questionnaires.

- **Standardization and harmonization**: provide scientific grounds to standardise measuring methods

In order to facilitate cross fertilization across Europe and multidisciplinary approaches, specific attention should be given to:

- **Training young scientists**: organization of workshop and training courses to ensure dissemination of knowledge and facilitate access to new scientist in the field.

- **Mobility of scientist**: Facilitate cross-participation and mobility of personnel in projects conducted in the indoor environment field.

- **Research coordination**: encourage more coordination of research studies. Make meta-analyses and data compilation of the results from these studies. Identify missing information. Define focused studies.

**Emerging issues**

The emerging issues in the field of indoor air quality are mostly to be considered directly or indirectly in connection with progresses that can be made in the following areas:

Basic toxicology and epidemiology regarding chemical substances which can be found in the human built environment. For example, progress in the risk health assessment of endocrinian disruptors may require specific indoor surveys to identify indoor exposure determinants,

- Assessment of the heath effects of complex mixture (so called cocktail effects),

- Biology, molecular biology and microbiology. It is assumed that microbes and bio contaminants in general can play a determinant role in indoor air related pathologies although the domain remains complex to be addressed with “traditional methods”,

- Climate change and sustainable development implications on construction sector involving for example significant changes in building envelopes and/or air management systems
The critical question of bio terrorism has been recently put forward with some aspects linked to possible intentional contamination of indoor air, involving both biological and chemical materials and should therefore be put on the agenda.

Key references


5.9 Environmental exposure and the risk of adverse reproductive outcomes

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List of key words
Air pollution, Birth defects, Carbon monoxide (CO), Environmental noise, Environmental tobacco smoke (ETS), Fetal deaths, Infecundity, Low birthweight (LBW), Organochlorine-contaminated food, Particulate matter ≤ μm (PM\textsubscript{2.5}), Particulate matter ≤ μm (PM\textsubscript{10}), Pesticides, Polichlorinated biphenyls (PCB), Polycyclic aromatic hydrocarbons (PAHs), Small-for-gestational-age (SGA) infants, Spontaneous abortions, Sulfur dioxide (SO\textsubscript{2}), Total suspended particulates (TSPs), Trihalomethanes (THMs), Very low birthweight (VLBW), Waste landfill sites.

Summary
An assessment of the state of research on the role of environmental hazards in the development of adverse reproductive outcomes has been focused on three exposure scenarios recognised as the most prevalent in Europe, and four additional ones that are of importance for specific local populations. The first group included air pollution, environmental tobacco smoke (ETS) and environmental noise, and the second one trihalomethanes (THMs) in drinking water, hazards from waste landfill sites, residential exposure to pesticides and organochlorine-contaminated food.

All major adverse reproductive health outcomes have been considered, taking into account their high prevalence in the European population: infecundity, spontaneous abortions, birth defects, fetal deaths, low birth weight (LBW) and SGA.

State of research
The increased risk of LBW was the most consistent finding of the studies on populations exposed to ETS, environmental noise, waste landfill sites and organochlorine contaminated food. The increased risk of SGA infants was associated with exposure to air pollution, environmental noise and THMs. The elevated risk of infecundity was related to exposure to THMs, organochlorine-contaminated food and to residence close to waste landfills. Spontaneous abortions were mainly linked to exposure to THMs and organochlorine-contaminated food. As regards birth defects, an increased risk was confirmed only in populations living in the vicinity of waste landfill sites, while excess risk of fetal deaths was observed in rural residents exposed to pesticide drifts.

The biological mechanisms by which the examined environmental factors affect reproductive outcomes have not been clearly established for any of them. The most advanced research in this field so far has been performed in relation to the effects of exposure to air pollutants, ETS, environmental noise and organochlorine contaminants in food.

Postulated research needs:
Air pollution. Further investigation of the simultaneous impact of airborne particulates and PAHs on pregnancy outcomes is needed, especially their influence on fetal growth and fecundity. Since it was postulated that the effects of PAHs on the fetus may be affected by the
genotypes of the parents, the impact of air pollution on human health should be studied as a complex issue - i.e. from the interaction between genome and environment through gene expression to the effects on the health status at different developmental stages of the fetus, infant and child.

**ETS.** Very little is known about the impact of ETS on the risk of spontaneous abortion, birth defects, infecundity and male reproductive health. The methodological短coming of reproductive studies on ETS has been the difficulty in distinguishing whether the findings are due to the direct effect of male active smoking or female exposure to ETS.

**Noise.** The risk of other than reduced fetal growth, adverse reproductive outcomes in relation to environmental noise exposure should be assessed. Gender-related differences in response should be subject to further studies in order to verify the hypothesis that female fetuses are more sensitive.

**Trihalomethanes (THMs)** in drinking water. Taking into account the extent of THM exposures in Europe, the problem should be carefully examined in well-designed studies. In the event that the European studies confirm the increased risk of adverse reproductive outcomes in relation to THM exposures, the biological mechanism has to be proposed that would explain this relationship. Exposure to individual chemicals within the THM class should be examined, since the distribution of individual chemicals can vary regionally.

**Waste landfill sites.** More research into reproductive health effects of chemical mixtures and possible interactions between single chemicals is necessary to improve the understanding of the effects of multiple chemical exposures. It is essential to carry out systematic site assessments to underpin classification of the landfill sites according to health hazard. This will allow ranking the landfill sites according to their hazard potential by expert consensus.

**Residential pesticide exposure.** Standard protocols for the biological monitoring of the most prevalent pesticides have to be developed to achieve progress in assessing the risk of adverse reproductive outcomes in the population of rural area residents exposed to drifts of pesticides from agriculture fields. Systematic studies addressing the risk of each adverse reproductive outcome have to be undertaken.

**Organochlorine contaminants in food.** There is a need for a better understanding of the relationship between exposures to organochlorine contaminants in food and the risk of adverse reproductive and developmental outcomes. Further research on the relation between dietary intake of organochlorine-contaminated food (mostly fish) and time to pregnancy is expected to be pursued as a result of the recently announced 6FP calls in Food quality and Safety (Food and fecundity-Food-2003—T7.3)

**Introduction**

The aim of this document is to provide an assessment of the state of research on the role of environmental hazards in the development of adverse reproductive outcomes in order to identify research needs.

The analyses were focused on three exposure scenarios recognised as the most prevalent in Europe, and four additional ones that are of importance for specific local populations. The first group included air pollution, environmental tobacco smoke (ETS) and noise, and the second one trihalomethanes (THMs) in drinking water, hazards from waste landfill sites, residential exposure to pesticides and organochlorine contaminated food.
Six adverse reproductive health outcomes were considered, taking into account their high prevalence in the European population: infecundity, spontaneous abortions, birth defects, fetal deaths, low birth weight (LBW) and SGA. An attempt was made to evaluate the risk of each of the selected outcomes for every exposure scenario, however, in most cases only one or two outcomes were considered for investigation by the researchers.

The selection of the above listed health outcomes was made on the assumption that even a small increase in their risk could translate into a substantial number of affected infants and fetuses with an increased risk for mortality and for developing other serious health problems, including developmental disabilities and chronic respiratory conditions. For each environmental agent, a review of the existing knowledge on the risk of main adverse reproductive outcomes was performed with special emphasis on the evidence from epidemiological studies. Only quality studies, i.e. the ones employing valid exposure and health outcomes estimates and controlling for socio-economic, demographic and nutritional factors, were considered in the analyses.

The review of epidemiological evidence was followed by a report on the status on research on biological mechanisms for the most plausible exposure-reproductive outcome relationship. The gaps identified will constitute a rationale for further research in this area and have been specified in the concluding remarks on ‘Research needs’.

1. Air pollution

**LBW infants delivered on term, SGA infants and intrauterine growth retardation**

One Chinese (Wang 1997) and two US studies (Ritz and Yu 1999; Maisonet 2001) reported an increased risk of term LBW (a proxy for SGA infants) in relation to CO exposure but also some other indicators of air pollution (TSP, SO2). In a study conducted in China, Wang et al. reported an association between the risk for term LBW and third trimester exposure to TSP, SO2 and CO (Wang 1997).

In southern California, the infants of mothers with third trimester exposure levels above the 95th percentile of the CO exposure distribution (3-month average concentration >5.5 ppm) were at an increased risk of term LBW (Ritz and Yu (1999). No such relationship was observed when maternal exposure to PM10 and PM 2.5 and SO2 was related to the risk of term LBW.

Maisonet and al. (2001) in a study carried out in six northeastern cities of the United States confirmed the impact of CO and SO2 exposure on the risk of term LBW infants. When the data was stratified by maternal race, it was found that the association of CO with term LBW appeared to be limited to African-American infants, while the effects of SO2 appeared to be more consistent in white infants.

Dejmek et al., in a study in the Czech Republic, found an association between the risk of intrauterine growth retardation (diagnosed as birth weight below the 10th percentile) and exposure to PM10 and PM2.5 during the first month of pregnancy (Dejmek 1999). On the basis of further analyses, comparing populations with low and high exposure to PM10 but with similar exposure to polycyclic aromatic hydrocarbons (c-PAHs)), the authors concluded that exposure to c-PAHs in early gestation may negatively influence fetal growth (Dejmek 2000).

**Low birth weight (LBW)**

Ambient levels of TSPs, SO2 and CO have been examined in relation to the risk of LBW in several studies, but no consistent pattern of the relationship was established.
In Czech Republic, the relationship between average annual LBW in the country districts and the levels of SO$_2$, TSPs and NO$_x$ was investigated (Bobak 1999). A small increase in the risk was observed in the districts with high exposures to SO$_2$ but not to other contaminants.

In two other studies, no relationship between single indicators of air pollution and LBW was reported. Alderman et al. studied the relation between LBW and ambient levels of CO during the last trimester of pregnancy (1987). An insignificant increase in the risk of LBW was observed among infants exposed to CO levels equal to or greater than 3 ppm.

Dolk and colleagues examined whether populations residing near cokeworks were a major source of smoke and SO$_2$, and the proximity to the site was used as a surrogate for exposure to these contaminants. There was no evidence for a relation between LBW and residence near cokeworks (2000).

**Very low birth weight (VLBW)**

Rogers and colleagues examined the association between maternal exposures to ambient SO$_2$ and TSPs and the risk of very low birth weight (VLBW) (Rogers 2000). A positive association was reported between VLBW and maternal exposure above 95th percentile of exposure distribution of the combined contaminants.

**Effects on fecundity (i.e. biological capacity for reproduction)**

Periods with elevated air pollution were significantly associated with decrements in proportionately fewer motile sperm, proportionately fewer sperm with normal morphology and normal head shape and proportionately more sperm with abnormal chromatin. The mean sperm concentration and sperm count were not associated with the district of residence or the period of elevated air pollution (Selevan 2000).

**Status of research on biological mechanisms**

The biological mechanism by which air pollution might cause growth retardation has not been established. Studies on the effects of the smoking habit during pregnancy support the association of LBW with ambient levels of CO (Liberman 1994, Misra 1999) and ambient particles (Perera 1999). The increase in maternal carboxyhemoglobin levels associated with maternal smoking is the mechanism believed to explain the relationship between CO and LBW (Misra 1999).

The other hypothesis is that exposure to polycyclic aromatic hydrocarbons (PAHs) absorbed to airborne particles may influence fetal growth (Sram 1999). The role of PAHs as a major source of genotoxic and embryotoxic activities of organic mixtures related to air pollution was also supported by the results of in vitro cellular assay coupled with 32P-postlabelling of DNA adducts and chick embryotoxicity screening tests (Binkova 1999).

**Environmental tobacco smoke (ETS) exposure**

ETS exposure and birthweight

Windham et al. in their analysis of five studies ascertaining ETS exposure from multiple sources, after adjusting for confounders, demonstrated that the range of decrement was 10-50g (Windham et al. 2000). Misra and Nguyeyen reviewed the results of 11 studies on ETS and mean birthweight. The reduction in birthweight associated with ETS ranged from 25 to 90g. Recent studies have indicated that ETS exposure during pregnancy leads to birthweight decrease of about 25-40g (Lindbohm 2002).
Five studies used a biological marker to measure ETS exposure: cotinine in blood (Haddow et al. 1998, Eskenazi et al. 1995, Peacock et al. 1998), cotinine in mother’s saliva (Rebagliato et al. 1995) or nicotine concentration in maternal hair (Jaakkola et al. 2001). Two of these studies indicated a statistically significant decrease in the mean birthweight: 104 g with serum cotinine levels above 1 ng/ml (Haddow et al. 1998) and 87 g with serum cotinine levels above 1.7 ng/ml (Rebagliato 1995). Eskenazi et al. and Jaakkola et al. noted a smaller decrement (45 g and 17 g, respectively) (Eskenazi et al. 1995, Jaakkola et al. 2001) and Peacock (1998) hardly found any difference between exposed and unexposed infants.

**Spontaneous abortions**

As summarised in recent review by Lindbohm et al. (2002), *the evidence for the effects of ETS on the risk of spontaneous abortions is inconclusive*. Two studies showed a moderate association of spontaneous abortion with ETS exposure. In a Swedish prospective study (Ahlborg 1991) an excess risk of intrauterine death (spontaneous abortion and fetal death) was observed among working women spending most of their time at work in the rooms where other people smoked. Exposure at home was not related to abortion.

Windham (1992) also observed an increased risk of spontaneous abortion among nonsmokers, for ETS exposure of 1 hour or more per day. In the most recent prospective study, no evidence was found for an association between spontaneous abortion and exposure to ETS at home or at work. However, the risks were increased among exposed women who also consumed alcohol and caffeine in moderate to high amounts. A positive association between paternal smoking and the risk of spontaneous abortion may reflect male-mediated effect of ETS on the mother. This hypothesis was supported by the results of the studies on ETS-exposed women living with a nonsmoking partner (Ahlborg 1991, Windham 1992). A third study, however showed no association between any exposure to ETS at work in women living with nonsmoking partners (Windham 1999).

**Birth defects**

The most consistent finding was *the increased risk of nervous system defects; the finding was noted in all but one study out of five*. Increased risk for facial cleft was reported in three out of five studies (California Environmental Protection Agency 1997). A dose-response association has been suggested for paternal smoking and clefts, urethral stenosis (Savitz 1991), spina bifida, diaphragmatic hernia and the pigmentary anomalies (Zhang 1992). The dose-response association was observed between paternal smoking and the rate of major malformations (Mau and Netter 1974; Seidman 1990).

A possible direct effect via the father’s sperm cannot be ruled out when the father has been the source of exposure to ETS (Lindbohm 2002).

**Status of research on biological mechanisms**

There is no direct evidence that ETS exerts reproductive toxicity (Lindbohm 2002). The chemical exposure from passive smoking is similar in qualitative but different in quantitative terms from that of the smoker. *The undiluted sidestream smoke contains many harmful chemicals in greater amounts than the inhaled cigarette smoke* (eg. three times more tar, seven times more nicotine, five times more benzene and 100 times more carcinogenic nitrosoamines).

Per analogy to active smoking, it can be suspected that ETS may disturb the morphology and function of the placenta, and can exert a *mutagenic activity on germ cells*. **Nicotine may impair fetal growth by affecting uterine blood flow**. The data obtained by Hanke et al.
(2003) indicate an unfavorable effect of tobacco smoke on fetal growth measured in 20-24 weeks of pregnancy. Passive smoking was found to be a significant factor leading to increased umbilical blood flow resistance and to decreased fetal fetal biparietal diameter (BPD), as measured in 20-24 weeks’ gestation.

Benzo(a)pyrene is known to cross the placenta in humans and animals, and there is evidence in support of adduct formation in animal fetus tissues (Lindbohm 2002). **ETS exposure significantly increases the concentration of polychlorinated biphenyls (PCB) and hexachlorobenzene in newborns. Both chemicals are carcinogenic.** Although numerous adverse effects have been reported for the chemicals in sidestream smoke, their concentrations in ETS exposure are much lower than the experimental doses. It has been questioned whether the dose of reproductive toxicants from ETS can be high enough to cause adverse reproductive effects. **However, the studies assessing fetal exposure to nicotine suggest that this exposure may be substantial as a result of maternal exposure to ETS.**

**Environmental noise exposure**

**Birth weight**

Several studies examined the relationship between fetal growth and exposure to noise from airports in Amsterdam, Paris, Japan and the United States. In the US, **exposure to noise was related to lower birth weights** (Schell 1984, Schell and Hodges 1987) **while in a study of residents living near the Amsterdam Airport, an increase in the frequency of LBW among female births was found** (Knipshild at al. 1981).

The strongest evidence for an effect of airport noise on prenatal development is presented in several studies of the residents of an area near Osaka Airport in Japan (Ando 1977, Ando 1988). **Both reduced birthweight and higher frequency of smaller neonates were more common in the communities with greater noise exposure from the airport** (Ando 1977). In a study of changes in birthweight before and after the introduction of jet planes to the Osaka Airport, Ando (1988) found that the rate of births below 3000g increased dramatically just as the frequency of jet flights increased.

**Birth defects**

**There are inconsistent findings on the role of noise exposure in the development of birth defects.** In the study of 1475 Finnish mothers who delivered infants with structural defects and a similar number of reference mothers (Kurppa 1989), the frequency of self-reported noise exposure in the first trimester was not found to be higher in the mothers of children with defects.

Nowell-Jones and Tauscher (1978), using data from birth certificates, found a significantly higher incidence of birth defects in census tracts under the landing pattern at Los Angeles International Airport. However, Edmonds et al. (1979) were not able to replicate these findings with data from the Metropolitan Atlanta Congenital Defects Program (MACDP). The inconsistencies between the latter two studies may be due to differences in the definitions of noise exposure, or to differences in the ascertainment of birth defects.

**Status of research on biological mechanisms**

A plausible biological mechanism for the causal relationship between noise exposure and reduction in prenatal growth may be the development of the stress reaction. Another explanation could be that the auditory pathways of the central nervous system include direct pathways to the auditory cortex and indirect ones to the reticular endothelial activating system, thereby involving the limbic system, the autonomic nervous system and the
neuroendocrine system (Cohen 1970). Responses of the autonomic nervous system and the neuroendocrine system which include components that may impair growth, e.g. by frequent release of corticosteroids, were documented both in animal (Welch 1970) and human experiments (Westman 1981).

Trihalomethanes (THMs) in drinking water
Disinfection of tapwater through chlorination and chloramination produces trace amounts of by-products, such as chloroform, that belong to a class of chemicals called trihalomethanes (THM). Large population served by public water systems could be exposed to chemical contaminants present in treated tapwater. Routes of exposure include dermal absorption during hand washing and bathing, inhalation during showering and ingestion of drinking water. Owing to high prevalence of exposure, potential adverse health effects attributable to exposure to these chemicals have important public health implications.

Until recently total trihalomethane (TTHM) was the only disinfection by-product component for which routine monitoring was required. Toxicological studies, however, suggest that other classes of disinfection by-products, such as halocetic acids (HAAs) and acetonitriles also have a potential for adverse reproductive effects (Klotz 1998).

LBW
Using individual data on water consumption habits, a case-control study in North Carolina addressed the association of THMs with several reproductive outcomes (Savitz 1995). Slightly elevated risks for LBW were found for increasing concentrations of THMs in the community supply, but a slight decrease in the risk (protective effect!) was found when THM doses were used (dose= ppb x glasses of water per day) for the highest exposure group. No association was found for the risk of preterm delivery and exposure to TTHMs.

SGA
An increased risk of SGA births was found in Iowa among women living in communities with chloroform levels > 10μg per litre (based on finished water samples from municipal water survey) compared with a reference group with no detectable level of chloroform. One limitation of the exposure classification in this study was that individual exposures were based on samples taken from municipal water survey at least one year before the date of birth (Kramer et al. 1992)

In New Jersey, THM exposure was determined for each mother as the estimated monthly THM level in her town’s water supply, based on a quarterly sampling for these chemicals (Bove 1995). Slightly elevated OR was found for term LBW for exposure categories above 40 ppb THM. An increase in SGA births was reported, which was associated with THM concentrations higher than 100 ppb.

Gallagher et al. (1998) examined 1893 live singleton Colorado white births (28-42 week of gestation) for 1990-1993 and matched them to historical water sample data with respect to the time and location of maternal residence based on census information. A large increase in the risk of term LBW at the highest exposure level and no association between exposure and preterm delivery were observed

Spontaneous abortions
Exposure to THMs and the risk of spontaneous abortion was examined in a prospective study of 5144 pregnant women in California (Waller 1998). The exposure to individual THMs as well as TTHMs was calculated by averaging all measurements taken by the subject’s water utility during her first trimester of pregnancy. Women who drank ≥ 5 glasses per day of
cold tapwater containing \( \geq 75 \, \mu g \) per litre of TTHMs were at an increased risk for spontaneous abortions. Of the four individual THMs, only high bromodichloromethane exposure was associated with an increased risk for spontaneous abortions.

Basing on a prospective study, Swan concluded that the associations with cold tapwater and bottled water could not be explained by exposure to chlorination by-products, because the association was seen in the absence of high levels of these chemicals. The grounds for such reasoning was an observation that in one of the examined regions, the association appeared stronger in women who let the water stand before drinking it (Swan 1998).

**Effects on fecundity (i.e. biological capacity for reproduction)**
To our knowledge, only one study examined the relationship between THMs and semen quality. A population of 157 healthy men from couples without a known risk of infertility were examined in California and their exposure to THMs was assessed based on water utility measurements taken during 90 days preceding semen collection (Fenster 2003). Only for one motility parameter, a small decrease for every unit increase in bromodichloromethane exposure level was found.

**Status of research on biological mechanisms**
No mechanism has been proposed so far to explain the possible influence of THMs on the development of SGA infants or a spontaneous abortion.

**Waste landfill sites**
The disposal of wastes in landfill sites has increasingly caused concern about the possible adverse health effects for populations living nearby, particularly in relation to those sites where hazardous waste is dumped (Vrijheid 2000). Studies on the health effects of landfill sites have been carried out mainly in North America and only recently the first European multisite study (EUROHAZCON) has been reported (Dolk 1998).

**LBW**
An increase in the proportion of infants with LBW have been the most consistent findings in single sites studies (Vianna 1984, Goldman 1985, Berry 1997, Goldberg 1995).

The studies covered a population of residents of the Love Canal area in the state of New York (Vianna 1984, Goldman 1995), Lipari Landfill in New Jersey (Berry 1997) and the Miron County (the third largest county in North America) (Goldberg 1995).

No increase in the risk of LBW but a decrease in the mean birth weight (59g) was found in a population living in the high-odour complaint zone near hazardous waste disposal site in the Los Angeles County, California (Kharrazi 1997). Likewise, no excess in LBW was found in the Santa Clara County, California, following the contamination of two drinking-water wells (Deane 1989, Wrench 1990, Wrench 1992), in multisite studies assessing 1281 National Priority Listing (NPL) sites all over US (Sosniack 1994) and 300 landfill sites in the area of the San Francisco Bay, California (Shaw 1992).

As LBW is a pregnancy outcome that can be associated with several risk factors, investigators arranged for the control of such confounding factors as the socio-economic status (Goldman 1985), maternal education (Berry 1997), education, income and race (Kharrazi 1997), and education and age (Goldberg 1995).

**Birth defects**
An excess risk of at least one malformation category was found in a population of residents of the area close to the Love Canal (Goldman 1995) and 590 hazardous waste sites in the state of New York (Geschwind 1992), San Francisco Bay landfill sites (Shaw 1992), and 21 European sites (Dolk 1998). In the US studies, the specific type of malformations included those of the heart and circulatory system (Shaw 1992), nervous system, musculoskeletal system, and integument (skin, hair and nails) (Geschwind 1992).

Within the EUROHAZCON project, covering twenty-one waste landfill sites in Europe, a residence within 3 km of the site was associated with a significantly increased risk of congenital anomaly adjusted for maternal age and socioeconomic status (Dolk 1998). There was a fairly consistent decrease in the risk with the distance from the site. A significantly increased odds ratio was found for neural-tube defects, malformations of the cardiac septa and anomalies of great arteries and veins. Odds ratios of borderline significance were found for tracheo-oesophageal anomalies, hypospadias and gastroschisis. There was little evidence for differences in the risk between landfill sites, but the power to detect such differences was low.

No excessive risk of congenital anomalies associated with living near the site (after taking into account the socioeconomic variables) was found in a study of 1281 NPL sites over the entire United States (Sosniack 94). However, only 63% of women originally sampled for the first study returned the questionnaire and were included in the study. No subgroups of specific malformations were investigated. Likewise, no excess was observed in the follow-up study of residents living in the vicinity of 590 hazardous waste sites in the state of New York (Marshall 1997).

Spontaneous abortions
In an initial study investigating the risk of spontaneous abortions in the population of the Santa Clara County, California, an association was found between reported consumption of tap water containing high concentration of chlorinated solvents and the risk for this pregnancy outcome (Deane 1989, Wrensch 1992, Wrensch-1992). However, the follow-up study using more refined methods of exposure evaluation did not confirm the previous finding (Wrensch 1990).

No excessive risk for spontaneous abortion was found in the case of residents leaving close to Strinfellow waste dump in California (Baker 1988), Welsh landfill of Nat-y-Gwyddon (Filder 1997) and in Woburn, Massachusetts (Lagakos 86).

Status of research on biological mechanisms
In a recent review of toxicological hazards of Superfund waste sites, Johanson and DeRosa conclude that although a large body of toxicological research is under way to assess the toxicity of chemicals commonly contaminating the environment surrounding waste sites, equally significant work is still to be done before these chemicals have adequate toxicity profiles (Johanson 1997).

On the other hand the environmental hazard from a specific landfill site may be not only a function of the chemicals dumped and their possible interactions but also of geology, engineering, and management practices typical for this site.

Residential pesticide exposure
Studies of farmer families indicate that indirect maternal exposure to pesticides (e.g. bystanders exposure) may result in an increased time to pregnancy (Cock 1994, Curtis 1999), spontaneous abortions (Savitz 1997, Arbuckle 1999, Arbuckle 2001), SGA (Savitz 1997),
LBW (Sanjose 1991, Lima 1999), congenital malformations (Garcia 1998) and fetal death (Pastore 1997).

On the other hand, the data on the risk for adverse reproductive effects in the population of residents (nonfarmers) exposed to pesticides via their drift from agriculture fields are almost completely lacking. To our knowledge, only one study has addressed this issue (Bell 2001).

Residential exposure to pesticides and the risk of fetal death

The potential association between fetal death and residential proximity to agricultural pesticide applicators was examined in California. The risk of fetal death was observed for women who in the second trimester of pregnancy resided near the fields where the following pesticide groups were applied: carbamates, pesticides classified as ‘estrogen disrupters’ and carbamate acetylcholinesterase inhibitors. For women who during the third trimester resided near applications of pyrethroids, an increased risk of fetal death was found. Elevated risk was observed for carbamates and carbamate inhibitors when exposure occurred during months 3 and 4 of gestation (Bell 2001).

Status of research on biological mechanisms

Endocrine disrupting pesticides can interfere with normal blood hormone levels or the subsequent action of those hormones. The effect can disrupt the hormonal regulation of normal cell differentiation, growth, development, metabolism and reproduction throughout life.

The effects that can be seen in an organism exposed to an endocrine disrupting chemical (EDC) depend on which hormone system it is targetted. The mechanisms of endocrine disruption focused on sex hormone disrupters include: (1) binding and activating the estrogen receptor (therefore acting as an oestrogen); (2) binding but not activating the estrogen receptor (therefore acting as an anti-estrogen); (3) binding other receptors; (4) modifying the metabolism of natural hormones; (5) modifying the number of hormone receptors in a cell; (6) modifying the production of natural hormones.

Organochlorine contaminants in food

For the populations of the Baltic Sea and Great Lakes (Canada) fishermen and their families, an important source of exposure to persistent organochlorine compounds such as PCB and dioxins may be the consumption of fatty fish.

Birthweight

The possibility that exposure to PCBs may influence birthweight has been investigated in several studies where PCB exposure occurred through diet.

Fein (1984) examined the size of the newborn, gestational age, and maturity in relation to maternal consumption of fish from Lake Michigan. PCBs were measured in cord serum, and were estimated from maternal consumption of fish from Lake Michigan, weighting the PCB contribution of each species by the average contaminant level of that species in Lake Michigan. Fish consumption during pregnancy alone was analyzed separately from overall consumption. Detectable levels of PCBs in cord serum were associated with lower birthweight, smaller head circumference and shorter gestational age. There was also a consistent dose-response relationship between overall fish consumption and birthweight, head circumference and gestational age.
The studies concerning the wives of the Baltic Sea fishermen have also shown an association between high dietary intake of Baltic Sea fish contaminated with persistent organochlorine compounds and low birthweight (Rylander 1996, Rylander 1995, Rylander 1998). Likewise, in general Dutch population, a negative correlation has been observed between plasma levels of dioxins and PCB and the birthweight (Petandin 1998).

On the other hand, birthweight and head circumference were unrelated to average PCB levels in a study of 912 North Carolina infants (Rogan et al. 1986). The cohort was a sample from the general population and had no history of occupational exposure, or specific dietary exposure to PCBs.

**Spontaneous abortion and stillbirth**

Exposure to PCBs was not found to increase the risk of these pregnancy outcomes among women living near Great Lakes (Dar 1992, Mendola 1995). However, blood PCB levels among women with miscarriage were found to be higher than in women with normal deliveries in one study (Leoni 1989). However, many potentially confounding factors were related to PCB levels and the analysis included no adjustment for these.

**Effects on fecundity (i.e. biological capacity for reproduction)**

In a study of 170 semen samples that were screened for PCBs and p,p’-DDE (DDT metabolite) an inverse relationship was found between sperm motility and the concentration of PCB congeners 153, 118 and 138 which are rather ubiquitous in the human population (Bush 1986).

The findings of the pilot study carried out in the Boston area population are also indicative of an association between PCBs and p,p’-DDE and abnormal sperm count, motility and morphology (Hauser 2002).

As far as the studies on time to pregnancy are concerned, an increased time to getting pregnant was found only among heavy smokers in the east cost cohort of fishermen’s wives as compared to west cost cohort in Sweden (Axmon 2000). East cost fishermen and their wives were a group with a relatively high exposure to PCBs and dioxins because of their consumption of fish contaminated with these chemicals. Eastcost cohort also showed an increased risk for infertility (reported time to pregnancy of 12 months or longer and no children).

However, the results of the New York State Angler Cohort Study did not imply that the consumption of PCB-contaminated sportfish from Lake Ontario was a significant risk factor for either resolved (time to pregnancy > 12 cycles) or unresolved infecundity (time to pregnancy > 12 cycles without pregnancy). An insignificantly increased risk of infecundity was found for women with the highest duration of fish consumption (McGuinness 2001).

**Status of research on biological mechanisms**

PCBs and DDT are well known chemicals with estrogen-like characteristics and are referred to as estrogen disrupters. Animal studies suggest that these chemicals readily penetrate the blood-testis barrier and can directly affect spermatogenesis. It was also documented that PCB metabolites bind to estrogen receptors. Jansen hypothesised that adverse reproductive affects of PCBs may result from PCB congeners increasing gonadotropin-releasing hormone or affecting the production and release of luteinizing hormone from the pituitary (Jensen 1993). Kelce et al. showed that p,p’-DDE has an antiandrogenic activity (Kelce 1995).
Research Needs:

Air pollution

Further investigation of the simultaneous impact of particles and PAHs on the pregnancy outcome is needed, especially their impact on fetal growth and fecundity. Since it was postulated that the effects of PAHs on the fetus may be affected by the genotypes of the parents, the impact of air pollution on human health should be studied in a whole complex - i.e. from the interaction between genome and environment through gene expression to the effects on the health status at different developmental stages of the fetus, infant and child.

ETS

Very little is known about the impact of ETS on the risk of spontaneous abortion, birth defects, infecundity and male reproductive health. The methodological shortcoming of reproductive studies on ETS has been the difficulty in distinguishing whether the findings are due to the direct effect of male active smoking or female exposure to ETS. Further studies should be performed on populations of nonsmoking women exposed to ETS at work or during leisure time, but living with a nonsmoking partner.

Environmental noise

Several epidemiological studies described the relationship between noise exposure and reduction in prenatal growth. The risk of other adverse reproductive outcomes in relation to environmental noise exposure should be assessed.

The role of individual susceptibility should be investigated. Gender-related differences in response should be subject to further studies in order to verify the hypothesis that females fetuses are more sensitive.

Trihalomethanes (THMs) in drinking water

Basing on a prospective study, Swan et al. (19898) concluded that the associations with cold tapwater and bottled water could not be explained by exposure to chlorination by-products, because the association was seen in the absence of high levels of these chemicals.

Taking into account the extent of THM exposure s in Europe, the problem should be carefully examined in well-designed studies. In the event that the European studies confirm the increased risk of adverse reproductive outcomes in relation to THM exposures, the biological mechanism has to be proposed that would explain this relationship.

Exposure to individual chemicals within the TTHM class should be examined, since the proportional distribution of individual chemicals can vary regionally.

Waste landfill sites

Further research into adverse reproductive outcomes of exposure from landfill sites would greatly benefit from a more interdisciplinary approach deriving from the fields of landfill engineering, environmental sciences, toxicology and epidemiology.

More research into reproductive health effects of chemical mixtures and possible interactions between single chemicals is necessary to improve the understanding of the effects of multiple chemical exposures.
It is essential to carry out systematic site assessments to underpin classification of the landfill site according to health hazard. This will allow ranking the landfill sites according to their hazard potential by expert consensus. As biomarkers of exposure, susceptibility and health effects are a promising tool in epidemiology, more collaboration is required between epidemiologists and basic scientists to further develop biomarker techniques for use in the studies evaluating the risk related to the residence close to a waste landfill site.

*Residential pesticide exposure*

Standard protocols for the biological monitoring of the most prevalent pesticides have to be developed to achieve progress in assessing the risk of adverse reproductive outcomes in the population of rural area residents exposed to drifts of pesticides from agriculture fields. Systematic studies addressing the risk of each adverse reproductive outcome have to be undertaken.

*Organochlorine contaminants in food*

There is a need for better understanding the relationship between environmental exposures and semen quantity and quality. Further research on the relation between the dietary intake of organochlorine-contaminated food (mostly fish) and time to pregnancy should be perused.

*Conclusions*

*State of research*

- Increased risk of LBW is the most consistent adverse reproductive effect that was found for populations exposed to ETS, environmental noise, waste landfill sites and organochlorine-contaminated food.
- Reduced fetal growth was associated with exposure to air pollutants, environmental noise and THMs.
- Excess risk of infecundity was related to exposure to THMs, organochlorine-contaminated food and to residence close to waste landfills.
- The risk of spontaneous abortions was linked to exposure to THMs and organochlorine contaminants in food.
- Increased risk of birth defects was confirmed only in populations living close to waste landfill sites, while excess risk of fetal deaths was observed in rural residents exposed to pesticide drifts.
- The biological mechanisms by which reviewed environmental factors affect reproductive outcomes have not been clearly established for any of them. The most advanced research in this field so far has been performed in relation to the effects of exposure to air pollution, ETS, environmental noise and organochlorine contaminants in food.

*Postulated areas for further research:*

- Simultaneous impact of airborne particulates and PAHs on pregnancy outcomes, especially their impact on fetal growth and fecundity.
- The effect of ETS on the risk of spontaneous abortion, birth defects, infecundity and male reproductive health.
- The risk of other than reduced fetal growth, adverse reproductive outcomes in relation to environmental noise exposure should be assessed.
• Exposure to TTHMs as well as individual chemicals within this group and the risk of adverse reproductive outcomes.
• Adverse reproductive effects of chemical mixtures found at waste landfill sites and the role of the possible interactions between single chemicals.
• Assessment of the risk of adverse reproductive outcomes in the population of rural area residents exposed to drifts of pesticides from agriculture fields.
• Relationship between environmental exposure to organochlorine contaminants in food and the risk of adverse reproductive and developmental outcomes.

Relevance for policy development

For all the reviewed environmental hazards, there is a substantial evidence for an increased risk for at least one of adverse reproductive outcomes. Although the most consistent outcome was found for reduced birthweight, and not the major abnormalities like birth defects, fetal deaths, spontaneous abortion or infertility, the overall risk to reproduction should by no means be classified as a minor one. It is thus essential that research efforts be continued to further assess the risk of reproductive outcomes other than the reduced birthweight. On other hand, even a small increase in the level of LBW and SGA can translate into a substantial number of affected infants with an increased risk for mortality and for developing other serious health problems, including developmental disabilities and chronic respiratory conditions like cardiovascular and allergic diseases.

The elimination or substantial reduction of exposure is the only way of prevention as offered by current research. This action should be particularly emphasised in the case of exposure to such agents as eg. ETS, already known to have a variety of health consequences.

References

32. Schell LM: Auxological epidemiology and the determination of the effects of noise on
47. Gallagher MD, Nuckols JR, Stallones L, Savitz DA: Exposure to trihalomethanes and adverse pregnancy outcomes. Epidemiology 1998; 484-489
54. Goldman LR, Paigan B, Manant MM, Highland JH: Low birth weight and birth defects in
children living near the hazardous waste site, Love Canal. Haz Waste Haz Ma 1985, 2,209-23
56. Goldberg MS, Goulet L, Riberdy H, Bonvalot Y: Low birth weight and preterm delivery among infants born to women living near a municipal solid waste landfill in Montreal, Quebec. Environ Res 69, 37-50, 1995
61. Sosniack W, Kaye W, Gomez TM: Data linkage to explore the risk of low birthweight associated with maternal proximity to hazardous waste sites from the National Priorities List. Arch Environ Health 1994, 49, 251-55
73. Arbuckle TE, Savitz DA, Mery LS, Curtis KM: Exposure to phenoxy herbicides and the risk of spontaneous abortion. Epidemiology 1999, 10, 752-760
82. Rylander L, Stromberg U, Hagmar L: Dietary intake of fish contaminated with persistent organochlorine compounds in relation to low birthweight. Scan J Work Environ Health 1996, 22, 260-6
85. Rogan WJ et al.: Neonatal effects of transplacental exposure to PCBs and DDE. J Pediatr 1986, 109, 335-41
88. Leoni V et al.: PCB and other organochlorine compounds in blood of women with or without miscarriage: a hypothesis of correlation. Ecotoxicol Environ 1989, 17, 1-11
5.10 Environmental factors and cardiovascular disease

By A. Peters, Forastiere

Keywords:
Air Pollution, Atherosclerosis, Cardiovascular disease, Climate change, Environmental Tobacco Smoke (ETS), Mortality, Morbidity, Myocardial Infarction, Particles, Noise, Socio-Economic Factors, Traffic.

Summary

Acute exacerbation of cardiovascular disease by environmental exposures
1. Role of environmental exposures in triggering myocardial infarction, arrhythmia and sudden cardiac death
2. Susceptibility to environmental triggers of acute coronary disease based on pre-existing cardiovascular disease, on genetic predisposition and on individual risk factor profiles
3. Early physiological changes in different population subgroups ranging from children to patients with cardiovascular disease

Chronic effects of environmental exposures on cardiovascular disease
4. Role of chronic environmental exposures on cardiovascular disease morbidity and mortality
5. Role of socio-economic status and unhealthy life-styles in augmenting the impact of environmental exposures
6. Genetic susceptibility to develop cardiovascular disease in association with environmental exposures
7. Role of chronic environmental exposures on initiating and promoting atherosclerosis

BACKGROUND OF THE PROBLEM ON THE EUROPEAN LEVEL

Evidence has been found that environmental exposures such as environmental tobacco smoke (ETS), ambient air pollution, noise, and extreme weather conditions are associated with mortality and morbidity from cardiovascular diseases, in particular ischemic heart diseases. However, little is known on the role of these environmental exposures in young adults in initiating and promoting asymptomatic states of cardiovascular disease, their role in determining the severity of cardiovascular disease latter in life, and their potential to trigger acute events of cardiovascular disease like myocardial infarction. In addition, it is likely that subgroups within the population are at higher risk than the majority of the population. Individual susceptibility might be determined by genetic predisposition, socio-economic status or unhealthy life-styles.

CURRENT RESEARCH ACTIVITIES IN EUROPE AND FUTURE PRIORITIES

Health effects of ambient air pollution and noise are being addressed as part of the quality of life program – key action 4 as part of the 5th framework. While its major focus for air
pollution is on respiratory health there are studies being funded assessing acute health effects of air pollution in patients with cardiovascular disease.

- The HEAPSS Study assesses the impact of ambient air pollution on myocardial infarction survivors. It indicates that after an incident myocardial infarction the risk of re-admission to the hospital is associated with the changing daily concentrations of ambient particles.
- The ongoing AIRGENE Study will characterise early inflammatory responses to ambient air pollution concentrations in myocardial infarction survivors and the modification of these responses by genetic predisposition.

The ongoing studies focus on acute health effects in myocardial infarction survivors who are a selected group as they have survived an acute coronary syndrome. Out-of-hospital cardiac death is a major public health burden, accounting for a large proportion of all fatal cardiovascular disease events. Research on the environmental triggers of out-of-hospital cardiac deaths is a high priority and air pollution is a good candidate to investigate. Also, little is known about the impact of environmental factors on those who present with different types of cardiovascular diseases. For example, it has been recently indicated that diabetics might be at increased risk of particulate matter-associated cardiovascular events (Zanobetti et al. 2000). In addition, specific cardiac factors, such as congestive heart failure or arrhythmia among people with ischemic heart diseases, have been suggested as indicators of susceptibility to the effects of air pollutants (d'Ippoliti et al. 2003). With the rise in temperatures through global warming, and the use of central heating and air conditioning, the relationship between cardiovascular events and weather conditions are of importance. Seasonal variation in the incidence of myocardial infarction has been described, and the possible role of several meteorological conditions (including humidity, barometric pressure, wind speed, and their abrupt changes) should be elucidated. The basic research question for myocardial infarction is whether the classical risk factors for the disease (gender, age, smoking, blood pressure, diabetes, obesity, cholesterol level) act as effect modifiers. It has been noted that persons with lower socio-economic status are at higher risk of air pollution effects; however, at the same time they might be more exposed to ETS and noise as well. A comprehensive assessment of these environmental impacts is needed to improve living conditions in urban environments. Early physiological responses in groups currently not being studied such as children and adolescents will provide insight into the design of healthier environments and might reduce the burden of disease later in life.

Evidence for the impact of chronic ambient air pollution on cardiopulmonary mortality has been found in the Netherlands, and in particular the role of traffic was emphasised (Hoek et al. 2002). However, this study had little power to evaluate cause-specific mortality or to assess the impact of air pollution exposures on cardiovascular disease morbidity. In addition, traffic might also exhibit its effects by noise pollution and potentially there are interactions between the different exposures. Furthermore, persons living at busy streets might have lower socio-economic status associated with other unhealthy lifestyles. The human genome project forms the basis for better understanding the aetiology of diseases. A number of polymorphisms have been identified increasing susceptibility to cardiovascular disease by modifying risk factor profiles. Classical risk factor assessment builds on a single measurement of a risk factor profile and subsequent follow-up of a population in a cohort study. Environmental exposures have been identified to alter the risk factor profiles, however, little is known whether responsiveness to external stressors poses a health risk or not. This question for example could be addressed in a follow-up study of the AIRGENE project. It is quite likely that not the entire population is vulnerable to develop cardiovascular disease in
association with environmental exposures. However, these sub-populations might be at higher risk than the general population which would be misclassified in health impact assessments. No evidence is however available assessing the role of these ambient exposures in initiating atherosclerosis. The development of atherosclerosis may start during adolescence and is thought to be related to overweight, smoking and unhealthy diets. Environmental exposures have, however, the potential to induce low-grade inflammation and might add to the oxidative stress which is a key factor in the atherosclerotic pathophysiology. One animal study has demonstrated that instillation of ambient particles might promote atherosclerotic plaques to more vulnerable states (Suwa et al. 2002).

**Relevance to policy**

Acute coronary events are a major cause of morbidity and mortality. A consensus report was published recently introducing the concept of a vulnerable patient prone to encounter acute coronary events (Naghavi et al. 2003). Key elements in the predicting disease are atherosclerosis with vulnerable plaques, vulnerable blood prone to form thrombi and a vulnerable myocardium prone to develop arrhythmia. Environmental exposures are likely to impact all three aspects of vulnerability, the plaques, the blood and the myocardium.

The exposures are ubiquitous and all persons in urban environments in Europe are exposed. Therefore, there is generally little escape from these exposures for large groups of the urban populations. Even if subjects perceive that they escaped they might be at relevant exposures during times spent in transport, at their workplace or at school.

The risk estimates available today are generally derived from studies evaluating the entire population. However, it is quite conceivable that only susceptible subpopulations are at considerably higher risk. There are no risk estimates available for these subpopulations in Europe with the exception of the results which will be derived from the HEAPSS study. It is also unknown whether and to which extent the environmental exposures enlarge the susceptible populations and whether exposures in early life make subjects vulnerable. Furthermore, susceptibility might be also determined by interactions between environmental exposures with life-style factors, socio-economic status and genetic predisposition. All these factors will be important for future risk assessment as research progresses in these areas.

**EMERGING ISSUES**

While combustion products from mobile sources are more and more controlled, there are still a growing number of vehicles and the distances travelled each time are still increasing. As urbanisations spreads also a higher proportion of the population is exposed to the related environmental exposures.

Susceptibility as a concept is emerging driven by advances in research on genetic predisposition. For a comprehensive risk assessment, susceptibility needs to be defined based on inherited and therefore non-modifiable on one side and life-style and environmental factors on the other side. Here the health impact of environmental exposures in urban environments is important to be incorporated.

Unhealthy life-styles such as lack of exercise and unhealthy diets are likely to diminish the normal protection of our body against the physiological stress induced by environmental exposures. It is therefore possible that in the future the impact of environmental exposures might increase as unhealthy lifestyles increase.
KEY References


5.11 Cocktail effect – cumulative risk assessment – combined exposure

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Keywords:
Cocktail-effect, cumulative risk assessment, complex mixtures, multi-causality combined exposures, multiple exposure routes

Summary:
- The “cocktail- or mixtures-effect” problem is highlighted in several EU policy documents, but only in few European scientific reviews
- Most research exists out in the area of air pollution/respiratory diseases and asthma, but it must be expanded also to other priority diseases
- Science on interactions, multi-exposure and biomarkers must be prioritised, but at the same time be more policy relevant using different assessment concepts

Background to the problem at an European level

The study of chemical mixtures is an important area of research because of its potential impact on how risk is assessed in populations exposed to multiple environmental agents. Clearly, individuals are exposed to myriad chemical agents during their lifetime. Low-dose chronic exposure to environmental agents and the additional lifestyle factors that may affect health are extremely difficult to assess by conventional approaches. Integrated approaches that address these issues will be necessary to advance our understanding of the health relevance of exposure to mixtures (Suk et al 2002)

There are many interpretations of the “cocktail-effect“ problem mostly depending of the chosen systems boundaries. The description made in the EU 6th Environmental Action Programme seems to focus on - “Interactions within the human body”. It is, however, important to see the problem in a more holistic perspective, also including exposure, pathways and even more holistic looking at the many factors causing a disease. As an example, the causative factors of allergies and asthma include food, indoor and outdoor air, lifestyle and genetics.

In view of a common multi-exposure situation to various chemicals in food, air, water and consumer products a discussion has occurred weather this might constitute a new risk situation not handled by the present one-at-the-time approach for risk assessment. It has been suggested that risks might be under-estimated and that combined, long-term and cumulative exposures sometimes at critical “time windows” of increased susceptibility have to be considered especially for children and vulnerable groups.

Combined action and interactions between chemicals, e.g. medicines administered to humans at high doses have been known for many years in the field of pharmacology. However these experiences are not directly useful for predicting toxic effects of mixtures of environmental chemicals because of the exposure levels of the general human population are relatively low and interactions occurring at high doses may not be representative for low-dose exposures.
Current research activities in Europe and future research needs

Childhood cancer. Carcinogenesis is often described as a multi-step process. The fact that different chemical, physical or biological agents may affect either step makes it obvious that cancer is most often the results of combined actions. The interaction of carcinogens affecting different steps in carcinogenesis has been known for half a decade to cause synergistic effects, strongly increasing the tumour response. Thus initiators promoters, converters, and co-carcinogens all act in concert to potentiate the final tumour outcome. Anti-carcinogens may prevent or inhibit cancer at either step, and are also known to potentiate each other in some cases. Compounds affecting the same step by different mechanisms can also cause potentiation. The possibilities for combined effects in carcinogenesis are therefore many.

Respiratory diseases and asthma. There are many well-known examples of synergistic effects on the respiratory system. Ozone, nitrogen oxide and fine particles are among the most critical agents in the urban environment. Aldehydes are important indoor air pollutants. Radon and passive smoking in indoor air is also shown to have a synergistic effect. The multi-causality of asthma is well demonstrated, with nutritional and immune status, biological agents like mites and pollen, and physical agents like humidity as important causal factors. Most of the past and current European research on mixtures is focused on air pollution research in urban areas, as well as screening of different kinds of emissions from vehicles.

In neurotoxicity, there are many possibilities for interaction between chemicals because of the complex hierarchical structure of the nervous system. A number of examples have been described of which the most well known are the additive narcotic effect of organic solvents, and the additive effect of acetyl cholinesterase inhibition by organo-phosphorus insecticides. The strongest interaction found in the literature was 5-fold increase in the neurotoxicity of hexane when methyl isobutyl ketone was co-administered. However, very few quantitative studies have been performed and interaction has no been studied systematically. Therefore the present state of knowledge does not allow general conclusions. The multi-exposure to lead is well-known leading to neurological effect on children.

Endocrine disruptions. Most of the work made within the field is based on in vitro experiments and only very few in vivo experiments on mixtures have been performed so far. Such experiments will be one of the future challenges within the field of endocrine disruption. The majority of the - especially the older – studies concluded that additive effects, i.e. no interaction between the compounds were found, although detailed mechanistic analysis were not applied in most cases. However, recent well-designed in vitro studies clearly show that the combined effect of estrogenic compounds do not deviate from the expected additivity. In addition, additive effects of two anti-androgenic compounds given in vivo were found. Therefore, it is important to incorporate synergy in the hazard assessment of weakly estrogenic chemical mixtures.

There are three main directions of the necessary research within this field:

- **Science on environment and health interactions.** Interactions of complex exposures may produce dramatically greater and different health impacts when compared to impacts of individual agents. Many of the unexpected and unexplained; and sometimes confusing health effects may be due such interactions – synergy or antagonism. Susceptible groups should be a special concern in environmental policy, because the first health hazards focus on them, and protecting them will, with a margin of safety also protect the general population. Multi-causality is common in Environment & human health (see EEA background Papers No 2 and 5 for EU E&H strategy) and has implications for multidisciplinary research; approaches to integrated
causality (in contrast to single factor causality, including elucidating the gene/environment interactions); and for approaches to impact analysis and policy options.

- **Exposure assessment.** Multi-media exposure where the sources of origin include consumer products and micro-environments, supports the policy work in focusing regulatory actions for maximum risk reduction efficiency.

- **Biomarkers.** Promising methods for assessing the body burden and possible health impact of multi-route, multi-chemical exposures and through the analysis of markers of exposure and early effects. Their applicability for environmental reporting and health relating monitoring should be carefully evaluated.

A research programme must focus on toxicology research, supplemented with synthesis work. Indeed, development of risk assessment/management concepts of mixtures must also be based on multidisciplinary research in epidemiology, biochemistry, chemistry etc but also on cooperation with experts in environmental policy and management.

In order to increase the policy relevance, suitable concepts and tools have to be developed that primarily do not lead to more testing, but rather on refinement of the methods and further development of the principles to add up risk contributions and for ranking and comparison of the risk factors.

There is also another desired integration between environmental research and research on pharmaceuticals. Principles for the interaction between different chemical compounds and various host factors is fundamental in the development of pharmaceuticals and has since long also been in focus in both food, environmental and occupational toxicology. Thus, there is a common basis for development and risk assessment of pharmaceuticals and development and risk assessment of chemicals of environmental concern.

Some key questions are listed in the table below:

<table>
<thead>
<tr>
<th>Research area</th>
<th>Key questions</th>
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<tbody>
<tr>
<td>Science on interactions</td>
<td>•</td>
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<tr>
<td>Multi-exposure</td>
<td>• For what do we need exposure assessment?</td>
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<tr>
<td></td>
<td>• What is the state-of-the art of exposure modelling?</td>
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<td></td>
<td>• What methods exist to attribute exposure to sources?</td>
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<td></td>
<td>• How to assess the exposure contributions from different environmental compartments?</td>
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<td></td>
<td>• Chemicals in products: how to assess human exposure?</td>
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<td></td>
<td>• Cumulative and aggregate exposures: What do they imply?</td>
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<td></td>
<td>• What are the strategic options to assist EU policy on human chemical-physical exposure?</td>
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<tr>
<td>Biomarkers</td>
<td>• For which exposures and effects are biomarkers relevant in relation to air, food, soil and water quality?</td>
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<tr>
<td></td>
<td>• How are biomarkers used for the assessment of:</td>
</tr>
<tr>
<td></td>
<td>- exposure (external exposures, target dose, internal exposures, cumulative exposures)</td>
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<td></td>
<td>- individual and population health effects and health risks</td>
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</table>
- susceptibility
- What are the requirements for validity, quality and applicability of biomarkers for practical use?
- What are the strategic options to assist EU policy on human exposure?

Some specific research needs

- Validation of methods developed to evaluate the potential health risk of (complex) mixtures such as the "top n" and "pseudo top n" approach. This method could be applied to certain defined complex exposure situations such as e.g. a certain waste site or an occupational exposure situation, to find out its applicability. There is indeed an urgent need for validation of existing methods, also by predicting the toxicity of a defined (simple) mixture followed by actual toxicity testing of the mixture. This is necessary to make progress with respect to the safety evaluation of mixtures (=real-life exposure situations). These methods are also excellent tools for detecting priority mixed exposure situations. In the Netherlands, a committee of the Health Council has developed a decision tree approach. It would be extremely helpful to test its usefulness in practice (Feron et al, 2002)

- There is a need to study the toxicity of cocktails of pesticides (which is particularly relevant for pesticide operators).

- There is convincing evidence that adverse effects in people, in particular children) living close to motorways or heavy traffic roads (e.g. there are several very bad situations in small towns situated in Germany close to the border with former East Germany) are due to the combination of air pollution and noise. There is here a very serious situation due to lack of co-operation between noise experts and toxicologists; indeed there is here a complete disconnect. Programmes should be developed to alter this situation. Do not forget: most of these people living in this sort of situations just have no opportunity (no means, no money) to escape.

- Studies of combinations of sensory irritants to find out whether at no-effect levels (sub-effect levels) of the individual compounds the combination at such sub-effect levels does induce sensory irritation

In their review, Feron and colleagues (2002) have listed some key issues in the risk assessment of mixtures:

- Simultaneous exposure to fine particles and gases in ambient air
- Chemical disinfectants such as chlorine and ozone contains disinfection byproducts in drinking water
- Safety evaluation of natural flavoring complexes
- Combined intake of food additives.
- Exposure to volatile organic compounds from building materials.
Relevance to policy

The problem with chemicals, environment and human health and risk assessment of mixtures are highlighted in the EU Sustainable Development Strategy list of six unsustainable trends, especially to protect human health including the effects of chemicals, the 6th Environmental Action Programme (especially the "cocktail-effect"), and finally the 6th framework programme stating: “identification of causal agents including contaminants and physiological mechanisms, of environmental, and food-linked environmental hazards; understanding of exposure pathways, estimation of cumulative, low dose, and combined exposures; long-term effects; definition and protection of susceptible sub-groups; environmental causes and mechanisms responsible for the increase in allergies; impact of endocrine disruptors; chronic chemical pollution and combined environmental exposures”.

The 6th Environment Action Programme “Our future, Our Choice” states: “we have a poor understanding of the effects of small quantities of pollutants that accumulate in our bodies as well as the way different contaminants interact with each other in our bodies (often referred to as the cocktail effect)”

References

- William A. Suk, Kenneth Olden, and Raymond S.H. Yang Third Chemical Mixtures Research: Significance and Future Perspectives. Environmental Health Perspectives volume 110 | supplement 6: 891-892


- World Health Organisation has addressed the problems in many monographs and expert groups, such as Biomarkers and Risk Assessment; Concepts and Principles (WHO, 1993); Assessing Human Health Risks of Chemicals; Derivation of Guidance Values for Health Based Exposure Limits (WHO,1994), Human Exposure Assessment (WHO, 2000)

- Biomarkers in Risk assessment; Validity and Validation. The EU Joint Research Centre and its collaborative action « Urban air, Indoor Environment and Human Exposure (JRC, Environment Institute, 2000) has underscored the importance of urban & indoor air exposure assessment.


5.12 Environmental stress and children

Flemming Cassee, RIVM, The Netherlands

Ambient stressors like noise, malodour, air pollution and external safety risks are among the most ubiquitous environmental influences. Especially at the local level, the immediate living environment, people are confronted with these stressors at a day-to-day basis. Many studies dealt with the (health) effects of exposure to these stressors in adults, however, little is known about exposure of children in their daily habitat with respect to these stressors.

Typically, ambient stressors are perceptible, have a negative tone, represent no imminent threat and are intractable. Although the immediate health affects are not dramatic, certainly not at an individual level, these stressors generate a serious policy problem because of the number of people affected and the possible health effects in the long run due to stress.

For instance, in the Netherlands up to 40% of the adult population is annoyed by noise (various sources). Various health effects have been documented ranging from annoyance and sleep disturbance to the development of chronic disease (e.g. CHD). The total burden of disease due to noise in the Netherlands is estimated to be > 10,000 DALY’s per year.

Children represent a very particular type of user of the living environment. Physiologically and psychologically they may respond/adapt to and cope with these stressors differently from adults. Also their time-use pattern is different from adults, the former spending more time outdoors than the latter.

Various index number specific to children are not formulated: prevalences, dose-response curves are missing. More general little, is known of the impact of context (when, where, with whom) on the exposure to and perception of ambient stressors. Finally, long-term effects have been studied seldom due to lack of studies with longitudinal designs.

What we need are large scale epidemiological studies to assess prevalences and establish dose-response curves, in-depth studies (e.g. diary studies) to collect data on time, place and person and studies with longitudinal design to assess long-term (health) effects of exposure to ambient stressors in children in their daily life.

Key References


Relevant web-links:

- www.ranchproject.org
- www.herry.at/the-pep
- www.pinche.hvdgm.nl
- http://www.icben2003.nl/ see contribution by P. Lercher (presentation no. 81-e6)

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13 An interesting exception is the EU, multi-centre study on Effects of Road and Aircraft Noise in Children on Cognitive functioning and Health (RANCH)
6 Appendix

6.1 A new regulatory framework in France since the late 90’s

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One of the main principles of the risk analysis is the need for separating risk assessment bodies from risk management bodies. This separation allows a better application of the precautionary principle. As a result and further to several sanitary crisis (BSE, contaminated blood…) a new law reinforcing the health monitoring system was laid down in 1998 and created several new agencies:

- AFSSA (The French Food Safety Agency) as the national tool for health and nutritional risk assessment for food from production to distribution. Water intended to human consumption is considered by AFSSA.
- AFSSAPS (the French Health Products Safety Agency) as the competent authority for all safety decisions taken concerning health products for human use from their manufacturing to their marketing with three skills: evaluation, control and inspection.
- InVS (the National Institute for public health surveillance) whose main mandate is to monitor the health status of the population. InVS took over the National Network of Public Health created in 1992.

Later on, AFSSE (the French Environmental Health Safety Agency) by law in may 2001. Main missions are described in the regulatory document as follows:

- Evaluate the health hazards related to the environment
- Supply the Government by all means with S&T expertise in view of policy making
- Propose to the competent authorities any precautionary or preventive measures with regards to health hazards related to the state of the environment
- Provide advice on orientations of the health control and surveillance programmes related to environment.
- Make public its recommendations and advice

A.2. Year 2003

The Proposal for the Environment Charter Bill to be linked to the French Constitution was adopted by the Council of Ministers on 25 June 2003. It is stated in the Charter “Chacun a le droit de vivre dans un environnement équilibré et favorable à sa santé”/” Every one has the right to live in an environment which is balanced and favourable to health”

In January 2003, the preparation of the French Health and Environment Plan was announced in the context of the Budapest Conference to be held in June 2004.

This Environment and Health plan is one piece of the French strategy for sustainable development adopted on 3 June 2003. This plan is also part of the new proposal for Public Health Law which will be discussed in fall 2003 by the Parliament. With regards to this National Plan to prevent health risks related to the environment, it is stated that this national plan will be reviewed every 5 years and will be translated into regional plans by local authorities (Regional competent authority). Environment at work is also included in this plan.
It is noteworthy that the National Environment and Health Plan is one of the 5 national plans described in the Proposal for Public Health Law (Cancer - Health impact reduction of violence, behaviours at risk and drug use – Improvement of the quality of life of people affected by chronic diseases – improvement of care and management of rare diseases).

Already several objectives related to public health in the field of environment have been identified in the annexes of the proposal of the Public Health Law.

Five quantified objectives have been identified for the 2004-2008 period

- Housing : 50% reduction of the prevalence of children affected by lead. From 2% to 1% of children with lead above 100 µg/l
- Public Premises : Reduction of exposure to radon in schools and heath and social premises below 400Bq/m3
- Air pollutants
  - Compliance with all the European limit values in 2008 for all cities (NOx and fine particles)
- Water Quality: Division by 2 of the % of population supplied with water for human consumption which does not comply with parametric values for pesticides and microbiology continuously.

Three quantified objectives for which epidemiological studies are needed at first.

- Housing : 30% reduction of mortality due to CO
- Noise : Reduction of noise level (traffic, neighbourhood, music) with comparison to levels measured in 2002
- Water : 50% reduction of legionellosis.

The National Commission for the Environment and Health Action Plan was set up on 17 September 2003. Three main steps were defined to elaborate this plan: first a scientific baseline report on the environmental health risks, second a regional consultation of the various stakeholders, and finally the drawing up of the provisions of the action plan by the French government. This final document should be made public for the first time at the Budapest conference in June 2004.

**Main objectives of the plan were defined as follows:**

- Give visibility, impulse and coherence to the already undertaken actions in the field of Environment & Health which are considered to be too scattered.
- Propose new actions to anticipate emerging issues in the context of an always changing scientific knowledge.

A special focus should be given in the baseline report to:

- The criteria and methodologies able to contribute to the prioritisation of risks (short term and long term priorities)
- Activities, stakeholders and population groups at stake with regards to these priorities
- Recommendations from research and expertise bodies/organisations to prevent environmental health risks
- Benchmarking of mechanisms, programmes and measures already existing in France and abroad to identify and reduce environmental health risks and their efficacy.

B. State of Environmental Health National Research Programmes

The description below is not a comprehensive overview of organisations, programmes and scientific communities involved on one hand in environmental research and on the other hand on health research, but it is an attempt to identify programmes dealing with cross-cutting issues in Environment & Health.

B.1. Organisation of the scientific community and funding mechanisms

In France not a single public research organisation is fully dedicated to scientific issues related to environmental health. The different scientific knowledge and skills necessary to investigate the complex relationship between environmental and health are shared by several multidisciplinary public organisations (research bodies and academia). The challenge is now to identify the competencies of the research teams and to improve coordination of research thanks.

One instrument has been national programmes most often funded directly by Ministries in view of developing knowledge for policy making.

Since 1994 several Ministries have supported research programs to rally more efficiently the scientific community on environmental health issues. When research teams apply to these programmes, funding is limited to additional costs (ca 20%) as staff, infrastructure and durable equipment is already funded the national public research organisations. Therefore comparing research expenses in the Env&Health field cannot be done by the simple addition of the budget available for each programme described below.

B.2. Overview of environmental health funded programmes

Programmes funded by Ministries

The “Environment & Health Programme” (Ministry of Ecology and Sustainable Development).

This is the only research programme fully dedicated to this field with a very large scope (one proposal/ year since 1996; ca 1.5 M€ is available each year to fund 3-year-projects).

The main purpose of this programme is to increase the basic knowledge seemed necessary to assess and analyse the impact of environmental disruption on health.

The funded projects concerned all media, chemical and biological pollutants, physical agents as well as a wide range of human health impacts. One of the criteria to select projects is the integration of the different skills in toxicology, ecotoxicology, microbiology, virology, metrology, epidemiology, social and economic sciences…

An overview of more than 100 projects funded since 1996 shows that Water has been the main medium investigated (30%), air being a second priority (10%). Regarding projects related to chemical substances, heavy metals (13%) and endocrine disrupters (10%).
Microbiology concerned 27% of the overall project.

Concerning the exploitation of the results in policy making, OST (Observatory of Sciences and Techniques) concluded in 2001 that ca 50% of projects funded during the 1996 - 2000 period had some impact on environmental regulation and standards.

Since 2002, there is an increasing trend of projects with health impact focus (e.g: respiratory diseases, cancer, repro-toxicology).

In this programme environment is understood widely as environment at work is included. This is done in purpose since environment at work is essential to identification of health hazards. This specific field has been supported as well through two calls of proposals of the “Health at Work” programme, run by the Ministry of Health and Social Affaires. The current programme priorities aim to increase knowledge on some specific impacts: reproduction and solvents, allergy and respiratory diseases. Current funding concerns also professional cancers such as brain tumour and pesticides, mineral fibbers and mesotheliome, acute leukaemia.

Since 2002, the Ministry of Ecology and Sustainable development has transferred the Environment & Health programme to AFSSE. The priority research topics for the “Environmental Health programme” above mentioned will be updated as soon as the French Environment & Health Plan will be finalised.

Research in the field beneficiates also from the other programmes focused on specific themes: air quality, pesticides, eco-toxicology, EMF.

“PRIMEQUAL”: (Research Programme for better air quality at the local level, Ministry of Ecology and Sustainable Development).

PRIMEQUAL was initiated in 1995 (ca 1,5 M€ is available each to fund 3-year-projects) with two main objectives : (1) identification of the different factors responsible for air pollution and (2) evaluation of the technical and socio-economic conditions allowing improvement of local air quality.

The focus was initially on motorised transportation with a priority on volatile organic compounds and fine particles. Part of the funding was dedicated to impact studies on human health and improved significantly our knowledge on respiratory (including asthma and allergies) and cardio-vascular diseases. At present a more integrated approach to air pollution is promoted, both outdoor and indoor air are to be considered as well as all the different aspects from emission sources to health impact. Long-term exposure to specific pollutants and combined exposure is encouraged. Studies on aerosol and ultra-fine particles are actually a priority, gaps of knowledge were identified on the precise identification of the different components of these particles as well on their fate in the human body.

More generally priorities of this programme are defined in the context of European legislation on reduction of air pollutant emission and as such involved international collaborations.

Foreseen priorities in the next future are related to the combined exposure either between chemicals or between chemical and physical factors.


PNETOX was initiated in 1996 to answer the increasing need for risk assessment of the
industrial and agriculture activities. Since 2000 priorities are defined in the context of the new legislation on water and biocides. The funded projects concern multidisciplinary studies on biological effect (cellular level and ecosystem) and the fate of contaminants in different media (transfer between media and bioavailability). Projects include studies on endocrine disruptors, metals, POP (persistent organic pollutants), PBT (persistent bio cumulative and toxic pollutants), plant protection products (long term effect), ...

Concerning plant protection products used in agriculture a more specific programme was launched in 2001 entitled “Pesticide use: risk assessment and risk reduction”, part of it concerns pesticide dynamics in the environment with emphasis on air transfer on which gaps of knowledge were identified whereas concerning water and soil dispersion models start to emerged.

Although direct impact on human health is not evaluated under these two programmes (flora, fauna, micro-organisms mainly) they contribute to a better knowledge (toxic properties and dispersion in different media) of different sources of contaminants and as such are an essential prerequisite to human exposure studies.

“Sanitary and biological impact of mobile phones”. This new programme (fall 2003) is funded by the Research and Technology Ministry and is complementary to research activities funded as well by Ministry of Finance and Industry (COmmunication Mobile and BIOlogy program, 1998-2001) to contribute to the certification process of mobile phone. In 2003, two public reports from the French environmental health and safety agency (AFSSE) and the French senate assembly guided some research priorities linked to safeness of mobile phone use. The 2003 program focus essentially on some specific aspect of the biological impact of the EMF (hemato & encephalic barrier permeability, vestibulary apparatus, focal epilepsy, sleep) on human and animals and at the cellular level trough in vitro studies (Heat shock protein, genotoxicity, neuronal cell activity).

Other national programme initiated by research organisations.

This programme while initiated by one research organisation receives complementary funding from Ministries and involves several other organisations.

INSERM (Medical and Public Health Research Institute), is funding since spring 2003 a 3 year -concerted thematic action on environmental health intended to the scientific community, beyond the institute, to investigate impact (beneficial as well) on human health of all form of environmental disruption (at the national or international level) with a special focus on 4 major lines: (i) environment and transmissible diseases (ii) environment and acute diseases (iii) gene and environment (iv) environmental health and social economic development.

This overview of the French programmes relevant to the area of environment and health overview is far from being exhaustive. The recent report elaborated by the Expert Committee for the French National Environment and Health Action Plan (Feb 2004) has identified more than 10 nationally funded programmes by several public bodies (this is without taking into consideration the activities undertaken by more than 20 large research organisations, universities and sanitary agencies).

The first added value of these different funding is the important mobilisation in the past years of 3 scientific communities, environment, medical and life sciences and the cross fertilisation between them leading to an increasing number of multidisciplinary projects.
Although part of the funding was precisely dedicated to risk perception, individual behaviour, risk management, cost–benefit studies of risk reduction/prevention, generic tools for appropriate evaluation of public policy, economic and social sciences are still under represented.

The weakness of policy evaluation research may be the result of the youth of these programmes.
C. French participation to the FPV in the Environment & Health area

Only participation to Quality of Life and to Energy, Environment and Sustainable Development has been looked at.

C.1 Quality of life programme, key action 4 “Environment and Health”

Although France is at the third rank of the European countries (after UK and Germany) as participants and project co-ordinators considering all actions of the Quality of Life Programme, the French participation to Key Action 4 “Environment and health” is rather low with an average of 8% (of funded projects) as participant as well as coordinator.

Key words to present the French participation to the Env & Health topics can be presented as follows:

- **Prevention and treatment of Diseases and allergy**: analysis and quantification of impact (respiratory allergies, acute health effect and weather conditions, transport system (noise and air impact)); interaction between factors (genetic susceptibility and air pollution and environmental smoke); risk management (EMF, wood dust)

- **Development of new methods of diagnosis and risk assessment**: assessment of low dose and mixture effect of endocrine disrupters; development of markers of genomic integrity; role of nano-particles in biomaterial induced pathologies.

One project coordinated by INRA (National Institute for Agronomic Research) “Biotic and Abiotic mechanisms of the TSE infectivity retention and dissemination in Soil” has involved 8 French partners.

C.2. Energy, Environment and Sustainable Development

Environment and Health risk is also part of this programme in Key Action Water. 9 projects with French participation appear to be particularly relevant for SCALE (Pesticides in Groundwater, Microbiological risk assessment, Pharmaceuticals for human or animal use, beauty care products and endocrine disrupters)

D. Relative role of national and European programmes and needs for further coordination

Most probably it would be useful to have a better overview of national funded programmes in the field of environment & health both in terms of funding mechanisms, research organisations and programme content. This would allow to contribute to a better national programme planning and would increase multilateral cooperation in addition to EU-funded projects.

As the trend in FP6 is to fund a maximum of one project per topic, there is a need to better include the research efforts undertaken at the national level. Flexibility schemes should be provided to allow such inclusion once projects are funded by the Commission in order to increase capacity building at the EU level.

E. Gaps of knowledge in children’s health environment-Priorities (to be completed)

Generic needs:

- development and validation of integrated risk assessment methodologies,
- development and validation of QSAR (Quantitative Structure Activity Relationship)
- better exposure evaluation to environmental hazards in specific settings and media,
- understanding of children’s special vulnerability,

Asthma allergies and respiratory health:
- investigate the role of embryo-foetal and early life exposure on the immune responses

Pesticides and biocides:
- better evaluation of exposure and health effects

Neurodevelopmental disorders:
- Insufficient data from neurotoxin exposure (eg: from household)
- Increase Neurotoxicity & Neurobehavioural studies in animal models

Policy efficiency assessment
6.2 Effects of land use in Europe on human health – research needs

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Key words
land use, spatial planning, hierarchy of socio-economic sectors, human activities, traffic, noise, stress, water, soil sealing, habitats, disasters, risk

Summary in bullet form

- Land use is a high level socio-economic activity that causes lower-level activities which then have strong effects on human health. Thus, land use has a strong indirect affect on human health.
- Land use patterns cause increased traffic which is the most important human activity negatively affecting human health
- Land use destroys recreational areas and thus decreases options to reduce stress
- Land use produces stress by urbanizing once quite and peaceful areas
- Land use causes soil sealing which affects ground and surface water bodies which are essential for human health
- Land use increases particular natural disasters such as flooding events which then affect human health
- Land use destroys natural habitats and thus negatively affects the biological balance, which in the long term also affects human health or well-being.
- Nevertheless, land use is not recognised as one of the most important socio-economic activities affecting health. Research is needed in both quantifying such effects and recommending amendments to policy makers.
- The most important measure needed is research on how a Europe-wide spatial planning could be designed that better preserves human health.

Background paying particular aspect to European problems in the field (why this is important for Europe)

Environmental issues can be viewed from various perspectives. Commonly, either environmental media (water, air, soil) are considered, particular substances (endocrine disruptors, heavy metals) or human activities (industry, traffic, tourism). The latter activities define socioeconomic sectors and show a hierarchical arrangement, e.g. air traffic results from tourism or from trade etc.

Either perspective is important, since considering environmental media or chemical substances means measuring the results of human activities, whereas investigating these activities means to search for the causes of observed environmental problems. Moreover, investigating socio-economic sectors also provides means for identifying options to improve the situation.

High-level human activities are currently not considered in a sufficient was. E.g., it is not enough to relate particular unhealthy chemicals in the air to car-traffic (chemical substance in
a medium resulting from a human activity), but one also needs to consider the causes why car traffic is increasing, and which measures could be taken to reduce it. Land use is among these high level socio-economic activities. It strongly influences many other human activities. In turn, many effects on human health appear.

The following list describes problems. Research needs are described below. The list is by far not complete but describes important examples:

**Land Use and Traffic**

Traffic, particularly by individual cars, is known as one of the most health-related human activities. Every year, there are tens of thousands of people killed by traffic. Traffic accounts for large portions of air pollution, which, in turn, directly infects the health of those people who inhale air with enriched exhaust gases. The way land is used strongly affects traffic. Therefore, in a chain-like relationship, land use via resulting traffic affects human health. The larger residential structures are, the more traffic will be needed for both work and leisure activities. Currently, all of the large European cities are growing more or less uncontrolledly, since more and more people prefer living in a detached house in a suburb rather than in a flat within the city. The growing standard of living enables this process. These large-structure suburbs are very difficult to be handled effectively by public transport. Therefore, many of their inhabitants favour using their private car e.g., to go to work. Smaller structures, i.e. densely populated areas within the original cities, however, are well served by public transport, which in these areas is economical owing to their being densely populated.

**Land Use and Stress**

It is well established that urban environments are less favourable for human health than more natural ones in remoter areas. Many of the environmental problems known to have adverse effects on human health are most prominent in urban areas. By the current urbanisation of vast areas in Europe, these effects are transferred to places that once were not or less affected by these problems.

Firstly, those people who already inhabit once remote and quiet areas now are affected to processes such as noise and loss of peace, i.e. to causes of stress, whereas those who move into these areas may lead a more healthy life than they did before in a town. Tourism-related research documents that natural areas have a way higher recreation potential than areas with a lot of human infrastructure. However, by urbanising areas around cities, recreation areas are lost. Indeed, in many cases, historical literature describes excursions to beauty spots that now no longer exist. Again, a higher stress level of many people is the result, since recreation areas particularly in the vicinity of cities are essential as a stress reducing factor. Stress in turn has many negative effects on human health.

Natural recreation areas also enable people to exercise. E.g., people are jogging through forests, but not along highways or in residential areas. Exercising is, however, an essential prerequisite for maintaining a high standard of health.

**Land Use and Soil Sealing**

By urbanising large areas particularly the former vicinity of cities, vast areas are subjected to soil sealing. Soil sealing influences ground water resources in that aquifers may not be restored by precipitation in a sufficient way. Runoff velocities are dramatically increased and the remaining water may not be sufficient for a long-term aquifer restoration. However,
abundant high quality ground water is the prime source for drinking water in Europe and, thus, is essential for maintaining a high health level in Europe. Moreover, the highly increased runoff velocities likely enhance flooding events. If precipitation is unusually high, the sealed soil surfaces cannot uptake this water, and it directly flows into surface water bodies. Flooding events strongly affect human health, in that many people are killed or injured or subjected to enormous stress, such as losing their home and being unsure whether they can return.

Land Use and Natural Disasters

Settlements increasingly are placed in areas that are unsuitable for this purpose such as river valleys which are regularly subjected to flooding or areas in the lower parts of mountains that are subjected to avalanches and the like. Such settlements impose a permanent risk to their inhabitants. The effects on human health are obvious as described above.

Land Use and Loss of Habitats

Natural habitats may not appear to be clearly linked to human health, but to a degree they nevertheless are. Many habitats serve as recreation areas (e.g., they are also beautiful because they have a particular flora), and, as mentioned above, recreation areas are essential to reduce stress. However, land use in many cases has negative aesthetic effects on landscapes, and, thus, on human well-being.

Moreover, the natural equilibrium depends on a multitude of kinds of organisms. Currently, land use practices permanently reduce natural habitats and lead to the loss of species, and, thus, affects the biological equilibrium. To a degree, humans are also part of this biological community. E.g., the loss of forests may result in a lower air quality or negative effects on groundwater regimes.

Research activities in the field in Europe

Currently, there is research regarding several of the effects of land use, e.g. health effects of traffic or noise or stress etc.. However, land use is not sufficiently identified as one of the main reasons behind these activities.

Relevance to policy

Land use is regulated in spatial planning. However, most problems, such as settlements in areas that are unsuitied for this purpose, or building shopping malls in villages close to large cities, result from the lack of a binding high-level spatial planning which would regulate subordinate spatial planning on a regional level. ESPON (European Spatial Planning Observation Network) could become a basis for preparing a joint initiative for a Europe-wide approach to human health related spatial planning. The target should be to obtain Europe-wide binding regulations for spatial planning that consider the effects on the natural environment and, thus, on human health.

Research priorities for the future

Human health as one of our greatest goods should be clearly related to our activities. Preventing or reducing activities that have adverse effects on human health should become a prime target and to the largest degree possible supersede any actions to restore health that has been damaged.
Thus, specific health related effects of land use should be the subject of research projects. The most pressing issue apparently is traffic. Fortunately, health effects of traffic are already investigated in several research programmes. However, more emphasis should be placed on the causes behind the increase of traffic in Europe. Land use practices are among these causes. Such research should focus on not only identifying specific behavioural patterns that lead to more traffic but on possible amending activities, such as contents of a high level spatial planning. Such results should be formulated as support to European and national policy makers.

Emerging issues (threats)

Threats are mentioned in part 3.

A few key references
6.3 EUROCITIES and TWG research health and environment: initial comments

Comments made by Gavin Tringham, from Birmingham City Council, on 13th November 2003

(NOTE: She is already a representative of Eurocities on the heavy metals working group. As a result she is already doing a lot of work within that group and part of that is Research and Health).

In general I would say that the starting point for research should be what ill health effects are being seen in children that may be attributable to environmental effects. The most common ones attributable to environmental exposure are; asthma, childhood cancer, neurodevelopment abnormalities, endocrine and reproductive effects' and immunotoxic effects. To that list I would add food disorders such as overeating and being overweight. I would therefore suggest that research should be geared to identifying what in the environment is implicated in any of the above.

In addition we know that some pollutants are causing health problems, eg PM10 and O3. Whilst the mechanism for ozone is reasonably understood, how PM10/2.5/1.0 actually acts is uncertain. Therefore I would suggest that research should be channelled in to areas where we know an effect is occurring but don’t know why.

I would suggest that research should be prioriterised into areas of potential greatest benefit.

Comments made by Dr Charles Price, Director of Public Health, Sheffield

1. There are few papers I know which give an overview of this whole field. Here is one enclosed to this document (article from Professor Anthony J. McMichae). It refers to developing countries but the same issues apply to developed. Otherwise there is a need to go to specific fields eg housing, air pollution, transport, social exclusion, etc. The healthy cities web site has some material http://www.euro.who.int/eprise/main/WHO/Progs/HCP/Home

2. Health effects of housing improvement: systematic review of intervention studies.

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OBJECTIVE: To review the evidence on the effects of interventions to improve housing on health. DESIGN: Systematic review of experimental and non-experimental housing intervention studies that measured quantitative health outcomes. DATA SOURCES: Studies dating from 1887, in any language or format, identified from clinical, social science, and grey literature databases, personal collections, expert consultation, and reference lists. MAIN OUTCOME MEASURES: Socio-economic change and health, illness, and social measures. RESULTS: 18 completed primary intervention studies were identified. 11 studies were prospective, of which six had control groups. Three of the seven retrospective studies used a control group. The interventions included rehousing, refurbishment, and energy efficiency measures. Many studies showed health gains after the intervention, but the small study populations and lack of controlling for confounders limit the generalisability of these findings. CONCLUSIONS: The lack of evidence linking housing and health may be attributable to pragmatic difficulties with housing studies as well as the political climate in the United Kingdom. A holistic approach is needed that recognises the multifactorial and
complex nature of poor housing and deprivation. Large scale studies that investigate the wider social context of housing interventions are required.

Comments made by Elisabeth Södeström, Stockholm Region

The Stockholm region consisting of the Stockholm County Council, the City of Stockholm and the Stockholm County Association of Local Authorities in Stockholm County, welcomes the Strategy presented on the July 11th, 2003 at the stakeholders meeting.

The Stockholm region foresees a positive approach regarding the collaboration of the DG’s behind the Strategy (Environment, SANCO, Research and JRC).

The Stockholm region wishes to take full part in the proposed technical working groups. The expert’s applications have been submitted to DG Environment.

The Stockholm region has some comments on the Strategy and the actions included realising the Strategy:

1. General comments
   Every action which can reduce the need for medical care and costs for care is not only important from a humanitarian perspective but also from a public finance point of view. A society is not sustainable if it is forced to use a lion part of its public resources to ease illnesses which arises when the same society allows pollutions or other distortions to the environment. The new Strategy is therefore most welcomed.

2. Increased awareness
   An increased awareness of the authorities and the public is a prerequisite to implement preventive or corrective actions. Still, there are people unaware of the dangers with smoking. Also, there are few persons aware of the consequences of an intake of heavy metals and there are virtually none who is aware of the possible dangers with an increased amount of pharmaceuticals in the drinking water (see separate paragraph below). Therefore, the Stockholm region would like to see a further description on how the Commission foresees to share the new knowledge, of the research in the enlarged EU, brought forward in the working with the Strategy. When it is shared among the countries the information could improve judgements and decisions in various contexts. Today we lack an overall image over the exposure of the environment regarding the human health. In the recent decades we have seen an increase of allergy throughout EU and the Western part of the world. Asthma and allergy has over a short period become some of the most frequent chronic diseases and are still continuing to increase. Apart from heritage and environment the lifestyle is also affecting the development of allergy or other oversensitivity. Research in this area is therefore of importance. Other important questions regarding the health of the children is the exposure of noise and the quality of air in the environment of the children, especially in kindergarten and school. A sound environment also involves consideration to minimise the risk of accidents for children at home and in the traffic.

As an example of achievements within the Stockholm region, the City of Stockholm environmental programme the City is working towards sustainable development. By choosing ecological products the load on the environment is reduced. The departments of the City shall increase the rate of purchased products which are ecological to at least 15%. The food served at schools and kindergarten is made of “purer provisions” and at the same time the City receives a lesser load on the environment.
3. Pharmaceuticals in drinking water and quality

The Stockholm region would like to see considerations or comments in the Strategy regarding the environmental effects of the pharmaceuticals in the drinking water. This problem is still inadequately mapped out but it is known that drinking water in Central Europe contains several types of pharmaceuticals. It is also known that the uncritical use of antibiotics in medical care and agriculture in European countries has resulted in vast resistance with many bacteria’s causing diseases.

To maintain a sufficient health situation, considerations also ought to be made to facilitate the support of drinking water and food supply of good quality. In order to achieve this in the long term an overall picture is required of the use of chemicals, (and pharmaceuticals as mentioned above) transports, the risk of accidents and the policy for farming (fertilizing and spray).

4. Mapping of Analysis and suitable changes

A mapping of and development of systems for national economy analysis of environmental and health effects is needed to place them on an equal footing with more conventional economical models. A broad introduction of an economical management of a span of a lifecycle in the decision making processes is needed.

To increase the effect of the sector overlapping achievements a mapping is needed of the factors that improve or prevent the implementation of the foreseen actions. A mapping should also present proposals on suitable amendments of EU-regulations in the environmental sector and the economical systems (taxation and accounting) in order to stimulate a faster exchange of, for example vehicles, other equipment or chemicals in the production.

5. The EU-citizen

The Stockholm region wishes that the Strategy in a larger extent should be directed towards the individual responsibility. A strong civil society, far-reaching directives and regulations and great knowledge of the authorities are essential but not sufficient in order to prevent environmental related diseases/illnesses. Every individual should be given enough knowledge to be able to take a personal responsibility for its health. This responsibility should be more explicit in the Strategy.

6. Timeframe

The Stockholm region notes that the implementation of the strategy is relatively extended. To use a large part of the period 2004-2010 to gather knowledge and adjust the strategy, and in the three pilot projects concerning dioxins and PCB, heavy metals, endocrine distort substances, while not grasp the possibility of intervention of preventive or therapeutically causes seems to be an act of too moderate proportions. It exist sufficient knowledge in several areas to motivate powerful actions. Thus, the pilot projects should be given a more offensive direction. As example the Polluter Pays Principle as well as the caution principle should be used parallel with an increased establishment of knowledge.

7. Understanding of regional differences

The new Strategy should be based upon an understanding of local and regional differences. The establishment of regulations and the performance of actions have to consider the authorities at local/regional level responsible for a significant part of the implementation.