EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Public Health and Risk Assessment
C7 - Risk assessment

SCIENTIFIC COMMITTEE ON HEALTH AND ENVIRONMENTAL RISKS

SCHER

Opinion on

"Research priorities for the 7th Framework Program Human Health and the Environment"

Adopted by the SCHER
by written procedure on 30 October 2006

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1. BACKGROUND

The European Commission's Environment and Health Action Plan, adopted in 2004, has as its main aim to improve the understanding of the link between environmental factors and health.

The implementation of the goals of this action plan through research has started in 6th Framework programme (FP6 - 2002-2006) via funding of several large- and small-scale research projects on topics identified as priorities in the Action Plan. The FP is managed by the EC DG Research.

The efforts will continue and intensify during the 7th Framework programme (FP7- 2006-2013), which should be launched by the end of 2006. The proposed 'Cooperation' programme will have a Theme called 'Environment' under which there is an activity called 'Environment and Health'.

This activity will fund research projects under three areas: (i) Health impacts of environmental stressors; (ii) Integrated approaches for environment and health risk assessment; (iii) Delivery of methods and decision to support tools for risk analysis and policy development.

2. TERMS OF REFERENCE

The SCHER is requested to provide an opinion on research priorities regarding the three areas mentioned above. This will provide a useful input for DG Research for the elaboration of future work programmes and calls for the Environment and Health activity.

3. OPINION

3.1. Introduction

The programme Environment and Health that is part of the Climate change, pollution and risks activity is defined as

> *Interaction of environmental stressors with human health including identification of sources, biomonitoring research for environment related health, indoor air quality and links to indoor environment, urban environment, car emissions and impact and emerging risk factors; integrated risk assessment methods for hazardous substances including alternatives to animal testing; quantification and cost-benefit analysis of environmental health risks and indicators for prevention strategies.*

Four different actions have been identified:

- Integrating and exploiting research results for policy development (action 5).
- Analysis of environment/health interactions to improve understanding & prevention of the priority diseases (putting emphasis on children, e.g., asthma, allergy, neuro-immune disorders, cancers, endocrine disruption (action 6).
- Developing methodologies to assess better the risks coming from environmental factors and improving economic valuation (externalities concept) and impact analyses of prevention strategies (action 7).

- Launching research on emerging issues (action 8).

To address these issues three different overarching research priorities have been identified:

  - Health impacts of environmental stressors.
  - Integrated approaches for environment and health risk assessment.
  - Delivery of methods and decisions to support tools for risk analysis and policy development.

These research priorities have been integrated into seven different specific research areas that are the priorities for the 1st call. Four of these areas are within the SCHER area of responsibilities.

3.2. Environmental influences on reproduction and development

This subject area was covered by extensive research activities in FP5 and FP6 with the focus on "endocrine disrupters" (ED). Further research in "endocrine disruption" should only be initiated after a critical review of the results obtained and should be based upon valid hypotheses that have evolved from the initial work.

This review should specifically evaluate whether sufficient information for appropriate risk assessment is available on the three major points described below. Needed research to fill the data gaps identified should focus on epidemiological studies based upon a valid exposure assessment preferentially assessing the impact of combined exposures, and consideration of naturally occurring chemicals with hormonal activities.

The SCHER recommends the following research when data gaps become apparent by the critical review:

- Assessment of environmental influences (environment should not only include chemicals, but also other stressors such as dietary habits, over nutrition…) on human reproductive health taking into account long latencies of effects, exposures at critical time points and interplay between multiple factors. Studies should mainly focus on the effects such as:
  - Male and female infertility.
  - Adverse pregnancy outcome.
  - Childhood development, including neurobehavioral development and precocious puberty.
  - Foetal origins of male and female reproductive disorder, i.e. sub fecundity.
  - Nature and timing of menopause or andropause.
  - Hormone dependent cancers.

- Development and validation of toxic equivalent factors (TEFs) based upon relevant biological response markers. Many of the compounds with effect on reproduction and development belong to specific groups of chemicals sharing the same basic structure (e.g. organotin compounds).

- Evaluation of the potency of naturally occurring EDs, i.e. food, botanicals and development of a model to predict the exposure to natural EDs in order to estimate their contribution as potential risk factors.

The SCHER recommends to:

- Use European wide parent-child cohort with associated biobanks as tool to investigate early health outcomes like neurobehavioral effects and urogenital malformations.
- Evaluate functional genomics and related fields of proteomics and metabonomics as tools for understanding mode of action of environmental reproductive hazards, and for determination of TEFs.
- Analyse the effects of endocrine active compounds on cellular mal-differentiation as a result of faulty programming early in foetal life, i.e., epigenomics.

3.3. Health impacts of indoor air quality

The SCHER has identified the following needs for further research:

- Develop methods of identifying objective effects of exposure to indoor air contaminants, including dose-response relationships.
- Studies on adverse health effects of micro-organisms in indoor air, especially in tissues other than the respiratory tract; identification of responsible micro-organisms and mechanisms of toxicity.
- Contribution of indoor air pollutants to childhood respiratory diseases.
- Comprehensive review on the indoor air pollutants; definition of the major pollutants and the range of their concentrations in each Member State of EU, and a pan European database on them.
- Quantitation of exposure (short and long term in different environments), and identification of the most relevant exposure indicators.
- Quantitative source apportionment of the pollutants in indoor environment (e.g. building materials, consumer products).
- Characterisation of harmful emissions in water damaged buildings, contributing factors to toxicity and features of the exposure.
- Effects due to combined exposure to indoor air pollutants and methods for their evaluation including development of validated modelling.

3.4. European network on human biomonitoring

The development of a coherent approach to Human Biomonitoring in Europe was a key commitment in the European Environment and Health Action Plan 2004-2010 adopted by the European Commission in 2004. Human biomonitoring is a tool to assess human exposure to environmental pollutants that can be correlated to potential health effects. Biomonitoring can provide an estimate of the *total* human exposure to environmental pollutants, data that are more relevant for risk assessment than extrapolations from chemical concentrations in soil, water, air and/or food. Many Member States are carrying out human biomonitoring programmes and

activities, but they use different methodological approaches, and it is therefore presently difficult to draw comparable or common conclusions at EU level. Exposure monitoring in humans is an essential tool to assure appropriate risk management for chemicals that influence human health.

The SCHER recommends the establishment of a European network on human biomonitoring which will focus on developing scientific methods for:

- Identification of priorities in exposure reduction strategies.
- Provision of a signal as to the urgency of specific activities to reduce environmental exposure.
- Follow-up of the efficiency of risk reduction strategies.
- Development of relevant environment and health indicators.
- Using geographical information systems to establish a link between environmental exposure and health effects taking confounding factors into consideration (cluster analysis).

The network on human biomonitoring should include elaboration of methods to:

- generate representative data on body burdens of pollutants, or the response of the human body to chemical, physical or biological environmental agents taking advantages of the recent developments in analytical chemistry and system biology;
- establish and use of European environmental specimen banks;
- provide information on distribution of exposures to specific pollutants within the European population and permit the identification of groups at high risk;
- set priorities for actions based on endpoints that are relevant for human health.

A high priority should be given to “new” compounds, including degradation products of high production volume chemicals. Experts in photolysis, chemical and microbial degradation, and metabolism should predict possible compounds, which could then be the focus of a monitoring program.

3.5. European cohort on air pollution

The Clean Air for Europe (CAFE) programme has demonstrated that the long term exposure to particulate air pollution shortens life expectancy. However, the research basis for the risk quantification comes mostly from non-European studies. Furthermore, earlier EU supported projects show large geographic and seasonal variations in particle characteristics which may be an important risk factor.

The SCHER has concluded in a recent opinion that currently there is not sufficient data to support PM2.5 as the major risk factor for chronic effects.

The SCHER recommends to:

- Establish or take advantage of already established national cohorts to investigate the health effects of long term exposure for PM2.5 and PM0.1.

- Develop harmonized study protocols.
- Develop and validate accurate exposure models to assess exposure for ambient air pollution, including PM2.5, and obtain more information on exposure-response of PM2.5.
- Develop biomarkers of exposure and effects to validate the exposure models.
- Investigate systematically the toxicity of PM2.5 and PM0.1 to support the cause-relationship assessments made on the basis of epidemiological studies.
- Identify markers to be used in source apportionment.
- Focus on potential high-risk populations, i.e., children and the elderly.

3.6. Research on nanoparticles

There is an increasing attention to the potential hazards using nanotechnology products, and safety considerations are very important for the success of these emerging technologies. The risk characterization of these products should be based on solid scientific evidence.

The SCHER recommends research on:

- Development and validation of toxicity test systems for nanoparticles, both in vitro and in vivo taking 3R principles (replacement; reduction and refinement of animal experimentation) into considerations and addressing both chronic and acute effects
- Toxicity of nanoparticles not related to ambient air particles. The focus of such projects should be on effects in humans and on the environment.
- Investigations on uptake, distribution, biotransformation and excretion and of mechanisms of toxicity as a function of size and particle characteristics
- Development of methods to determine and characterize nanoparticles in biological systems.
- Development of models/methods for exposure assessment of nanoparticles.

3.7. Overarching research priorities

The SCHER would also like to give the following general comments on some urgent research needs based on the work with risk assessments of a large number of chemicals.

3.7.1. Exposure assessment

The research projects that have been supported in the 5th and 6th FP regarding health and environment have mainly been dealing with effect studies. This is also true for the outline of the first call in the 7th FP.

The SCHER recognises that the difficulties in risk assessments are often connected to deficiencies in exposure assessments. A lack of exposure information may result in severe limitations in health effect studies in human populations. Especially the knowledge on the

contribution of dermal exposures to total systemic exposure is insufficient. Special focus of research calls in this area should also be on estimation of uncertainties in exposure assessment.

The SCHER has identified the following research issues of high importance:

- Development of technologies to make quantitative measurements of personal exposure with a high precision.
- Integration of biomarkers with the development of biosensors.
- Biomarkers to determine dermal exposure as well as total exposure from many pathways.
- Bioavailability of chemicals from different matrices.
- Toxicokinetics after dermal exposures.
- Development and validation of exposure models, including low dose exposure situations.
- Estimation of uncertainties in exposure assessments.

3.7.2. Optimisation of test systems

Considerable efforts have been made to establish alternative in vitro test systems in toxicology. However, as soon as the complex interaction of the organism is involved, there are considerable limitations of the in vitro systems, and testing with laboratory animals is necessary. However, there is a potential in reducing the number of animals required in assessing the safety of a compound by the use of more refined testing protocols. Therefore, research should be encouraged which aims at the reduction of number of animals.

Research efforts should include validation of the methods applied with suitable compounds and aim at the development of guidelines for future testing.

The SCHER recommends:

- Validation of endpoints for reproductive toxicity in repeated dose toxicity studies.
- Investigation of new endpoints including toxicogenomics, proteomics, metabonomics.
- Statistical considerations, e.g., impact of the “benchmark dose” approach on dosages and number of animals per dosage.

3.7.3. Low dose effects

Recent discussions based on an EFSA opinion have focused on issues of extrapolation of effects incidence in animals at high doses and the extrapolation to low doses. New approaches for risk assessment for genotoxic agents have been proposed using either application of “margin of exposure” or „threshold of toxicological concern” approaches. Moreover, hormesis as a low dose beneficial effect of toxic chemicals is also intensively discussed. However, data on the actual shape of the dose-response curve in the low dose region for toxic and genotoxic agents is not well defined. New developments in analytical chemistry, “omix”-technology and molecular biology may now help to generate data on cellular responses to toxicants in low dose regions relevant to human exposures.

The SCHER recommends the following activities:

- Development of tools to assess interaction of chemicals at low dose, including natural stressors, comparison of dose-response of several interrelated biomarkers (systems biology) focusing on chemical carcinogenesis.
- Shape of dose-response relationships for low level exposures to chemicals
- Explore the possibilities to establish threshold for genotoxic carcinogens.
- Integration of physiologically based toxicokinetic models into the risk assessment process.

3.7.4. Vulnerable populations

Risk estimates for vulnerable subgroups in the populations are needed, and whether and to which extent environmental exposure, socio-economic status and genetic predisposition enlarge the susceptible populations. The SCALE programme focuses on the health of children.

Children have more years of life ahead than adults and may therefore develop diseases with long latency periods that may be triggered by early environmental exposure. The impact of lifestyle/environment factors and of all exposure pathways and sources at life stages of interest, i.e., windows of susceptibility for each organ, require consideration for integrated and harmonized exposure and effects assessments in vulnerable groups.

The SCHER recommends research that improves our knowledge on:

- Possible effects during windows of susceptibility and early life, time-series information and identification of critical time windows
- Differences between children and adults and within different age groups of children, e.g. mechanism of actions, bioavailability, distribution, metabolism, and excretion of environmental pollutants
- Elucidation of specific exposure patterns in children
- Novel assays and biomarkers to study gene-environment interactions in children.

3.7.5. Other recommendations

The SCHER recognizes that there are a considerable number of urgent environmental research needs. However, these are not detailed in the present opinion but will be subject of a separate opinion.

The SCHER also strongly supports capacity building in the area of risk assessment. Under the specific programmes “People – Human potential” development of a European School in Environment and Health should be considered.

The REACH Programme, scientific activities and regulatory needs in the chemical and pharmaceutical industry urgently require scientists proficient in all areas of eco- and human toxicology. Scientific expertise should also be sufficiently developed to enable the individual to translate scientific results into relevant conclusions for risk assessment of chemicals. Toxicology education within the EU at present is limited and in several member states, the capacity for toxicology education is declining. At the same time the need of toxicologist and safety scientists

in Industry and Regulatory Agencies, e.g., in connection with implementation of REACH is required.

Specific support actions by the commission outside of the normal collaborative competitive approaches or exchange programmes may establish a network of competent institutions and help stop to decline. Both research activities and education in the network should focus on practical applications of exposure assessment toxicology to risk assessment.

4. REFERENCES

EFSA Scientific Committee opinion on A harmonized approach for risk assessment of substances which are both genotoxic and carcinogenic. Adopted on 18 October 2005

SCHER opinion on New evidence of air pollution effects on human health and the environment. Adopted on 18 March 2005

5. ACKNOWLEDGEMENTS

Members of the working group are acknowledged for their valuable contribution to this opinion. The members of the working group are:

Prof Autrup (Rapporteur), Prof Dekant, Prof Hanke, Prof Jansson, Prof Janssen, Dr Mansgeldorf, Prof Steenhout, Dr Viluksela.