Methodology for assessment of Environmental burden of disease

Prepared by:

David Kay
Centre for Research into Environment and Health
Aberystwyth, United Kingdom

Annette Prüss
World Health Organization
Protection of the Human Environment
Geneva, Switzerland

Carlos Corvalán
World Health Organization
Protection of the Human Environment
Geneva, Switzerland

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Joe Eisenberg  University of California, Berkeley, USA
Keith Florig  Carnegie Mellon University, Pittsburgh, USA
Scott Grosse  Centers for Disease Control & Prevention (CDC), Atlanta, USA
Tord Kjellström  New Zealand Environmental and Occupational Health Research Centre, Auckland, New Zealand
Eric Lebret  National Institute of Public Health and the Environment, Bilthoven, The Netherlands
Tony McMichael  London School of Hygiene and Tropical Medicine, London, United Kingdom

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1. Introduction

The disease burden caused by an environmental exposure, and the preventable part of it, are major elements which can guide decision-making, priority setting and resource allocation in health and environmental management. Quantitative assessment of the burden, together with information on the effectiveness and cost-effectiveness of interventions within a social and ethical framework, provide a rational basis for research, implementation and policy development.

Since the Global Burden of Disease study was published in 1996\(^1\), the overall burden of disease has mainly been estimated by ‘disease outcome’ rather than by ‘risk factor’. A few approaches to estimating the burden of disease from environmental risk factors have been tested and some have produced promising results.

For comparison of disease burden estimates across risk factors, estimates need to employ a harmonized methodology. This requires the development of:

- working definitions,
- the definition of ‘zero-exposure’ and/or
- appropriate hypothesised ‘alternative’ exposure scenarios, and
- a common approach to evidence or uncertainty underlying an estimate.

To address these issues, a consultation was held in Buffalo, New York, 23-24 August 2000, following the 12\(^{th}\) Annual Meeting of the International Society for Environmental Epidemiology (ISEE 2000).

2. Objectives

The overall aim of the consultation was to advance the agenda of the evaluation of disease burden from environmental risk factors. This consultation was part of an ongoing process aiming primarily at the following:

- To provide methodological guidance on the quantitative assessment of the burden of disease from environmental risk factors at national or regional level; the process should result in a practical guide.
- To create a network of experts interested in developing the conceptual and practical implementation of environmental disease burden assessment and sharing experience to define priorities in future developments.

This meeting constitutes the first consultation of experts in the framework of this project. The participants undertook a structured review of the proposed elements and methodological approaches for environmental burden of disease assessment. A first draft of the methodological elements is provided below. This was tabled in a series of presentations and developed during the meeting.

This project builds upon a previous consultation organized by WHO/ILO\(^2\). Several papers from that consultation were published in the September 1999 issue of the journal Epidemiology. It also builds upon and adapts concepts put forward in the global

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assessment methodology of the GBD study\textsuperscript{3,4}. In 1999 the Department of Protection of the Human Environment intensified its efforts and started a project to specifically address the Environmental Burden of Disease (EBD). This is the first meeting dedicated to this project.

Annex 1 contains the background document on this project for the consultation.

A special session on EBD was organized in the 12\textsuperscript{th} Annual Meeting of the International Society for Environmental Epidemiology on 22 August 2000. Its objective was to report on progress in these activities and bring the project to the attention of environmental health professionals.

Programme and summaries of the presentations of the special session are presented in Annexes 3 and 4 of this document.

3. Organization of the meeting

A total of 39 participants, with various specialities in environmental health, participated in the 1½-day consultation (a list of participants is presented in Annex 2). It was chaired by Professor Tony McMichael, London School of Hygiene and Tropical Medicine, UK. Professor David Kay, Centre for Research into Environment and Health, UK, acted as rapporteur.

The meeting was composed of plenary sessions of discussions and brief presentations to introduce each topic (agenda in Annex 3, summaries of presentations in Annex 4). The main topics discussed included:

- Framework & challenges
- Concepts and examples
- Describing level of uncertainty and evidence
- Further steps and improvements

The group was split into the following working groups during part of the meeting:

- Water & sanitation
- Air quality
- Global environment
- Chemicals

The working groups were asked to address the following issues:

- List useful categories of risk factors to consider
- Propose relevant alternative scenarios
- Address the strength of evidence in each area
- Address the geographical resolution, i.e. the feasibility of size of the area at which the burden of disease assessment can be performed
- Recommendations on the methodology – with reference to the background document
- Other relevant issues – way forward.


\textsuperscript{4} Guideline for comparative risk assessment, web site http://www ctr.u.auckland.ac.nz/CRA/
The results of the working groups are presented in Annex 5.

4. Meeting recommendations

The main recommendations which emerged during the discussion sessions are summarized below.

General issues

- Decision-making in environmental health should be based on national or regional EBD estimates (with the exception of a number of global risk factors, such as climate change, or greenhouse gas emissions); therefore, the emphasis will lie on national and regional EBD assessment.

- The distribution of EBD within a population should be assessed in addition to the total numbers per age category. The distribution will provide information about the equity in exposures and health outcomes. Such information for policy making in view of the protection of vulnerable groups or high-risk communities.

- Limited transferability of the evidence to populations where empirical data are lacking may restrict the assessment of EBD of “data-poor” populations. Before assessing burden of disease, the applicability of available dose-response relationships to the study population needs to be evaluated.

- Although a general methodology is needed for the sake of comparability, it should be flexible enough to allow for making the most sensible choices regarding categorization of risk factors, summary measures of population health, etc.; The parameters and methods currently used in the global assessment of risk factors would be too restrictive for a number of potential applications in environmental health.

Categorizing risk factors

Various types of categories can be chosen for estimating the related health impacts: the type of human activity (e.g. energy generation, transportation), the type of pollutant (e.g. exposure to lead, arsenic) or by pathway (e.g. air pollution, water). Also, the categories can be more or less aggregated or split into subcategories. For instance water & sanitation could theoretically be split into exposure to recreational water, drinking water intake, access to sanitation etc.

- Categorizing risk factors should be carefully considered, as they may have an impact on the use of resulting estimates of disease burden. In particular, the grouping of risk factors or their splitting into several subcategories may seemingly reduce or increase their importance.

- The choice of risk factor categories should be policy relevant and seek to address parameters policy makers can directly influence (e.g. include sector policies as risk factors, such as transportation policy or energy policy, in addition to risk factors such as ‘air quality’, ‘noise’ etc.). In particular, for assessment at regional or national level, risk factor categories should be adapted to policy needs.

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EBD: Environmental burden of disease

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• The categories of risk factors to be considered for global, national and regional EBD assessment should be relevant to policy making and reflect a logical framework and hierarchy. The DPSEEA framework (Driving Force – Pressure – State – Exposure – Effect – Action) would be very suitable. Adapting to the decision-making process would also facilitate the use of EBD data.

**Summary measures of population health**

Summary measures of population health are measures that combine information on mortality and non-fatal health outcomes to represent the health of a population in a single figure or unit.

• The suitability of health valuation should be further investigated and the utility of this approach for informing EBD assessed.

• It was noted that DALYs (the Disability-Adjusted Life Years, being the most widely used measure) do not currently accommodate ‘quality of life’ issues, which are however included in WHO’s definition of health.

• The use of other measures (such as QALYs) should be investigated as potential unit for quantifying disease burden and compared with assessments based on DALYs.

• The EBD process needs to be flexible and be able to describe areas such as “life style” or “annoyance”, which may, in turn also result in indirect health impacts.

• Issues such as discounting of health should also be addressed to satisfy policy relevance. For example, discounted health impacts of risk factors with very delayed effects, as may be predicted for emission of greenhouse gases, will probably be represented as negligible even if a small discount rate is applied.

The considerations in this section may require a number of cross-disciplinary views in environmental health.

**Alternative scenarios**

Alternative scenarios are baseline scenarios for comparison with the exposure scenario to be studied.

• The term “counterfactual scenarios”, cited by Murray & Lopez and borrowed from the social science literature, is often misunderstood, and should be replaced by another term, such as “alternative scenarios”. Such scenarios need to be defined to compare the results with those of an alternative scenario where other

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policies, practices or technologies prevail, or simply of other societies or regions where lower exposures have been achieved.

- In addition to the alternative scenarios described by Murray & Lopez, scenarios which are closer to environmental health policy scenarios should be considered (e.g. the shift from one transportation policy to another, the shift from one energy policy or technology to another).

- The choice of risk factors and alternative scenarios should depend on the planned use of resulting estimates. For example, if disease burden estimates are to be used as elements in decision-making in transportation policies, the risk factor to consider should be transportation.

**Causation**

- EBD assessment should rely and draw upon all available science and evidence (i.e. “best available evidence”) and reviews where available. An “objective” description of the available evidence on exposure-outcome relationships, according to best environmental health practice (e.g. *Environmental Epidemiology*, Evaluation and Use of Epidemiological Evidence for Environmental Health Risk Assessment), is necessary in order to maintain the credibility of the estimates. An analysis of the uncertainty around estimates should accompany the EBD estimate.

- The evidence underlying any burden of disease estimates should be described in a systematic and comparable way. It is, however, questionable whether the policy maker will make use of information on strength of evidence or information on level of uncertainty.

**Potential consequences of factors affecting the quality of life**

- Issues affecting the quality of life, such as “annoyance” or “small cognitive disorders”, should be considered in the assessment of burden of disease. In particular in modern societies, “annoyance” caused for example by noise, can account for a significant part of the disease burden.

- Apparently small impacts on health or quality of life may potentially result in a large impact on a population. For example, a shift of a whole population by the reduction of just a few IQ points (from exposure to lead) may produce a significant increase in the small proportion of the population who exhibit learning difficulties. As loss of IQ points may impact on education, and level of education is associated with a number of health outcomes, real health impacts may be higher than expected.

**Suitable methodologies**

- The often limited availability of data needs to be reflected in the type of analysis carried out. For example, it may be possible (or necessary) to use data on distal causes in the estimation of disease burden. E.g. use of cooking fuel has been observed to be associated with ARI (acute respiratory infections). Although

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10 WHO/Regional Office for Europe, Denmark, 2000 (EUR/00/5020369).
personal exposures are not generally assessed in most of these studies, such associations could be used in evaluating the burden of disease. It would, in such circumstances, be useful to assess the relationships between distal causes (such as ‘use of cooking fuel’) and personal exposures examined in smaller scale investigations to obtain additional information on the links within the causal web. This process would permit the use of data from population surveys, which often assess distal causes at very large scales.

- The different risk factors will determine the suitable approaches which may have to be adapted to the specific case, rather than prescribing a common method. For comparability, however, a common framework is recommended. Specific approaches will depend on data quality and availability of exposure, their relation to dose-response relationships, the complexity of causal relationships and competing causes, the possibility of extrapolating data to data poor regions etc.

- Probability-density functions (PDFs), or parametric value exceedences, have been shown to be useful tools in modelling chronic exposure to, for example, lead. Using PDFs to represent exposure distributions in a population rather than using mean values or only few exposure categories will provide better estimates of disease burden, in particular when dose-response relationships are not linear or when they have thresholds.

- Wherever possible, the assessment of burden of disease should be based on comprehensive models integrating the various interacting or competing risk factors. Occupational exposures and environmental exposures to chemicals, for example, should be part of integrated risk factor assessments where they both play a role. As risks are not merely additive, a combined assessment would usually provide better results.

- Also for modelling health impacts from water & sanitation, a common framework is essential to take into account the interactions between the various exposures and health. Such a model, integrating various distal and proximal determinants of water and sanitation related disease, is yet to be developed. Many of the determinants of faecal-oral disease transmission are interrelated, and should be assessed jointly.

**Prioritisation and choice of risk factors to be addressed**

- Risk perception should play a role in the selection of risk factors to evaluate. Also the quantification of a relatively low disease burden caused by a risk factor raising concern in the population may constitute important information for policy setting and risk communication.

- Because of the difficulty in assessment, risk factors such as ‘housing’, ‘indoor temperature’, ‘domestic accidents’, ‘noise’, ‘natural disasters due to climate change’, ‘transportation system’ may not necessarily receive the attention they deserve. They may cause quite significant disease burdens, which can however not be evaluated, mainly due to the lack of evidence on dose-response or other difficulties in assessment.
• More distal risk factors (for example ‘environmental refugees’ due to land degradation or climate change) could also have significant impacts, but such disease burden is, however, currently very difficult to estimate. In fact, risk factors which are not directly linked to health outcomes are more difficult to quantify, as a number of additional parameters may intervene.

• Disease burden assessment should focus on risk factors with potentially high impacts. Risk factors causing high disease burden may require priority public health action, provided that the burden is preventable and interventions are cost-effective.

• If data are available, ‘the environment’ should be considered in a much broader manner than would be the case by simple consideration of the ‘exposure’ or easily quantifiable ‘risk factor’ commonly dealt with. For example, environments promoting certain behaviours or risks, such as ‘accident promoting environments’ (or ‘traumagenic environments’) could also be considered.

**Diverse issues**

• Positive health impacts should also be considered when evaluating disease burden from health determinants, such as the positive effects of development or increasing living standards.

• A network of environmental health professionals interested in the environmental burden of disease work should be promoted, to exchange experiences and learn from them. WHO plans to set up a information exchange mechanisms for experts involved in environmental burden of disease activities.

Additional recommendations are contained in the reports of the working groups in Annex 5.
Annex 1: Background document

Annette Prüss

Protection of the Human Environment, World Health Organization

1. Introduction

A large number of countries engage in burden of disease studies, to describe their national situation in terms of disease burden due to various disease groups. Countries are increasingly interested in looking for causative life-style, social or physical factors that contribute to this disease burden, such as smoking, dietary patterns, or air pollution. Such information, together with estimates of preventable burden, can become major elements for consideration in the decision-making process for priority setting and resource allocation in health and environment.

A number of studies have been undertaken to assess the disease burden from selected environmental risk factors at global and national level, using a variety of approaches. There is an increasing demand to aid these efforts by providing methodological support to countries.

WHO is currently developing guidelines for comparative risk assessment at global level. These guidelines cover the underlying principles of risk factor assessment in general, without addressing issues which are specific to environmental health.

This initiative builds on the workshop ‘Methods for health impact assessment in environmental and occupational health’, July 1997, which addressed basic features of burden of disease assessment.

This project aims to provide practical recommendations for the evaluation of specific environmental risk factors for disease burden estimates at national and global levels, and analyse methodological elements on the basis of current approaches. The expected outcome of the project is a practical guide for countries to estimate the disease burden from environmental risk factors. It will address issues such as indicators and parameters to collect, on which frequency data should be collected, how to make estimates for data-poor areas or populations.

This work will be based on the Comparative Risk Assessment and Burden of Disease initiatives of WHO, which may be adapted and completed to satisfy the requirements of environmental health.

2. Relative importance of environmental risk factors per region

Before engaging in national or regional studies on environmental disease burden and assessing or compiling the necessary parameters, the orders of magnitude of risk factors can be estimated according to development status. Environmental conditions and their impact on health are strongly linked to demographic and socio-economic development and the pressures these have on the environment. The health transition accompanying development and socio-economic change has been described as a transition from traditional to modern risks (Smith, 1996; WHO, 1997; Frenk, 1991). Environmental health risk in developed societies will depend upon the risk management efforts (Figure 1).
From previous studies assessing disease burden from environmental risk factors (Murray & Lopez, 1996, Smith, 1999, De Hollander, 1999), orders of magnitude can be outlined for developed and developing regions (Table 1).

The differences in orders of magnitude between least developed and most developed regions will be even greater as exemplified by the disease burden in the Sub-saharan region which is known to be much higher than the mean values in the developing world. Also, the rural/urban differences or the differences for high-risk communities even within one nation, are likely to be important.

This initial classification has, however, a number of limitations, mainly because of the difficulty in the assessment of environmental disease burden:

- Developing societies have been relatively poorly studied in terms of environmental disease burden
- Several risk factors, in particular those which are locally specific (exposure to solid waste, natural disasters, disease vectors, chemical hazards, land degradation etc.) are difficult to assess.
3. Basic approaches for estimating disease burden due to environmental risk factors

As described in the previous workshop, there are two basic approaches to assess disease burden from environmental risk factors: the exposure-based and the outcome-based approach (WHO/ILO, 1998). While the exposure-based approach estimates the disease burden on the basis of population exposure, the outcome-based approach is based on the attributable fraction of a disease burden to a certain risk factor. These two approaches require different sets of data, although they share the same underlying assumptions on a health-environment link and its quantification.

Ideally, disease burden due to a specific risk factor should be estimated by both approaches, and the results should match. In practice, this may rarely be possible. The principles of assessment according to these two approaches areas follows:

(i) Exposure-based approach

- Identification of outcomes associated with the relevant risk factor
- Assessment of exposure in the study population
  The exposure distribution of the study population needs to be estimated on the basis of measured data.
- Dose-response relationships
  A dose-response relationship as a function of the exposure parameter assessed for the study population needs to be defined. It needs to be based on a ‘sufficient level of evidence’.

Exposure distribution and dose-response relationships are then combined to yield health impact distributions in the study population. Health impact distributions, usually expressed in terms of incidence, can then be converted into health summary measures, for examples DALYs (by existing models).

As an example, the disease burden of outdoor air pollution for Santiago, Chile, was calculated by measuring the concentration of particulate matter (PM10) in the air, estimating the susceptible population, and combining these data with relevant dose-response relationships. A reduction of PM10 levels to recommended standards would result in a reduction of about 5'200 deaths, 4'700 respiratory hospital admissions, and 13'500'000 restricted activity days per year, for a total population of 4.7 million (WHO, 1996).

(ii) Outcome-based approach

- Identification of outcomes associated with the relevant risk factor
- Collection and compilation of disease outcome data
- Definition of fraction attributable to relevant risk factor

The disease burden due to a given risk factor is estimated by combining the attributable fraction of a certain disease burden with the amount of disease burden.

As an example, Smith et al. (1999) recently estimated the total disease burden attributed to the environment by an outcome-based approach. They estimated that 25
to 33% of the global disease burden expressed in DALYs can be attributed to environmental risk factors. After establishing a number of working definitions and assumptions, the authors analysed disease outcomes regarding the likely contribution of the environment for each of these diseases. These estimates rely on scientific knowledge and expert opinion. For example, tuberculosis “has important household environmental risk factors, including crowding, chilling, and, probably, air pollution”, leading to an attribution of 20-25% of the burden caused by this disease to the environment. Acute respiratory infections are known to be eliminated by environmental and nutritional improvements in developed countries, therefore indoor and outdoor air pollution, and housing conditions are estimated to contribute 40-60% of the burden.

The estimation of disease burden attributable to water, sanitation and hygiene in the Global Burden of Disease Study (Murray & Lopez, 1996) was based on outcome. Relevant diseases, such as diarrhoea and parasitic diseases, were attributed by a certain percentage to likely modes of transmission, in this case water, sanitation and hygiene. In the same study, the disease burden attributable to outdoor air pollution was estimated by an exposure-based approach. Exposures were roughly estimated for the world’s population, and then combined with the relevant dose-response relationships.

Diseases which are specifically related to one single risk factor will typically be used in an outcome-based approach. Examples include legionellosis, fluoridosis, methaemoglobinemia, trachoma, helminth infestations, hepatitis A, which are related to water, sanitation, food or hygiene. Risk factors which could reasonably be assessed through simple indicators at a large scale and which result in a number of unspecific disease outcomes may be assessed through an exposure-based approach. Examples include outdoor air quality, chronic exposure to lead, indoor air pollution, community noise, recreational water quality etc., which are related to various disease outcomes.

*Example of approach using a causal inference model for assessing environmental disease burden*

In environmental health, as in many other health areas, cause-to-effect models often involve a multitude of distal and proximal causes relating to each other, and a number of outcomes. To illustrate this type of application to the environment, a preliminary version of a causal web (intended to be only illustrative) is shown in Figure 2. A causal web is a cause-to-effect model, in which relationships among risk factors and between risk factors and disease outcomes are modelled. The more proximal a cause is to a disease outcomes, the more direct analytical relationship is expected with the health outcome. Distal causes operate through proximal causes on the disease outcome.
Figure 2: Causal web for chronic exposure to lead

Each link among causes, or between causes and disease outcome, could be characterized by a function. It may result in a mathematical model yielding results on disease burden if exposure data were introduced.

The causal web approach provides an interesting framework for disease burden assessment in environmental health. While distal parameters are often available at national level (from economic parameters assessed at national level, such as use of leaded gasoline, or from household surveys performed at large scale), proximal parameters characterizing individual exposure are more difficult to assess at a sufficient frequency to be representative for a study population (e.g. indoor air quality). Box 1 outlines the application of a causal web to the example of chronic exposure to lead.
Scenario-based approach

Where it is not feasible to describe key relationships between distal and proximal causes and/or disease outcomes, for example because of complex and competing relationships between exposures, a simplified approach can consist in the selection of a number of characteristic and representative exposure scenarios. The study population can be categorized into a number of defined exposure scenarios, corresponding to a specific health risk. For exposure to lead, such scenarios could include:

- Urban environment and degraded housing
- Urban environment without degraded housing
- Rural environment, no use of leaded pipes for drinking water
- Urban environment with use of leaded gasoline

The basic steps required for disease burden estimation for the exposure-based and the scenario-based approach are shown in Figure 3.
Figure 3: Steps in disease burden estimation for exposure based and outcome based approaches

**Exposure-based approach**

- Exposure distribution in the population
- Counterfactual exposure scenario
- Dose-response relationship
- Intermediate parameters, e.g. hospitals admissions
- Incidence
- Model for disease burden estimation
- Disease burden estimates per disease

**Scenario-based approach**

- Definition of exposure scenarios
- Categorization of population into exposure scenarios
- Relative risk per exposure scenario
- Incidence
- Model for disease burden estimation
- Disease burden estimates per disease
4. Choosing counterfactual scenarios

The estimation of disease burden from a specific risk factor requires that the exposure distribution of interest be compared to an alternative scenario, or *counterfactual scenario*. Counterfactual scenarios are ‘what if’ scenarios, as a thought experiment to describe a situation in which the exposure by the risk factor has been reduced or not occurred. Many counterfactual scenarios are potentially of interest, in particular when they are relevant for policies. Murray & Lopez outlined four scenarios of interest *(Murray & Lopez, 1999)*, including the theoretical, plausible, feasible and cost-effective minima. Counterfactual scenarios can thus be chosen according to theoretical considerations (*theoretical minimum risk*), distributions observed in other environments, populations or regions (*feasible minimum risk*), the optimization of a specific parameter (e.g. *cost-effective minimum risk*) or according to situations resulting from a particular process (e.g. implementation of a policy). *Theoretical distributions* could consist of a theoretical minimum risk, being the distribution of exposure which would yield the lowest population risk. For environmental exposures, this would usually correspond to the absence of the risk factor altogether (e.g. absence of pollution), or a scenario where air pollution levels would not cause any health impacts. In general, the use of theoretical minimal scenarios seems relatively sound in the area of environmental health, as there is a high potential for pollution reduction by innovative technologies. The *feasible minimum risk* could for example correspond to an urban centre with a successful policy for clean air.

For policy relevance, it would be useful to define comprehensive scenarios which could lead to modified exposure distributions and disease burden, in particular when estimating the preventable burden.

The formulation of alternative scenarios may, however, become relatively complex, as they often imply a shift in environmental exposures rather than simple removal. For example, a reduction in exposure caused by a change in the energy policy should be compared to exposure distributions corresponding to alternative energy scenarios.

For the preventable fraction, estimating disease burden against clean air in the near future would not make much sense, as this cannot be achieved in many urban centres of the world. It would be more relevant for policy makers to be presented with estimates for alternative scenarios which can realistically be achieved in the given time frame. This does not preclude from taking into account creative scenarios, in which innovative technologies could see the day, in particular in the more distant future (e.g. 20 years).

Elaborate scenarios of the future environment have been developed, which could also be used as comparative scenario for the evaluation of disease burden. The Global Environmental Outlook *(UNEP, 1999)* describes future scenarios for every continent, based on demographic, economic and policy developments. Scenarios include the ‘business-as-usual’ scenario, a ‘policy’ scenario and an ‘accelerated policy’ scenarios, aiming at more sustainable developments.

McMichael *et al.* *(1998, 1999)* propose scenario-based forecasting of health impacts addressing global environmental changes such as climate change, the depletion of freshwater supplies or food-producing systems, or the accumulation of pesticides. More generally, they recommend extension beyond proximal, individual-level risk factors and application with a large scale social-ecologic systems perspective.
The International Institute for Applied Systems Analysis has also analysed and forecasted various environment scenarios (Nakicenovic et al, 1998a; Stigliano, 1989) and energy scenarios beyond 2050 (Nakicenovic, 1998b). The International Panel on Climate Change forecasts future emission scenarios. These scenarios address the issue of alternative scenarios in a comprehensive way, which may be relevant for assessing the impact of environmental changes on health.

Future scenarios to be used for the estimation of preventable burden should be characterised by the projection of the current scenario with unchanged policies or trends.

5. Parameters for environmental disease burden assessment at national level

A selection of parameters can be provided for the assessment of environmental disease burden at national level. For every risk factor, the following data sets can be proposed (example in Box 2):

- Selection of suitable indicators
- Frequency of indicator assessment
- Dose-response relationships or relative risk for exposure scenarios
- Applicability of the dose-response relationships

Box 2: Example of chronic exposure to lead

Parameters to assess at national level:
- Blood lead levels (ug/dl)
- Use of leaded gasoline (%)
- Use of lead-glazed ceramics (%)
- Households with leaded drinking-water pipes (%)
- Use of other leaded, region-specific products

6. Evaluation of uncertainty

Before estimating a disease burden, it should be established that there is sufficient evidence that the risk factor – disease relationship is causal. This concerns the dose-response relationship in the exposure-based approach, or the attributable fraction in the outcome-based approach. Every disease burden estimate should furthermore contain an estimate on the uncertainty interval around the estimate.

In certain cases, however, it would be relevant to undertake a disease burden estimate even without the sufficient evidence that a relationship is causal. This would be the case for risk factors potentially generating a very important and preventable disease burden, which could apply to climate change.

Acknowledging that the other sources of error can dwarf the statistical uncertainty in GBD estimates, it is still of use to consider methods that can be used to quantify statistical uncertainty. GBD estimates can be complicated functions of other estimates (e.g., estimates of incidence, prevalence and relative risks). Several techniques have been described for deriving inference for an estimates which is itself
a function of existing estimates, for instance meta-analysis of epidemiological data. The statistical techniques one could apply, given the information exists, are straightforward (Boxes 3 and 4; source: Alan Hubbard).

Box 3: Statistical uncertainty in GBD estimates

Let $\hat{\theta} = g(\tilde{\gamma})$, where $\theta$ is the GBD estimate, $\gamma$ is the vector of parameters and $g$ is the function used to calculate $\theta$ and the hat (^) notation indicates that estimates of the parameters are being used. The first step in deriving inference of the GBD estimate, such as confidence intervals for $\hat{\theta}$, is an estimate of the variance of $\hat{\theta}$. A delta-method approximation for the variance of $\hat{\theta}$ is:

$$\text{var}(\hat{\theta}) = [g'(\tilde{\gamma})]V\hat{C}(\tilde{\gamma})[g'(\tilde{\gamma})]$$

where $g'$ represents the vector of first partial derivatives of $g$ w.r.t. $\gamma$ and $V\hat{C}(\tilde{\gamma})$ is the estimated variance-covariance matrix of the vector $\tilde{\gamma}$. If the estimates used to construct the GBD estimate are from independently drawn data, then one expects $V\hat{C}(\tilde{\gamma})$ will be diagonal. Finally, if there is good reason to believe that $\hat{\theta}$ is normally distributed, for instance if $g(.)$ is a linear function, then confidence intervals for $\theta$ are easily derived. However, if one can not assume that $\hat{\theta}$ is normally distributed, then the joint distribution of $\tilde{\gamma}$ needs to be specified and a Monte Carlo method can be used to estimate the distribution of $\hat{\theta}$.

Box 4: Monte Carlo Estimation of Uncertainty

An attractive method that works more generally than the traditional method discussed above uses the computer to construct a set of new GDB estimates, say $\gamma^*_i$, $i=1,...,M$, and investigate uncertainty in $\hat{\theta}$ by simple graphs or summary measures (see De Hollander, et al., 1999; Nurminen, et al., 1999). The technique can be thought of as a generalization of calculating a GBD based on several scenarios, for instance, estimating a GBD for the minimum and maximum possible values of a risk factor prevalence. The technique works as follows: using the joint distribution of $\tilde{\gamma}$ one random generates a vector of $\gamma^*_i$, then calculate and record $\theta^*_i = g(\gamma^*_i)$, and repeats this procedure $M$ times. Then, the confidence interval for $\theta$ can be derived straightforwardly from this computer generated sample.

The above discussion assumes that the distribution of $\tilde{\gamma}$ is known. This probably is only true if one has derived the necessary information for the parameters used in the GBD estimates from independent studies, and thus one can assume that the estimates contained in $\tilde{\gamma}$ are at least roughly statistically independent. Often, it will be the case that the information on the distribution of $\tilde{\gamma}$ will be limited and consist of a mix of reported standard errors and simple regions of plausibility (e.g., the prevalence of a risk factor lies somewhere between 5 and 20%). The Monte Carlo technique can still be used, but one can not interpret the distribution of the $\theta^*$ as an approximation of the distribution of $\theta$, and thus, one can not construct confidence intervals for $\theta$. However, the Monte Carlo method can still provide a rough estimate of the level of uncertainty of $\theta$ and ranges of plausible values for $\theta$. 

7. **Risk factors which are difficult to assess at large scale**

At national, regional or global scale, it will be difficult, if not impossible, to describe the whole picture of environmentally-caused disease. This is due to the following reasons, some of which may change as knowledge around certain issues develops:

- Exposure is difficult to assess for local ‘events’, which are not representative for a larger scale (e.g. industrial emissions or hazardous waste).
- Evidence is still relatively low for establishing certain dose-response relationships (e.g. noise).
- Relationships and competing risks between risk factors are often complex, and influence the dose-response relationship according to the scenario (e.g. in the example of water, sanitation & hygiene, a dose-response relationship may become ‘saturated’ when the level of faecal-oral pathogens in the environmental is very high).

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Annex 2: List of Participants

**Dr Ruth H. Allen**  
Health Effects Division  
Office of Pesticide Programs  
USEPA 7509-C Ariel Rios Bldg  
1200 Pennsylvania Ave.  
Washington, D.C. 20460  
USA  
Tel. : +1 703 305 7191  
Fax : +1 703 305 5147  
E-Mail : allen.ruth@epa.gov and ra78n@nih.gov

**Professor Vladimir Bencko**  
Head, Institute of Hygiene & Epidemiology  
First Faculty of Medicine  
Charles University of Prague  
Studnickova 7  
CZ 128 00 Prague 2  
Czech Republic  
Tel/Fax : +420224919967  
E-mail: vbencko@lf1.cuni.cz

**Dr. C. Pedro Mas Bermejo**  
Director General  
Instituto Nacional de Higiene, Epidemiologia y Microbiologia  
Infanta no. 1158  
e/. Llinas y Clavel  
La Habana  
CP 10300  
Cuba  
Tel. : (537) 781479 786755 705531-34  
Fax : (537) 662404  
E-Mail : director@inhem.sld.cu

**Dr Rebecca Calderon**  
MD-58C  
U.S. Environmental Protection Agency  
Research Triangle Park, NC 27711  
USA  
Tel. : +1 919 966 0617  
Fax : +1 919 966 0655  
E-Mail : calderon.rebecca@epa.gov

**Dr Diarmid Campbell-Lendrum**  
Disease Control and Vector Biology Unit  
Infectious Diseases Department  
London School of Hygiene and Tropical Medicine  
Keppel Street  
London WC1E 7HT  
United Kingdom  
Tel. : +44 207 927 2497  
Fax : +44 207 580 9075  
E-Mail : Diarmid.Campbell-Lendrum@lshtm.ac.uk

**Dr Augustinus de Hollander**  
Laboratory for Exposure Assessment & Environmental Epidemiology  
National Institute of Public Health and the Environment (RIVM)  
P.O. Box 1  
3720 BA Bilthoven  
The Netherlands  
Tel. : +31 30 274 4535  
Fax : +31 30 274 4407  
E-Mail : AEM.de.Hollander@rivm.nl
Dr Kristie L. Ebi  
Manager, Epidemiology  
Electric Power Research Institute (EPRI)  
3412 Hillview Ave.  
Palo Alto, CA 94304  
USA  
Tel.: +1 650 855 2735  
Fax: +1 650 855 2950  
E-mail: krisebi@epri.com

Dr Joseph Eisenberg  
Environmental Health Sciences & Epidemiology  
University of California, Berkeley  
School of Public Health  
140 Warren Hall # 7360  
Berkeley, CA 94720-7360  
USA  
Tel.: (510) 643-9257  
Fax: (510) 642-5815  
E-Mail: eisenber@socrates.berkeley.edu

Dr Lorna Fewtrell  
Centre for Research into Environment and Health  
5 Quakers Coppice  
Crewe Gates Farm  
Crewe  
Cheshire CW1 6FA  
UK  
Tel:+44 1270 250583  
Fax:+44 1270 589761  
E-mail: lorna@creh.demon.co.uk

Dr Jay M. Fleisher  
United States Navy Environmental Health Center  
2510 Walmer Avenue  
Norfolk, VA 23513  
USA  
Tel.: +1 757 462 5417  
Fax : +1 757 444 9691  
E-Mail: fleisherj@nehc.med.navy.mil

Dr Keith Florig  
Risk Analysis Group  
Department of Engineering and Public Policy  
Carnegie Mellon University  
Pittsburgh, PA 15213-3890  
USA  
Tel: +1 412 268 3754  
Fax: +1 413 581 6294  
E-mail: florig@cmu.edu

Dr Scott Grosse  
Centers for Disease Control & Prevention (CDC)  
National Center for Environmental Health  
4770 Buford Highway, Mail Stop F29  
Atlanta, GA 30341  
USA  
Tel.: +1 770 488 4575  
E-Mail: sgg4@cdc.gov

Dr Heraline E. Hicks  
Great Lakes Program Director  
Agency for Toxic Substances and Disease Registry  
1600 Clifton Road, N.E., Mail Stop E 29  
Atlanta, Georgia 30333  
USA  
Tel.: +1 404 639 5097  
Fax: +404 639 6315  
E-Mail: heh2@cdc.gov
**Methodology for assessment of environmental burden of disease - Annex 2**

**Professor A.J. McMichael**  
Department of Epidemiology and Population Health  
London School of Hygiene and Tropical Medicine  
Keppel Street  
London WC1E 7HT  
U.K.  
Tel. : (020) 7927.2254  
Fax : (020) 7580.6897  
E-Mail : tony.mcmichael@lshtm.ac.uk

**Sumi Mehta**  
School of Public Health  
Division of Environmental Health Sciences  
140 Warren Hall # 7360  
Berkeley, CA 94720-7360  
USA  
Tel. : (510) 643-5580  
Fax : (510) 642-5815  
E-Mail : sumim@uclink4.berkeley.edu

**Dr Patricia A. Murphy**  
U.S. Environmental Protection Agency  
National Center for Environmental Assessment  
MS-272  
2890 Woodbridge Ave.  
Edison, New Jersey 08837-3679  
USA  
Tel. : (732) 906-6830  
Fax : (732) 906-6845  
E-Mail : murphy.patricia@epa.gov

**Dr Harris Pastides**  
School of Public Health  
University of South Carolina  
Columbia, SC 29208  
USA  
Tel. : (1) 803 777 5032  
Fax : (1) 803 777 4783  
E-Mail : hpastides@sph.sc.edu

**Dr Paulina Pino**  
Division of Environmental and Occupational Health  
School of Public Health  
Faculty of Medicine  
University of Chile  
Independencia 939  
Santiago de Chile  
Chile  
Tel. : (56-2) 678-6152  
Fax : (56-2) 735-5582  
E-mail: ppino@machi.med.uchile.cl

**Dr Isabelle Romieu de Hernandez**  
Regional Advisor in Environmental Health, PAHO/WHO  
Instituto nacional de salud Publica  
Av. Universidad no. 655  
Col. Sta. Ma. Ahuacatitlan  
C.P. 62508  
Cuernavaca, Morelos  
Mexico  
Tel. : (52) (73) 11 01 11 Ext. 2200  
Fax : (52) (73) 11 11 48  
E-mail: iromieu@insp3.insp.mx

**Professor Kirk Smith** (unable to attend)  
School of Public Health, University of California  
140 Warren Hall # 7360  
Berkeley, CA 94720-7360  
USA  
Tel: +1 510 643 0793  
Fax: +1 510 642 5815  
E-mail: krksmith@uclink4.berkeley.edu
Professor Stanislaw Tankowski
Head, Department of Environmental Health Hazards
Nofer Institute of Occupational Medicine
8, Sw. Teresy st. Tel.: +48 42 631 4842
90-950 Lodz Fax: +48 42 631 4572
Poland E-mail: tarko@imp.lodz.pl

Dr Shilu Tong
Centre for Public Health Research
Queensland University of Technology Tel.: +61 7 3864 5437
Kelvin Grove, Qld. 4059 Fax: +61 7 3864 5941
Australia E-mail: s.tong@qut.edu.au

Professor John E. Vena
University at Buffalo
State University of New York
Department of Social and Preventive Medicine
School of Medicine and Biomedical Sciences
Farber Hall Rm. 270 Tel.: (716) 829.2975 Ext. 602
3435 Main St., Bldg. 26 Fax: (716) 829-2979
Buffalo, NY 14214-3000 USA E-Mail: jvena@buffalo.edu

Dr Susan T. West
Environmental Health Education and Outreach
Physicians for Social Responsibility
1101 Fourteenth Street, NW Suite 700 Tel.: (202) 898-0150 Ext. 224
Washington, DC 20005 Fax: (202) 898-0172
USA E-Mail: swest@psr.org

WHO

Dr Roberto Bertollini
Global Change and Health
WHO European Centre for Environment and Health
Via Francesco Crispi, 10 Tel.: +39 06 487 2042
I-00187 Rome Fax: +39 06 487 7599
Italy E-Mail: rbe@who.it

Xavier Bonnefoy
Division of Technical Support and Strategic Development
World Health Organization
Regional Office for Europe
8 Scherfisgvej Tel: +45 39 17 1427
2100 Copenhagen Fax: +45 39.17 1818
Denmark E-mail: xbo@who.dk
Dr Carlos Corvalán  
World Health Organization  
Department of Protection of the Human Environment (PHE)  
20, avenue Appia  
CH-1211 Geneva 27  
Switzerland  
Tel: +41 22 791 4208  
Fax: +41 22 791 41 27  
E-mail: corvalanc@who.ch

Dr Dafina Dalbokova  
EH Information Systems  
WHO European Centre for Environment and Health  
Bilthoven Division  
P.O. Box 10, 3730 AA De Bilt  
Netherlands  
Tel.: +31 30 2295 324  
Fax: +31 30 2294 120  
E-mail: dda@ecb.who.nl

Majid Ezzati  
Global Programme on Evidence for Health Policy (GPE)  
World Health Organization  
CH-1211 Geneva 27  
Switzerland  
Tel.: +41 22 791 23 69  
Fax: +41 22 791 43 28  
E-mail: ezzatim@who.ch

Dr Luiz Augusto Galvão  
Regional Advisor, Environmental Quality Program-HEQ  
Health and Environment Division-HEP  
Pan American Health Organization-PAHO  
Regional Office for the Americas of the World Health Organization-WHO  
525, 23rd Street, NW, Room 535  
Washington, DC-20037-2895  
USA  
Tel: +1(202) 974 3156  
Fax: +1(202) 974 3645  
E-mail: galvaolu@paho.org

Dr Bettina Menne  
Global Change and Health (HIA-GCH)  
WHO European Centre for Environment and Health  
Via Francesco Crispi, 10  
I-00187 Rome  
Italy  
Tel.: +39 06 487 7546  
Fax: +39 06 487 7599  
E-mail: bme@who.it

Annette Pruess  
World Health Organization  
Department of Protection of the Human Environment (PHE)  
20, avenue Appia  
CH-1211 Geneva 27  
Switzerland  
Tel: +41 22 791 35 84  
Fax: +41 22 791 41 59  
E-mail: pruessa@who.ch

Francesca Racioppi  
Transport  
WHO European Centre for Environmental Health  
Via Francesco Crispi, 10  
I-00187 Rome  
Italy  
Tel.: +39 06 487 7545  
Fax: +39 06 487 7599  
E-mail: frr@who.it

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Annex 3: Agenda

23 August
9:00-9:30 Aims, objectives & introduction
   Welcome and background: Carlos Corvalán (10 min)
   Aims, objectives & concept: Annette Pruess (15 min)
9:30-10:30 Framework & challenges
   CRA framework: Majid Ezzati (15 min)
   Challenges in a national study: Guus de Hollander (10 min)
10:30-11:00 Break
11:00-12:30 Concepts and examples
   Selected conceptual issues: Lorna Fewtrell (20 min)
   Use of probability-density functions
   Scenario-based approach
   Practical guide – IAP example: Sumi Mehta (10 min)
   Break-up into working groups
12:30-13:30 Lunch
13:30-15:00 Group work – concepts and examples
15:00-15:30 Break
15:30-17:30 Describing the level of uncertainty and evidence
   Uncertainty: Alan Hubbard, Majid Ezzati (10 min)
   Level of evidence – considerations: Jay Fleisher (10 min)
   Level of evidence in practice: Sari Kovats (10 min)

24 August
9:00-10:30 Report of the group work – concepts and examples
10:30-11:00 Break
11:00-13:00 Discussion and further steps and improvements

Proposed working groups:
- Water & sanitation
- Air quality
- Global environment
- Chemical exposures

Tasks for the working groups
- Counterfactual scenarios
- Strength of evidence
- Geographical resolution
- Comments on proposed approaches
- Way forward
- Other issues?