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METHODOLOGY FOR ASSESSMENT OF EXPOSURE TO ENVIRONMENTAL FACTORS IN APPLICATION TO EPIDEMIOLOGICAL STUDIES

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ABSTRACT

Assessment of exposure to environmental factors is a crucial step in each study investigating the impact of these factors on health, and is an essential component of the risk assessment process. The methodology of exposure assessment is developing rapidly, creating new opportunities for environmental epidemiology. At the same time, the practical requirements of population studies impose several restrictions on the feasibility of measurement methods, and determine certain requirements related to the method's validity. To evaluate existing exposure assessment methods in terms of their applicability to environmental epidemiology, the Consultation reviewed exposure assessment needs in studies of acute and delayed health effects, methods of assessing exposure through specific media or routes, and issues related to study design and exposure modelling. The recommendations refer to study design and conduct, methods of evaluation and publication, and to the policy issues and applications.

Keywords

ENVIRONMENTAL EXPOSURE
RISK ASSESSMENT
ENVIRONMENTAL MONITORING
METHODS
EUROPE

CONTENTS

INTRODUCTION

The extent of effects on health related to various environmental factors is still a subject of intensive studies, and assessment of exposure is a crucial element of every such study. Many of the epidemiological studies performed up to now have used very crude indicators of exposure. This may result in biased estimators of the studied association and decrease the power of the study, undermining its usefulness and leaving unresolved questions of the existence and magnitude of effects on health. Rapid progress in the methodology of exposure assessment would create an opportunity to apply improved exposure assessment methods in epidemiology, since some of the new methods are less costly and are suitable for use in population studies, and their validity is well tested. Each new method should be validated and tested, however, especially in terms of its feasibility for population studies and its cost–effectiveness, before it is applied in epidemiology. It is in the interest of environmental epidemiology to use the best available methods and in the interest of exposure assessment specialists to provide methods suitable for wide application. This is especially true in situations where research funds are limited and studies are conducted to provide data for policy decisions, such as in central and eastern Europe.

To contribute to the evaluation of the existing exposure assessment methodologies and of their applicability in epidemiological studies, the WHO European Centre for Environment and Health (ECEH) organized a Consultation in Stockholm on 14–15 August 1993 with the specific objectives of:

(1) formulating basic practical requirements concerning validation of exposure assessment methods and their applicability to epidemiological studies;

(2) identifying available exposure assessment methods that comply with the criteria formulated in objective (1); and

(3) identifying areas where validation of existing exposure assessment methods, or further progress in their development, are necessary to improve their usefulness in epidemiological studies.

Eleven temporary advisers from various disciplines including epidemiology, toxicology, biostatistics, air quality research, chemistry and physics took part in the meeting. A list of participants is presented in Annex 3. The working papers, listed in Annex 2, were prepared before the consultation and constituted the basis of the discussion. (The working papers will be published in a special issue of the journal *Science of the total environment.*)

The meeting was chaired by Professor Bernd Seifert; Dr Erik Lebret was the Rapporteur.

It was recognized that the objectives of a study that involved exposure assessment could include:

- estimation of the dose–response relationship between exposure and a health effect;
- assessment of the population distribution of exposure; and
- assessment of the health effect of a given exposure situation (even if only weakly supported by the present understanding of a biological meaning of the exposure situation).

All the above applications of exposure assessment were within the scope of the Consultation, and all environmental media and exposure routes were open to discussion. The emphasis was on measurements in the environment and on indirect methods of exposure assessment. In particular, the following issues were considered:

- exposure to chemical contaminants in air, drinking-water, recreational water and food;
- exposure to ionizing radiation and nonionizing electromagnetic fields; and
- study design and methods of data analysis.

Exposure assessment methodologies for studies directed at acute as well as delayed health effects were discussed. Topics related to the development, validation and use of biological markers were excluded from the discussion since they had been the subject of a previous WHO/ECEH consultation in September 1993.

The working papers were briefly introduced and discussed in plenary. Four working groups were then formed to address specific aspects of exposure assessment methodology, i.e. study design; study conduct; evaluation and publication; and policy application. The topics discussed by the groups are listed in Annex 1.

DISCUSSION

General issues

Validity criteria for exposure assessment methods

The interpretation of basic definitions of measurement validity and study validity[a] in the context of exposure assessment was discussed in more detail. Special emphasis was placed on the requirements for producing valid information on exposure through direct and indirect measurements such as personal monitoring, questionnaires and time–activity patterns. Among the minimum requirements to be considered in direct measurements are a meaningful relation between the sampling strategy and the biodynamics of the pollutant under study, and a sound quality control/quality assurance programme. For indirect measurements the elements used in the assessment procedure (e.g. concentration distributions, time–activity patterns and models) should be made explicit and be validated to the extent possible.

Exposure assessment needs in studies of acute health effects

In studies of acute health effects, both short and long exposure times are important. Temporal characteristics of exposure, in terms of

[a] Last, J.M. *A dictionary of epidemiology*, 2nd ed. Oxford, Oxford University Press, 1988.

duration, time of occurrence and repetition, can be important in estimating an exposure–response relationship and in characterizng the response (or lag) time. All the exposure parameters should be assessed. Among the methods potentially providing exposure estimates with sufficient time resolution are those combining measurements of pollutant concentrations in micro-environments with time–activity data on individuals in the study group. Appropriate time-specific assessment of confounders and effect modifiers is also necessary. Exposure modelling techniques are needed, as well as the development and application of appropriate methods of statistical analysis.

Exposure assessment needs in studies of delayed health effects

In studies on the delayed effects of environmental exposure there is a need to accurately reconstruct the exposure to the environmental factor under study in a large number of individuals. There is also a need for similar assessments of exposure to possible confounding factors in the same population. Exact reconstruction is usually not possible, but it is often possible to estimate exposures as they would probably have occurred. This requires selecting populations and circumstances that allow such estimates to be made. For each environmental exposure and for each disease outcome to be evaluated, it is likely that the optimum exposure assessment methodology will be different. In each case these opportunities will have to be identified, tested and validated to the extent possible. Exposure will almost always have to be assessed retrospectively, if for no other reason than that prospective designs would not yield results until long after the initiation of the study.

Exposure through specific media or routes

Assessment of exposure to chemical contaminants in water and food

The main questions on the validity of studies and routine monitoring (e.g. within the scope of the WHO/UNEP GEMS programme) for assessing exposure to chemicals through ingested water and food are the following:

- *Sampling*. Variations due to sampling strategy and approach usually exceed analytical errors.
- *Measurement*. Quality assessment and quality control procedures are essential. However, potential limitations of measurement error resulting from these procedures should be kept in perspective with other errors and confounding factors.
- *Methodology*, depending on the variability of the intake patterns in the population (resulting, for example, from cultural and behavioural differences) as well as on the adequacy of the information on the consumption of food of a specified type as an indicator of the intake of a specific chemical. These factors should be considered in particular in studies using "food basket" methods. Whenever possible, the structure of the population in respect to factors determining typical diet should be registered.
- *Form of reporting*, limiting the possibilities of re-analysing exposure estimates. Typical problems to be considered are the distinction between "not detected", "zero" and "limit of detection values", as well as the specification of "mean" or "median".

Routinely collected data on exposure through food and water should be used with care in epidemiological studies. Assessment of exposure conducted specially for an epidemiological study should consider possible changes in diet with time. Data on confounders are crucial for exposure estimates.

Assessment of exposure to air pollution

Instruments are becoming available that continuously record personal exposure, but their operating performance should be thoroughly assessed for accuracy, precision, interference, etc. Even after validation of the method, it will be difficult and expensive to undertake continuous personal exposure monitoring in large groups. The specification of exposure across a large population is probably best carried out with a combination of measurements and models.

Detailed exposure measurements can be valuable in small-scale studies of exposure patterns, in pilot studies, or in assessing the validity of surrogate or proxy measures of exposure.

Assessment of dermal exposure to chemicals

Dermal exposure has generally received rather scanty attention outside pesticide use in agriculture, even though contact with (contaminated) water and soil and with contaminated surfaces occurs in everyday life. In general, dermal exposure is the most important in occupational settings. The methods for assessing dermal exposure vary in complexity and are in some ways complementary. The easiest methods to use involve a "pseudo-skin" approach such as gloves, and removal by washing. The experimental methods can indicate and even quantify the presence of chemicals on the skin, thus permitting studies on the occurrence of local effects in relation to exposure. When the interest is in systemic effects, dermal exposure is of interest only if it represents the amount that is available for penetration through the skin. This may vary largely between compounds due to the large variation in dermal absorption. When the degree of absorption is not known, the alternative method may be biological monitoring, at least when it is based on a detailed pharmacokinetic knowledge of the compound. The most sophisticated method, applied to study occupational exposures, is a combination of monitoring on clothing, hand washing and biological monitoring. In any case, assessment of dermal exposure should be based on a sampling strategy that takes into account the distribution of contamination on the body, the variation of exposure with time, the duration of exposure, and the degree of skin protection afforded by clothing.

Assessment of exposure to nonionizing radiation

The unique challenges facing those investigating exposure to electric and magnetic fields are the absence of a biological marker and the diverse sources of exposure. Owing to concerns about the possible association of exposure with some cancers, the need for retrospective exposure estimation makes assessment even more complicated. Historical residential exposure have been estimated

from wiring configurations near the home and present-day field measurements. Wire codes are favoured for their historical stability, high coverage of the target population, and clear identification of the field source. Electrical appliances have not received adequate attention, so the feasibility and value of assessing exposure from this source is uncertain. Occupational exposure have been and will continue to be based on job title, but research is needed to better characterize and judge the adequacy of this approach. For all exposure sources, models are needed that link present information based on interviews, measurements and environmental observations to historical exposure. Integration of exposures from multiple sources are needed, as well as clearer guidance from the laboratory on the biologically most important parameters of exposure.

Assessment of exposure to ionizing radiation

During the last several years, methods for the passive measurement of gamma radiation and radon have improved. Relatively cheap and reliable dosimeters are now available. Results exist from national and worldwide surveys of natural radiation in bedrock and soils and of radon concentrations indoors. These can be used to pinpoint more precisely areas with higher than normal exposure to gamma radiation, indoor radon levels, and radium and radon levels in household water. Besides direct measurements of radiation intensity, additional information (such as residence history and house ventilation habits) is required to reconstruct a historical exposure level for epidemiological investigations. The availability and accuracy of this information may influence the validity of exposure estimates.

Methodological issues

Questionnaire-based exposure assessment methods

In environmental epidemiological studies, questionnaires may be the method of choice for assessing exposure because no other source of information is available. They may be used alone or in combination with other types of data, such as those from environmental monitoring. Problems may arise from a lack of content validity (the

questionnaire does not cover all sources of exposure to the hazard of interest) or criterion validity (e.g. through inaccurate recall or misunderstanding of questions). The validity of exposure data obtained by questionnaire can be tested by comparison with biological monitoring, personal exposure monitoring, other monitoring with time–activity data, or historical records of exposure. Also, poor repeatability on questioning and logical inconsistencies between answers to different questions may point to poor criterion validity even in the absence of a reliable standard. Needs for the future include agreement on the items to be covered in questionnaires to assess various specific exposures, more published data on validity assessments for questionnaires looking at different aspects of exposure (e.g. occupational and residential histories), and more consideration of questionnaire validity in the design and interpretation of studies. Validated "standard" questionnaires have some value, particularly in allowing comparison between studies, but their validity should not be automatically assumed when they are applied to populations other than those in which they have been tested. Thus, standards based on validation in multiple studies (multiple places and times) should be pursued further.

Models of human exposure based on environmental monitoring

The relevant exposure to environmental pollutants or relevant confounders can virtually never be measured directly in sufficient detail in a sufficient number of people. Instead, surrogate indicators of exposure are used that are implicitly or explicitly linked by (conceptual) models to the "relevant exposure". Using specified indices (e.g. the coefficient of alienation and forecasting efficiency), the models of different forms can be compared and tested in special investigations. This can evaluate the validity of the model through an analysis of the agreement between modelling based on measured surrogate indicators of exposure and actual exposure. The perspective on the construct under study may change the validity of exposure indicator. Therefore, substudies evaluating the quality of exposure indicators should be considered an integral part of any study in environmental epidemiology, preferably as a preliminary or pilot study.

Study design for exposure assessment in epidemiological studies

The choice of exposure assessment method in epidemiological studies, and in particular the optimal allocation of resources devoted to improving the accuracy of exposure assessments, may have important implications for efficiency. For this purpose it is useful as a general rule to assume that the efficiency of a study based on approximate exposure relative to one based on exact exposure is equal to the square of the validity coefficient of the approximate assessment. This implies that to maximize study power, investment in increased precision is worth while up to the point at which proportional increase in total costs per subject exceed the proportional gain in the square of the validity coefficient. "Classical" exposure measurement error (that uncorrelated with true exposure) also biases estimates of effect. Information from validity or reliability substudies can be used to correct for this bias (but not in general to recover lost efficiency). The existing published results can be used for the optimal allocation of resources to a validity substudy.

CONCLUSIONS

Results from validated human exposure studies are a necessary part of the evaluation of risks to human health. Available information on population exposure, however, is still deficient in many ways. Currently available information on the contribution of the various exposure routes to total exposure is still insufficient, and more work is necessary to establish valid distributions of population exposure from air, water, food, dust and soil, and through the skin. Owing to differences in "boundary conditions", numerically identical exposures to a pollutant may lead to different health outcomes in different populations. Such boundary conditions may include nutritional, ethnic, climatic or geographical conditions, as well as the type of pollutant mixture or temporal (diurnal, seasonal or long-term) patterns in exposure.

RECOMMENDATIONS

General

1. The terminology used in exposure assessment and in environmental epidemiology should be harmonized to the extent possible, taking into account the need to translate terms into different languages. An internationally coordinated process to achieve this should be developed.

2. Initiatives should be taken to improve opportunities for training in both short-term and long-term exposure assessment, etc. The results should form the basis of WHO training materials on methods for exposure assessment, to be used at regional and national levels.

3. WHO should take initiatives for the development of criteria and guidelines (including ethical guidelines) for applying meta-analysis in exposure assessment and environmental epidemiology, since the future use of data on exposure is likely to involve various types of meta-analysis. This will create new opportunities for more detailed quantitative analysis of environmental health effects. It will also involve a number of methodological problems and pitfalls, as well as ethical issues concerned with re-analysing existing data.

Study design and conduct

4. The selection of exposure measurement method should always be based on the biological relevance of exposure to the health effect considered.

5. All routes of exposure should be defined, i.e. respiratory, oral and dermal, and the importance of each should be assessed in relation to the objectives and study design.

6. Exposure assessment typically involves the use of a set of methods, to be applied in the entire population or in subpopulations. In designing a study, an optimal (in respect of the objectives) set of exposure assessment options should be considered. The extent of a compromise due to limited resources should be addressed.

7. The variability of exposure in the population(s) should be considered. Exposure range should be optimized with regard to the effectiveness and objectives of the study.

8. The confounders of exposure–health endpoint relationship should if possible be controlled for at the design stage. Otherwise, the confounders and effect modifiers should be assessed to enable their consideration in the analysis.

9. Allocation of resources to exposure assessment should ensure optimal efficiency of the study.

10. The feasibility of the planned exposure assessment methods (e.g. in terms of acceptability to those under study) should be pre-tested in a pilot study.

11. A validation study of exposure assessment methods in a pilot study should precede their application in a population study.

12. Quality assurance should control the main sources of error so as to protect the overall validity of the study. The main sources of possible error need to be defined during the design of the study.

13. Techniques to assess exposures retrospectively should be improved, expanded and validated.

Evaluation and publication: policy issues and applications

14. Results from exposure characterizations are often reported only in highly aggregated and summarized form (e.g. mean and range) which restricts the interpretation of study results. Publication of results only in scientific journals may restrict the detailed description of relevant exposure data. Specialized journals dedicated to exposure assessment should be used when publication of the epidemiological study does not allow sufficient documentation of the relevant exposure conditions studied.

15. The process by which investigators summarize the raw data to the form of exposure data used in the analysis needs to be fully explained and justified. This includes removal of unacceptable observations, condensation of exposure data into summary measures or categories, and relating the categorized exposure information to health outcomes. The documentation of observed exposure should, as far as possible, describe the full distribution of exposure in the (sub-) population(s).

16. The raw (exposure) data need to be retained in a form suitable for re-analysis. This would include all rules for acceptable observations and the statistical treatment of exposure data. Although the practical and ethical issues involved with data sharing are complex, researchers should retain the capability of doing so.

17. Results from studies in environmental epidemiology describe associations between a surrogate of exposure and health outcome. Inferences based on such associations with surrogates should be identified in view of the *a priori* operational definitions of exposure indicators.

18. To make a study useful for regulatory purposes, as much information as possible should be provided on the population's exposure distribution, and on the uncertainties of exposure

assessment and their consequences. The relation between population exposure and exposure indicators obtained from (routine) environment quality monitoring should be established.

19. The uncertainties of assumptions used in the study design, definitions of exposure, statistical models and inferences should be evaluated in a quantitative manner. This might include comparison of alternatives used in the study or used in similar studies. Simulation may be helpful in addressing the combined effects of uncertainty in more complex situations.

Annex 1

WORKING GROUPS: COMPOSITION AND ISSUES DISCUSSED

Validity issues in design phase (Armstrong, Lebowitz, Stolwijk)

- Definition of aim of study and construct
- Contrast in high/low exposed
- Competing risk factors
- Selection of controls
- Study efficiency/resource allocation (measurements, logistics, QA/QC)
- Pilot studies (basis for power calculation)

Validity issues in study conduct (Åkerblom, Coggon, Williams)

- Quality assurance and quality control
- Selection of measurement methods
- Internal and external validation
- New technologies (e.g. videos)

Validity issues in evaluation and publication (Van Hemmen, Lebret, Savitz)

- Validity of data analysis
- Validity of statistical procedures
- Presentation of data and results
- Model validation
- Readership
- New technologies (e.g. CD-i)

Validity issues in policy application (Seifert, Peterson, Williams)

- Validity of study results for regulatory purposes
- External validity of results
- Population exposure distributions

Annex 2

WORKING PAPERS

ICP/CEH 238/6	Validity criteria for exposure assessment methods, by B. Seifert
ICP/CEH 238/7	Exposure assessment needs in studies of acute health effects, by M.D. Lebowitz
ICP/CEH 238/8	Exposure assessment needs in studies of delayed health effects, by J.A.J. Stolwijk
ICP/CEH 238/9	Assessment of exposure to chemical contaminants in water and food, by P.J. Peterson
ICP/CEH 238/10	Assessment of dermal exposure to chemicals, by J.J. van Hemmen
ICP/CEH 238/11	Exposure assessment strategies in epidemiologic studies of health effects of electric and magnetic fields, by D.A. Savitz
ICP/CEH 238/12	Assessment of exposure to natural ionizing radiation, by G. Åkerblom
ICP/CEH 238/13	Monitoring of exposure to air pollution, by M. Williams
ICP/CEH 238/14	Questionnaire based exposure assessment methods, by D. Coggon
ICP/CEH 238/15	Models of human exposure based on environmental monitoring, by E. Lebret
ICP/CEH 238/16	Study design for exposure assessment in epidemiological studies, by B. Armstrong

Annex 3

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