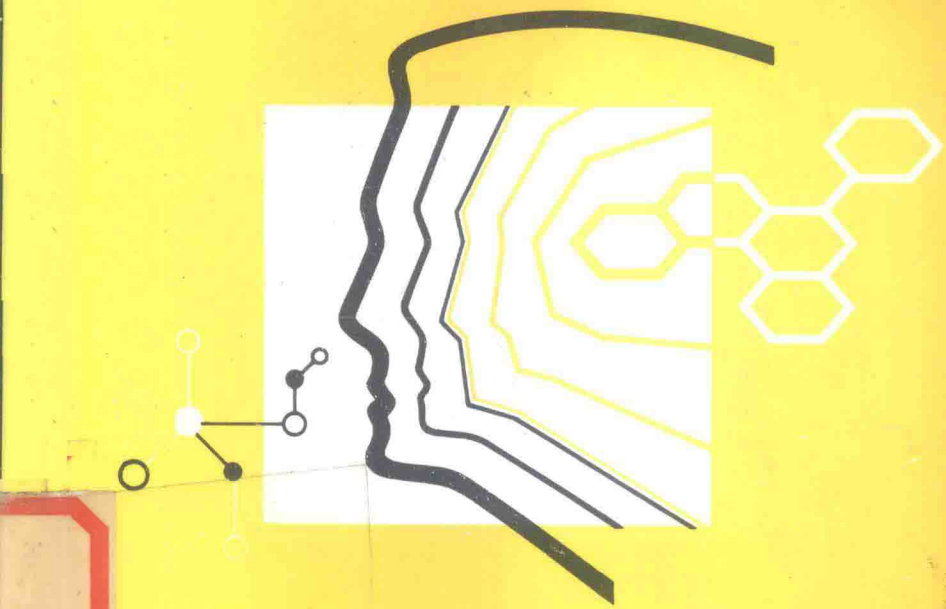
IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

Environmental Health Criteria 222

Biomarkers in Risk Assessment: Validity and Validation



IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among UNEP, ILO, FAO, WHO, UNIDO, UNITAR and OECD

WORLD HEALTH ORGANIZATION

Environmental Health Criteria 222

BIOMARKERS IN RISK ASSESSMENT: VALIDITY AND VALIDATION

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organization, and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.

World Health Organization
Geneva, 2001

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer-review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (telephone no. + 41 22 - 9799111, fax no. + 41 22 - 7973460, E-mail irptc@unep.ch).

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Environmental Health Criteria

PREAMBLE

Objectives

In 1973 the WHO Environmental Health Criteria Programme was initiated with the following objectives:

(i) to assess information on the relationship between exposure to environmental pollutants and human health, and to provide guidelines for setting exposure limits;

(ii) to identify new or potential pollutants;

(iii) to identify gaps in knowledge concerning the health effects of pollutants;

(iv) to promote the harmonization of toxicological and epidemiological methods in order to have internationally comparable results.

The first Environmental Health Criteria (EHC) monograph, on mercury, was published in 1976 and since that time an ever-increasing number of assessments of chemicals and of physical effects have been produced. In addition, many EHC monographs have been devoted to evaluating toxicological methodology, e.g. for genetic, neurotoxic, teratogenic and nephrotoxic effects. Other publications have been concerned with epidemiological guidelines, evaluation of short-term tests for carcinogens, biomarkers, effects on the elderly and so forth.

Since its inauguration the EHC Programme has widened its scope, and the importance of environmental effects, in addition to health effects, has been increasingly emphasized in the total evaluation of chemicals.

The original impetus for the Programme came from World Health Assembly resolutions and the recommendations of the 1972 UN Conference on the Human Environment. Subsequently the work became an integral part of the International Programme on Chemical Safety (IPCS), a cooperative programme of UNEP, ILO and WHO.

In this manner, with the strong support of the new partners, the importance of occupational health and environmental effects was fully recognized. The EHC monographs have become widely established, used and recognized throughout the world.

The recommendations of the 1992 UN Conference on Environment and Development and the subsequent establishment of the Intergovernmental Forum on Chemical Safety with the priorities for action in the six programme areas of Chapter 19, Agenda 21, all lend further weight to the need for EHC assessments of the risks of chemicals.

Scope

The criteria monographs are intended to provide critical reviews on the effect on human health and the environment of chemicals and of combinations of chemicals and physical and biological agents. As such, they include and review studies that are of direct relevance for the evaluation. However, they do not describe *every* study carried out. Worldwide data are used and are quoted from original studies, not from abstracts or reviews. Both published and unpublished reports are considered and it is incumbent on the authors to assess all the articles cited in the references. Preference is always given to published data. Unpublished data are used only when relevant published data are absent or when they are pivotal to the risk assessment. A detailed policy statement is available that describes the procedures used for unpublished proprietary data so that this information can be used in the evaluation without compromising its confidential nature (WHO (1999) Guidelines for the Preparation of Environmental Health Criteria. PCS/99.9, Geneva, World Health Organization).

In the evaluation of human health risks, sound human data, whenever available, are preferred to animal data. Animal and *in vitro* studies provide support and are used mainly to supply evidence missing from human studies. It is mandatory that research on human subjects is conducted in full accord with ethical principles, including the provisions of the Helsinki Declaration.

The EHC monographs are intended to assist national and international authorities in making risk assessments and subsequent risk management decisions. They represent a thorough evaluation of

risks and are not, in any sense, recommendations for regulation or standard setting. These latter are the exclusive purview of national and regional governments.

Content

The layout of EHC monographs for chemicals is outlined below.

- Summary – a review of the salient facts and the risk evaluation of the chemical
- Identity – physical and chemical properties, analytical methods
- Sources of exposure
- Environmental transport, distribution and transformation
- Environmental levels and human exposure
- Kinetics and metabolism in laboratory animals and humans
- Effects on laboratory mammals and *in vitro* test systems
- Effects on humans
- Effects on other organisms in the laboratory and field
- Evaluation of human health risks and effects on the environment
- Conclusions and recommendations for protection of human health and the environment
- Further research
- Previous evaluations by international bodies, e.g. IARC, JECFA, JMPR

Selection of chemicals

Since the inception of the EHC Programme, the IPCS has organized meetings of scientists to establish lists of priority chemicals for subsequent evaluation. Such meetings have been held in Ispra, Italy, 1980; Oxford, United Kingdom, 1984; Berlin, Germany, 1987; and North Carolina, USA, 1995. The selection of chemicals has been based on the following criteria: the existence of scientific evidence that the substance presents a hazard to human health and/or the environment; the possible use, persistence, accumulation or degradation of the substance shows that there may be significant human or environmental exposure; the size and nature of populations at risk (both human and other species) and risks for environment; international concern, i.e. the substance is of major interest to several countries; adequate data on the hazards are available.

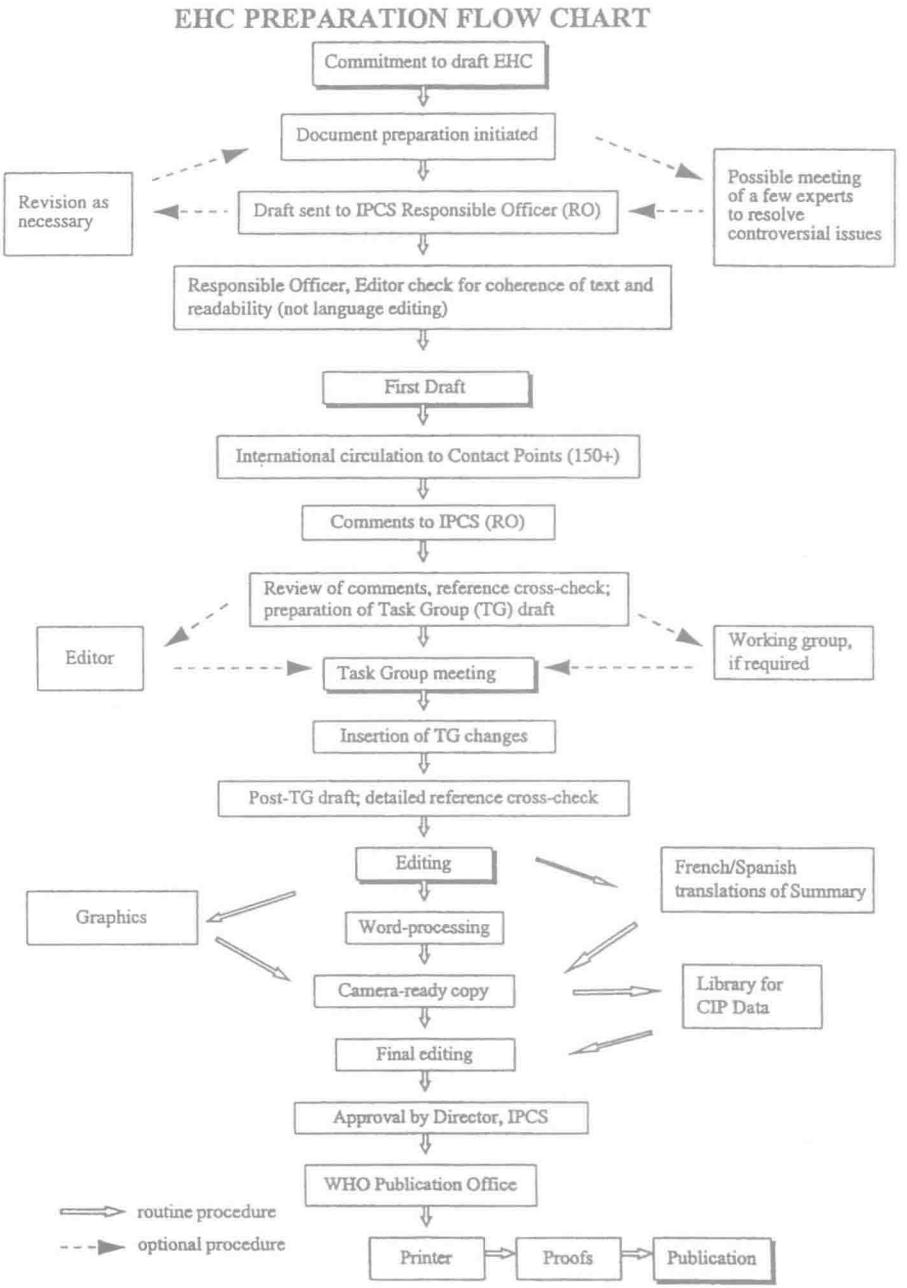
If an EHC monograph is proposed for a chemical not on the priority list, the IPCS Secretariat consults with the Cooperating Organizations and all the Participating Institutions before embarking on the preparation of the monograph.

Procedures

The order of procedures that result in the publication of an EHC monograph is shown in the flow chart on p. x. A designated staff member of IPCS, responsible for the scientific quality of the document, serves as Responsible Officer (RO). The IPCS Editor is responsible for layout and language. The first draft, prepared by consultants or, more usually, staff from an IPCS Participating Institution, is based initially on data provided from the International Register of Potentially Toxic Chemicals, and reference data bases such as Medline and Toxline.

The draft document, when received by the RO, may require an initial review by a small panel of experts to determine its scientific quality and objectivity. Once the RO finds the document acceptable as a first draft, it is distributed, in its unedited form, to well over 150 EHC contact points throughout the world who are asked to comment on its completeness and accuracy and, where necessary, provide additional material. The contact points, usually designated by governments, may be Participating Institutions, IPCS Focal Points, or individual scientists known for their particular expertise. Generally some four months are allowed before the comments are considered by the RO and author(s). A second draft incorporating comments received and approved by the Director, IPCS, is then distributed to Task Group members, who carry out the peer review, at least six weeks before their meeting.

The Task Group members serve as individual scientists, not as representatives of any organization, government or industry. Their function is to evaluate the accuracy, significance and relevance of the information in the document and to assess the health and environmental risks from exposure to the chemical. A summary and recommendations for further research and improved safety aspects are also required. The composition of the Task Group is dictated by the range of expertise required for the subject of the meeting and by the need for a balanced geographical distribution.


EHC PREPARATION FLOW CHART
Commitment to draft EHC
Document preparation initiated
Revision as necessary
Draft sent to IPCS Responsible Officer (RO)
Possible meeting of a few experts to resolve controversial issues
Responsible Officer, Editor check for coherence of text and readability (not language editing)
First Draft
International circulation to Contact Points (150+)
Comments to IPCS (RO)
Review of comments, reference cross-check; preparation of Task Group (TG) draft
Editor
Task Group meeting
Working group, if required
Insertion of TG changes
Post-TG draft; detailed reference cross-check
Editing
French/Spanish translations of Summary
Graphics
Word-processing
Camera-ready copy
Library for CIP Data
Final editing
Approval by Director, IPCS
WHO Publication Office
routine procedure
optional procedure
Printer
Proofs
Publication

The three cooperating organizations of the IPCS recognize the important role played by nongovernmental organizations. Representatives from relevant national and international associations may be invited to join the Task Group as observers. Although observers may provide a valuable contribution to the process, they can only speak at the invitation of the Chairperson. Observers do not participate in the final evaluation of the chemical; this is the sole responsibility of the Task Group members. When the Task Group considers it to be appropriate, it may meet *in camera*.

All individuals who as authors, consultants or advisers participate in the preparation of the EHC monograph must, in addition to serving in their personal capacity as scientists, inform the RO if at any time a conflict of interest, whether actual or potential, could be perceived in their work. They are required to sign a conflict of interest statement. Such a procedure ensures the transparency and probity of the process.

When the Task Group has completed its review and the RO is satisfied as to the scientific correctness and completeness of the document, it then goes for language editing, reference checking and preparation of camera-ready copy. After approval by the Director, IPCS, the monograph is submitted to the WHO Office of Publications for printing. At this time a copy of the final draft is sent to the Chairperson and Rapporteur of the Task Group to check for any errors.

It is accepted that the following criteria should initiate the updating of an EHC monograph: new data are available that would substantially change the evaluation; there is public concern for health or environmental effects of the agent because of greater exposure; an appreciable time period has elapsed since the last evaluation.

All Participating Institutions are informed, through the EHC progress report, of the authors and institutions proposed for the drafting of the documents. A comprehensive file of all comments received on drafts of each EHC monograph is maintained and is available on request. The Chairpersons of Task Groups are briefed before each meeting on their role and responsibility in ensuring that these rules are followed.

WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR BIOMARKERS IN RISK ASSESSMENT: VALIDITY AND VALIDATION

Members

Dr D. Anderson, TNO BIBRA International Ltd, Carshalton, Surrey, United Kingdom (*Rapporteur*)

Dr H. Autrup, Department of Environmental Medicine, University of Aarhus, Aarhus, Denmark (*Chairman*)

Dr S. Bonassi, Department of Environmental Epidemiology, National Institute for Research on Cancer, Genoa, Italy

Dr K. Hemminki, Department of Biosciences at Novum, Karolinska Institute, Huddinge, Sweden

Dr A. Mutti, Laboratory of Industrial Toxicology, Department of Clinical Medicine, Nephrology, and Health Sciences, University of Parma Medical School, Parma, Italy

Dr O. Pelkonen, Department of Pharmacology and Toxicology, University of Oulu, Oulu, Finland

Dr P.A. Schulte, Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, Ohio, USA

Secretariat

Dr A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland (*Joint Secretary*)

Dr Y. Hayashi, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland (*Joint Secretary*)

WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR BIOMARKERS IN RISK ASSESSMENT: VALIDITY AND VALIDATION

A WHO Task Group on Environmental Health Criteria for Biomarkers in Risk Assessment: Validity and Validation met at TNO BIBRA International, Carshalton, Surrey, United Kingdom from 3 to 6 April 2000. Dr A. Aitio, IPCS, welcomed the participants on behalf of the IPCS and its three cooperating organizations (UNEP/ILO/WHO). The Task Group reviewed and revised the draft monograph.

This Environmental Health Criteria monograph is composed of the main text and four authored papers. The main text was constructed by Dr P.A. Schulte, based on the source documents and was reviewed by the IPCS Contact Points. The comments received were considered by the principal author, and the revisions were discussed and approved by the Task Group. The source documents were similarly subjected to IPCS review and were then revised accordingly by the authors. However, they were not discussed thoroughly during the Task Group meeting and thus represent the views of the authors.

Dr A. Aitio and Mr Y. Hayashi of the IPCS Central Unit were responsible for the overall scientific content of the monograph and Dr P.G. Jenkins of the IPCS Central Unit was responsible for the technical editing of the monograph.

The efforts of all who helped in the preparation of the monograph are gratefully acknowledged.

* * *

The preparation of the draft was financially supported by the US Environmental Agency. Financial support for this Task Group was provided by the UK Department of Health as part of its contribution to the IPCS.

ABBREVIATIONS

BMD	benchmark dose
BP	benzo(a)pyrene
CYP	cytochrome P450
GC	gas chromatography
GST	glutathione *S*-transferase
IARC	International Agency for Research on Cancer
LOAEL	lowest-observed-adverse-effect level
MS	mass spectroscopy
NAT	*N*-acetyltransferase
NOAEL	no-observed-adverse-effect level
PAH	polycyclic aromatic hydrocarbon
PCR	polymerase chain reaction
PM	poor metabolizer
TCDD	tetrachlorinated dibenzo-*p*-dioxin
TLV	threshold limit value
TWA	time-weighted average
XME	xenobiotic metabolizing enzyme

CONTENTS

1. INTRODUCTION

The aim of risk assessments is to provide society with estimates of the likelihood of illnesses and injury as a consequence of exposure to various hazards. Risk assessments are needed when social policy decisions are in dispute, when the health consequences of alternative policies in question are not subject to direct measurement (at least in a timely fashion), and when the scientific analysis of a hazard is not complete (Hattis & Silver, 1993). The assessment procedure involves the development of an exposure-response curve for the target species (e.g., humans), based on animal and human information, followed by the projection of the curves to estimate levels of exposure that may be considered safe (NRC, 1987). For risk assessments to be useful they should lead to projections that are close to the true risks. A strong scientific basis for conducting risk assessments is the best way to assure that projections are close to true risks or at least provide an honest depiction of the state of knowledge and the degree of certainty about risks (Bailar & Bailer, 1999).

Risk assessment has a range of meanings. At the basic level it is an exercise to evaluate the potential of some hazard to induce an adverse human health response. It can be a qualitative or quantitative exercise at the individual or group (population) level. The term quantitative risk assessment (QRA) has been used to describe the response associated with a specific level of exposure (Bailer & Dankovic, 1997). The availability of adequate dose/concentration-response data is a prerequisite to conducting a QRA.

A biomarker is any substance, structure or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease. Biomarkers can be classified into markers of exposure, effect and susceptibility. If biomarkers are to contribute to environmental and occupational health risk assessments, they have to be relevant and valid. Relevance refers to the appropriateness of biomarkers to provide information on questions of interest and importance to public and environmental health authorities and other decision-makers. The use of relevant biomarkers allows decision-makers to answer important public health questions by being used in research or risk assessments in a

way that contributes useful information that cannot be obtained better by other approaches, such as questionnaires, environmental measurements or record reviews. For example, chronic exposure to organochlorines is better indicated by serum organochlorine levels than by market-basket studies or industrial hygiene measurements, and early kidney damage may be better indicated by a battery of urinary biomarkers than by morbidity records. Relevance also pertains to whether the questions on which a biomarker can provide information are important questions; not merely ones that can be answered, but ones that should be answered (Muscat, 1996). Thus, the ability to measure a biomarker after exposure to a toxicant may not be as important a question as whether individuals with exposure to the toxicant are at increased risk of disease.

The second characteristic of potentially useful biomarkers is validity. Validity of biomarkers has been widely discussed (Hernberg & Aitio, 1987; Schatzkin et al., 1990; Schulte & Perera, 1993; Boffetta, 1995; Bernard, 1995; Dor et al., 1999). It includes both laboratory and epidemiological aspects. Validity refers to a range of characteristics that is the best approximation of the truth or falsehood of a biomarker. It is a sense of degree rather than an all-or-none state. The validity of a biomarker is a function of intrinsic qualities of the biomarker and characteristics of the analytic procedures (Dor et al., 1999) (see Tables 1 and 2 for an example of this distinction). Additionally, three broad categories of validity can be distinguished: measurement validity, internal study validity and external validity (Schulte & Perera, 1993). Measurement validity (in terms of analytical chemistry, accuracy) is the degree to which a biomarker indicates what it purports to indicate. Internal study validity is the degree to which inferences drawn from a study actually pertain to study subjects and are true. External validity is the extent to which findings of a study can be generalized to apply to other populations. The use of invalid biomarkers can lead to invalid inferences and generalizations and ultimately to erroneous risk assessments.

Although biomarkers have a long history in medicine and public health, the systematic development, validation and application of biomarkers is a relatively new field in environmental health (Shugart et al., 1992; Anderson S et al., 1994), except for biological monitoring in occupational health (Hernberg & Aitio, 1987).