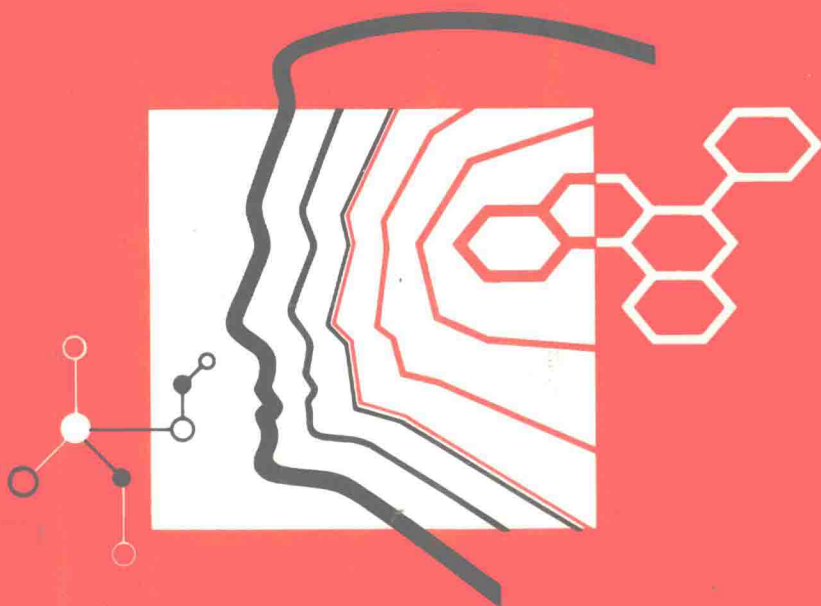


# IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY



## Environmental Health Criteria 224 Arsenic and Arsenic Compounds (Second Edition)



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

This report contains the collective views of international groups of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organization, or the World Health Organization.

## **Environmental Health Criteria 224**

# **ARSENIC AND ARSENIC COMPOUNDS**

**Second edition**

The first and second drafts of this monograph were prepared, under the coordination of Dr J. Ng, by the authors A. Gomez-Caminero, P. Howe, M. Hughes, E. Kenyon, D.R. Lewis, M. Moore, J. Ng, and by A. Aitio and G. Becking.

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.

WHO Library Cataloguing-in-Publication Data

Arsenic and arsenic compounds.

(Environmental health criteria ; 224)

1.Arsenic – toxicity 2.Arsenicals – toxicity 3.Environmental exposure  
I.International Programme on Chemical Safety II. WHO Task Group on  
Environmental Health Criteria for Arsenic and Arsenic Compounds III.Series

ISBN 92 4 157224 8

(NLM Classification: QV 294)

ISSN 0250-863X

The World Health Organization welcomes requests for permission to reproduce or translate its publications, in part or in full. Applications and enquiries should be addressed to the Office of Publications, World Health Organization, Geneva, Switzerland, which will be glad to provide the latest information on any changes made to the text, plans for new editions, and reprints and translations already available.

©World Health Organization 2001

Publications of the World Health Organization enjoy copyright protection in accordance with the provisions of Protocol 2 of the Universal Copyright Convention. All rights reserved.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the Secretariat of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

Computer typesetting by I. Xavier Lourduraj, Chennai, India

Printed in Finland

2001/13945 – Vammala – 5000

## 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](mailto:irptc@unep.ch)).

\* \* \*

This publication was made possible by grant number 5 U01 ES02617-15 from the National Institute of Environmental Health Sciences, National Institutes of Health, USA, and by financial support from the European Commission.

The Commonwealth Department of Health and Aged Care, Australia, contributed financially to the preparation of this Environmental Health Criteria monograph. The Task Group meeting was arranged by the National Research Centre for Environmental Toxicology, Australia.

---

## 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 (1990) Revised Guidelines for the Preparation of Environmental Health Criteria Monographs. PCS/90.69, 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**

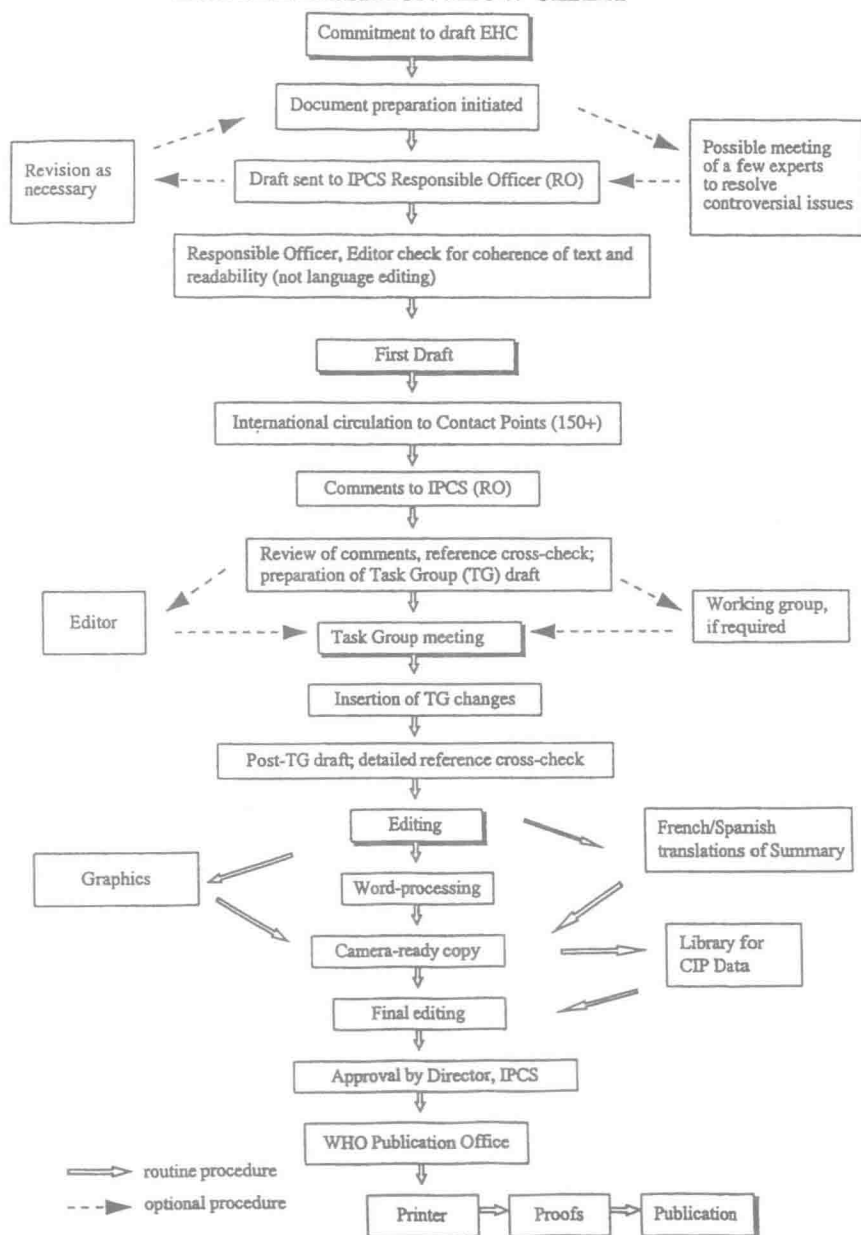
The order of procedures that result in the publication of an EHC monograph is shown in the flow chart on p. xvii. A designated staff member of IPCS, responsible for the scientific quality of the document, serves as Responsible Officer (RO). The IPCS Editor is responsible for layout and language. The 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



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 ARSENIC AND ARSENIC COMPOUNDS

### *Members*

Dr C. Abernathy, Office of Water/Office of Science and  
Technology, Health and Ecological Criteria Division, US  
Environmental Protection Agency, Washington, D.C., USA  
(*Chairperson*)

Dr D. Chakraborti, School of Environmental Studies, Jadavpur  
University, Calcutta, India

Professor J.S. Edmonds, Department of Chemistry, De Montfort  
University, Leicester, United Kingdom

Dr H. Gibb, US Environmental Protection Agency, National Center  
for Environmental Assessment, Washington DC, USA

Dr P. Hoet, Industrial and Occupational Medicine Unit, Catholic  
University of Louvain, Brussels, Belgium

Dr C. Hopenhayn-Rich, Department of Preventive Medicine and  
Environmental Health, University of Kentucky, Lexington, KY,  
USA

Mr P.D. Howe, Centre for Ecology and Hydrology, Monks Wood  
Experimental Station, Abbots Ripton, Huntingdon,  
Cambridgeshire, United Kingdom

Dr L. Järup, Department of Epidemiology and Public Health,  
Imperial College School of Medicine, London, United Kingdom

Dr A.A. Meharg, Department of Plant and Soil Science, Aberdeen,  
United Kingdom

Professor M.R. Moore, Director, Queensland Health Scientific  
Services and National Research Centre for Environmental  
Toxicology, Queensland, Australia (*Vice-Chairperson*)

Dr J. C. Ng, National Research Centre for Environmental  
Toxicology, Brisbane, Australia

Dr A. Nishikawa, Division of Pathology, National Institute of Health  
Sciences, Tokyo, Japan

Dr L. Pyy, Director of the Department, Oulu Regional Institute of  
Occupational Health, Oulu, Finland

Dr M. Sim, Unit of Occupational and Environmental Health,  
Department of Epidemiology and Preventive Medicine, Monash  
University, Victoria, Australia

Dr J. Stauber, CSIRO Energy Technology, Lucas Heights Science  
and Technology Centre, Bangor, NSW, Australia

Professor M. Vahter, Institute of Environmental Medicine,  
Karolinska Institute, Stockholm, Sweden

*Observers/Representatives*

Dr P. Imray, Scientific Adviser, Environmental Health Branch,  
Queensland Health, Brisbane, Australia

Dr L. Tomaska, Canberra, Australia (representing the Australia New  
Zealand Food Authority)

Mr D. Hughes, MIM Holdings Limited, Brisbane, Australia  
(representing the Mining Industry)

*Secretariat*

Dr A. Aitio, International Programme on Chemical Safety, World  
Health Organization, Geneva, Switzerland

Dr G. Becking, Kingston, Ontario, Canada (*Adviser to the  
Secretariat*)

Dr K. Buckett, Director DHAC, Public Health Division, Canberra,  
Australia

---

Mr P. Callan, Assistant Director, National Health and Medical  
Research Council, Canberra, Australia

Dr M.F. Hughes, NHEERL/ET/PKB, US Environmental Protection  
Agency, Research Triangle Park, NC, USA

Dr E.M. Kenyon, NHEERL/ET/PKB, US Environmental Protection  
Agency, Research Triangle Park, NC, USA

Dr D.R. Lewis, Human Studies Division, NHEERL, US  
Environmental Protection Agency, Research Triangle Park, NC,  
USA

Dr M. Younes, International Programme on Chemical Safety, World  
Health Organization, Geneva, Switzerland

## **WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR ARSENIC AND ARSENIC COMPOUNDS**

The first and second drafts of this monograph were prepared, under the coordination of Dr J. Ng, by the authors A. Gomez-Camirero, P. Howe, M. Hughes, E. Kenyon, D.R. Lewis, M. Moore, J. Ng, and by A. Aitio and G. Becking. The group of authors met at National Health and Environmental Effects Research Laboratory, US. EPA, North Carolina, on 20–22 July 1998.

A WHO Task Group on Environmental Health Criteria for Arsenic and Arsenic Compounds met at the National Research Centre for Environmental Toxicology, Brisbane, Australia, on 15–19 November 1999. The group reviewed the draft and the peer review comments, revised the draft and made an evaluation of the risks for human health and environment from exposure to arsenic and arsenic compounds.

After the meeting, and based on the peer reviewer comments and Task Group advice, Drs Gibb, Hopenhayn-Rich, Järup, Sim, and Aitio revised and updated the section on Effects on Human Health. This section was then sent for review to a selected group of experts.

The document was revised on the basis of the peer review comments received, these revisions were verified, and the document was finalized by a Review Board, consisting of Drs D. Anderson, H. Gibb, L. Järup, M. Sim and A. Aitio, in TNO BIBRA, Carshalton, UK. The document was finally approved by the Task Group in a mail ballot.

The cut-off date for the literature searches for the document was the Task Group meeting, i.e. November 1999, with the exception of the section on effects on human health, for which the last literature searches were performed in November 2000.

---

Peer review comments at the first stage international review were received from:

Dr J. Ahlers, Umwelt Bundes Amt, Germany  
Dr R. Benson, Region VIII, Environmental Protection Agency, USA  
Professor GB Bliss, N.N. Petrov's Research Institute of Oncology,  
Russian Federation  
Dr M. Bolger, Food and Drug Administration, USA  
Professor M. Cíkr, Centre of Industrial Hygiene and Occupational  
Diseases, Czech Republic  
Professor I. Dési, Albert Szent-Györgyi University, Hungary  
Professor J Duffus, The Edinburgh Centre for Toxicology, UK  
Dr P Edwards, Department of Health, UK  
Dr H Falk, Agency for Toxic Substances and Disease Registry, USA  
Dr H. Gibb, Environmental Protection Agency, USA  
Dr N. Kurzeja European Environmental Bureau, Germany  
Dr I. Mangelsdorf, Fraunhofer Institute, Germany  
Dr TG Rossman, NYU School of Medicine  
Professor H Taskinen, Finnish Institute of Occupational Health  
Mr S Tsuda, Ministry of Health and Welfare, Japan  
Dr G. Ungváry, József Fodor National Center for Public Health,  
Hungary  
Professor M. Vahter, Karolinska Institute, Sweden,  
Bureau of Chemical Safety, Canada  
Elf Atochem North America, USA  
Environmental Protection Agency Office of Research and  
Development, USA  
Eurometaux  
Finnish Institute of Occupational Health, Finland

Comments on the revised section on effects on human health were received from members of the Task Group, and from:

Dr D Anderson, TNO BIBRA International, UK  
Dr Michael Bates, Kenepuru Science Centre, New Zealand  
Dr R. Calderon, National Health and Environmental Effects  
Research Laboratory, US EPA  
Professor PE Enterline, University of Pittsburgh, USA  
Dr A. Gomez-Camirero, National Health and Environmental Effects  
Research Laboratory, US. EPA

Dr J Lubin, National Cancer Institute, USA  
Professor AH Smith, University of California, USA

Dr A. Aitio of the IPCS central unit was responsible for the scientific aspects of the monograph, and Kathleen Lyle for the technical editing.

The efforts of all, especially Queensland Health and the Natinal Research Centre for Environmental Toxicology, Australia, who helped in the preparation and finalization of the monograph are gratefully acknowledged.



---

## ABBREVIATIONS

AAS	atomic absorption spectrometry
ABI	ankle-brachial index
AFS	atomic fluorescence spectrometry
AgDDTC	silver diethyldithiocarbamate
ALA	aminolaevulinic acid
ASV	anodic stripping voltammetry
ATPase	adenosine triphosphatase
AUC	area under the curve
BAL	dimercaprol
BCF	bioconcentration factor
BFD	blackfoot disease
BFD-endemic area	Geographic area in south-western Taiwan, where arsenic-contaminated artesian well water has been used as drinking water, and where BFD is endemic; the area has been also called the "arseniasis" area, or "hyperendemic" area. In this document it is called BFD-endemic area, to differentiate it from other areas e.g. in Taiwan, where high arsenic concentrations in drinking water have been reported
BMI	body mass index
BSO	<i>L</i> -buthionine-(RS)-sulfoximine
CA	chromosome aberrations
CAS	Chemical Abstract Service
CCA	copper chrome arsenate
CCGG	cytosine-cytosine-guanine-guanine
cDNA	complementary DNA
CE	capillary electrophoresis
CI	confidence interval; unless otherwise stated, the 95% CI is given. Accordingly, the term statistically significant in this documents denotes significance at 95% level
CVD	cardiovascular disease